ORGANIC LETTERS

2010
Vol. 12, No. 14
3222−3225

Skeletal Diversity via Cationic Rearrangements of Substituted Dihydropyrans

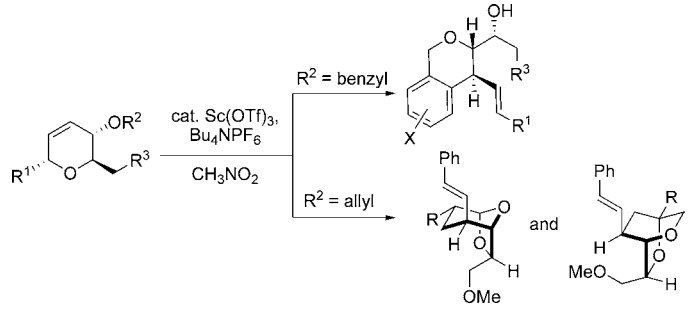
Matthew R. Medeiros, Radha S. Narayan, Nolan T. McDougal, Scott E. Schaus,* and John A. Porco, Jr.*

Department of Chemistry, Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

porco@bu.edu; seschaus@bu.edu

Received May 20, 2010

ABSTRACT



Substituted dihydropyrans, easily accessed from a commercially available glycal, undergo acid-catalyzed rearrangement to provide highly functionalized isochroman and dioxabicyclooctane scaffolds.

Diversity-oriented synthesis (DOS) has proven to be an exceptional strategy for exploring chemical space.[1] Synthetic approaches employing the principles of DOS address variations in three aspects of molecular structure: skeleton, substitution, and stereochemistry.[2] Following the tenets of DOS, controlled skeletal rearrangement processes offer rapid access to diverse, stereochemically rich frameworks.[3] As a method to access skeletal diversity, we recently reported the rearrangement of stereochemically well-defined dihydropyrans derived from glycals such as **1** to afford highly substituted tetrahydrofurans (Scheme 1).[4] In this transformation, dihydropyrans (**2**) underwent Au(III)-mediated ionization at the anomeric C−O bond to form an allylic carbocation intermediate (**3**) which was trapped by the C6 hydroxyl generating tetrahydrofurans **4**. We sought to exploit this reactivity by incorporating nucleophiles at different positions of the precursor pyrans (**5**).[5] We anticipated that this design

(1) Select reviews: (a) Liao, Y.; Hu, V.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, *10*, 2285. (b) Reayi, A.; Arya, P. *Curr. Opin. Chem Biol.* **2005**, *9*, 240. (c) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 700. (d) Grabowski, K.; Baringhaus, K.-H.; Schneider, G. *Nat. Prod. Rep.* **2008**, *25*, 892. (e) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep* **2008**, *25*, 719. (f) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Intl. Ed.* **2008**, *47*, 48.

(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Schreiber, S. L. *Chem. Eng. News* **2003**, *302*, 613. (c) Tan, D. S. *Chem. Biol.* **2007**, *2*, 483. (d) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149. (e) Shaw, J. T. *Nat. Prod. Rep.* **2009**, *26*, 11.

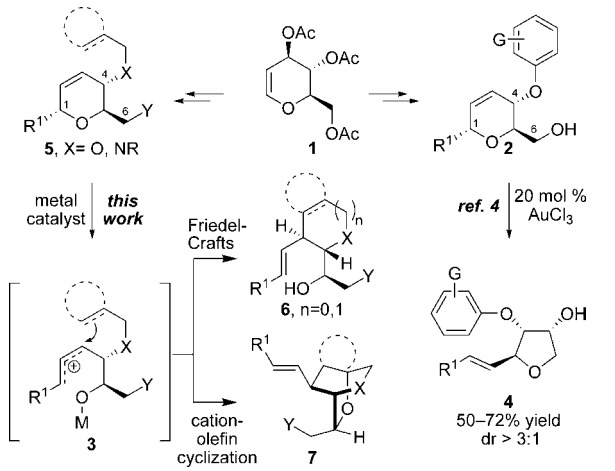
(3) (a) Schreiber, S. L.; Burke, M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Kesavan, S.; Panek, J. S.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 5203. (c) Su, S.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 4983. (d) Garcia-Cuadrado, D.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **2008**, 4619. (e) Aguilar-Moncayo, M.; Ortiz-Mellet, C.; Garcia-Fernandez, J. M.; Garcia-Moreno, M. I. *J. Org. Chem.* **2009**, *74*, 3595.

(4) Yeager, A. R.; Min, G. K.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065.

(5) For selected applications of glycals in synthesis, see the following. Heck reaction: (a) Bedjeguelal, K.; Bolitt, V.; Sinou, D. *Synlett* **1999**, *6*, 762. Pauson−Khand reaction: (b) Kubota, H.; Lim, J.; Depew, K. M.; Schreiber, S. L. *Chem. Biol.* **2002**, *9*, 265. Radical reactions: (c) Fraser-Reid, B.; López, J. C. *Curr. Org. Chem.* **2009**, *13*, 532.

10.1021/ol101144k
Published on Web 06/15/2010

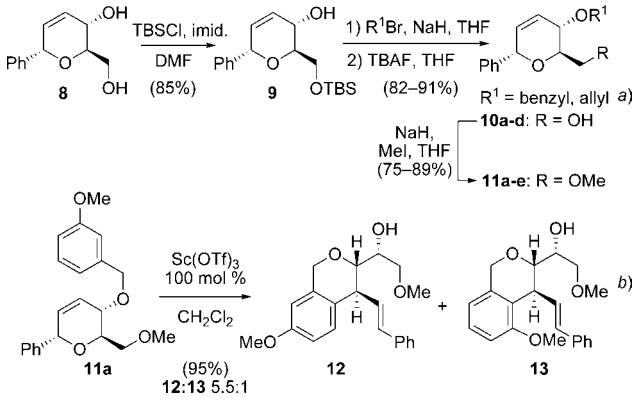
Scheme 1. Skeletal Diversification Strategies Based on Rearrangement of Substituted Dihydropyrans



might allow rapid access to a series of diverse skeletons (e.g., **6** and **7**) by changing the nature of the substituents at C1, C4, and C6 in the dihydropyran substrates. Herein, we demonstrate the realization of this concept employing terminating groups at C4 that dictate various reaction pathways involving Friedel−Crafts and cation-olefin cyclizations.

We initially focused our efforts on development of a general synthesis of the appropriate dihydropyran substrates containing benzyl or allyl ethers at C4. D-Glucal-derived diol **8**[4] was converted to substrates **10a**−**d** and **11a**−**e** in a straightforward manner (Scheme 2a). An aryl ether (cf. Table 2, entry 11) was synthesized via allylic alkylation of 3,4-dimethoxyphenol with the corresponding allylic carbonate using $Pd_2(dba)_3$ and (*S*,*S*)-DACH phenyl Trost ligand under microwave conditions.[6,7] Ferrier reaction of tri-*O*-acetyl-D-glucal (**1**) using ((4-(*tert*-butyl)phenyl)-ethynyl)trimethylsilane was employed to access an alkynyl dihydropyran (cf. Table 2, entry 12).[5]

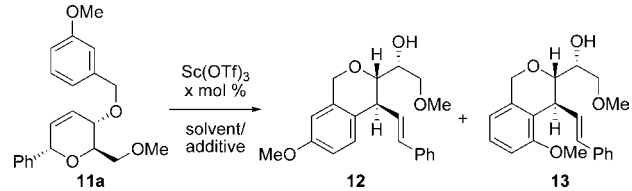
Scheme 2. (a) General Synthesis of Dihydropyran Substrates and (b) Initial Attempt at Pyran Rearrangement



Dihydropyran **11a** was selected to investigate the trapping of proposed carbocation intermediate **3** (Scheme 2b) using Lewis acid catalysis.[8] A preliminary screen revealed that scandium(III) triflate was the optimal Lewis acid for this transformation.[9] Indeed, exposure of **11a** to 100 mol % $Sc(OTf)_3$ in CH_2Cl_2 provided the isochroman regioisomers **12** and **13** (5.5:1) in 95% combined yield.

Encouraged by this result, we set out to decrease catalyst loading (Table 1). Reducing the amount of $Sc(OTf)_3$ to 25 mol % in CH_2Cl_2 resulted in a longer reaction time and low yields of **12**/**13** (entry 1). Substituting CH_3NO_2 for CH_2Cl_2, the former a cation-stabilizing and Lewis acid-activating solvent,[10] enabled use of 20 mol % catalyst while maintaining the reaction rate (entry 2). A desire to further improve the catalytic efficiency of the reaction led us to evaluate Bu_4NPF_6 as additive (entries 3−5). Organic salts having noncoordinating anions have been shown to activate Lewis acid catalysts.[11] Conducting the rearrangement in the presence of Bu_4NPF_6 increased the rate of the reaction. As a control, conducting the reaction in the absence of $Sc(OTf)_3$ resulted in recovery of **11a** (entry 6).

Table 1. Optimization of Catalytic Reaction Conditions[a]



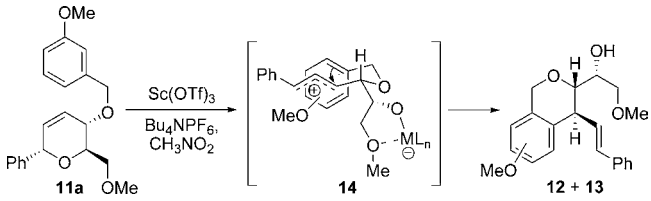
entry	*x*	solvent/additive (equiv)	% yield; **12**:**13**[b]
1	25	CH_2Cl_2/none	72; 5:1[c]
2	20	$MeNO_2$/none	94; 3.7:1
3	10	$MeNO_2$/Bu_4NPF_6 (2)	97; 3.3:1[d]
4	2	$MeNO_2$/Bu_4NPF_6 (2)	85; 2.8:1
5	20	$MeNO_2$/Bu_4NPF_6 (0.2)	93; 3.6:1[d]
6	0	$MeNO_2$/Bu_4NPF_6 (2)	*e*
7	0	$MeNO_2$/TfOH (0.2)	87; 2.5:1[d]
8	20	$MeNO_2$/Bu_4NPF_6 (0.2)/DTBMP (1)	*e*
9	20	$MeNO_2$/Bu_4NPF_6 (0.2)/3 Å MS	*e*

[a] All reactions conducted at 0 °C to rt for 2 h unless otherwise noted. [b] Isolated yield and ratios. [c] rt, 17 h. [d] Time = 30 min. [e] No reaction. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

Triflic acid (TfOH) has been shown to be an active catalyst in reactions employing metal triflates.[12] Accordingly, use of TfOH (20 mol %) provided a slightly lower yield and ratio of **12** and **13** in comparison to $Sc(OTf)_3$ (entry 7). Furthermore, inclusion of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as an acid scavenger completely inhibited the reaction (entry 8). Addition of 3 Å molecular sieves to the reaction to eliminate adventitious water also resulted in the recovery of **11a** (entry 9). Taken together, our

(6) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.
(7) See Supporting Information for complete experimental details.

Scheme 3. Proposed Mechanism of the Dihydropyran Rearrangement



results strongly suggest involvement of TfOH as a viable catalyst for the rearrangement.

A possible mechanism for the dihydropyran rearrangement is illustrated in Scheme 3. We propose initial $Sc(OTf)_3$- or TfOH-promoted ionization of the anomeric C−O bond to afford a highly stabilized allyl cation similar to our previously reported Au(III)-catalyzed process.[4] Subsequent Friedel−Crafts alkylation[13] likely proceeds through a chair-like transition state (**14**) in which both the hydroxymethyl ether and styryl substituents are oriented equatorially. This reactive conformer would lead to the observed *trans* stereochemistry of the newly formed pyran ring of products **12** and **13**.

We next explored the substrate scope of the Friedel−Crafts reaction employing 20 mol % $Sc(OTf)_3$ and 20 mol % Bu_4NPF_6 in CH_3NO_2 as standard conditions (Table 2). Functional group compatibility at C6 was first examined. Notably, in the case of substrates containing a competing nucleophile at C6, Friedel−Crafts alkylation was observed as the preferred pathway (80−95% yield, entries 1, 2, and 5). Dihydropyrans containing either acetate or bromide functionality at C6 also rearranged efficiently (entries 3 and 4). Within the C4 benzyl ether series, electron-rich derivatives produced the corresponding isochromans effectively (entries 6 and 7). On the other hand, 3-bromobenzyl ether substrate **10d** afforded the ring contraction product **28** in low yield (entry 8). Epimerization at C1 of the corresponding methyl ether derivative **11b** (entry 9) provided support for our proposed mechanism. The neutral benzyl ether substrate **11c** regained Friedel−Crafts alkylation reactivity producing a 2:1 mixture of *trans*:*cis* substituted isochromans in 78% yield (entry 10). Although moderately successful, rearrangement of C4 aryl ether **32** provided the distinct dihydrobenzofuran scaffold **33** (entry 11). Finally, the C1-alkynyl dihydropyran substrate **34** (entry 12) rearranged in good yield to afford isochroman enyne **35**.

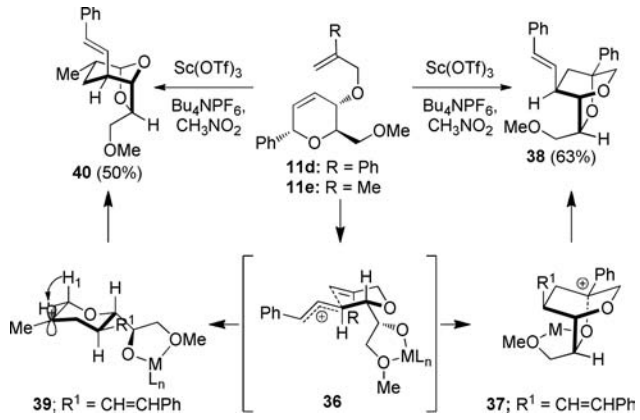
To investigate alternative reaction pathways accessible via the allylic cation, other π-terminating substituents at C4 were examined (Scheme 4). By replacing the benzyl group at C4 with an allyl group, we hoped to observe a sequential process where an initial cation-olefin cyclization[14] would provide a tertiary carbocation that could undergo further transforma-

Table 2. Dihydropyran Rearrangements Resulting from Friedel−Crafts Alkylation[a]

entry	substrate	product (% yield)[b]
1	X = OH (**10a**)	83; (**19**:**23** = 2.8:1)
2	OTBS (**15**)	95; (**19**:**23** = 5.5:1; X = OH)
3	OAc (**16**)	98; (**20**:**24** = 2:1)
4	Br (**17**)	93; (**21**)
5	N_3 (**18**)	80; (**22**:**25** = 4.5:1)
6	R = OMe (**10b**)	**26** (97)
7	R = Me (**10c**)	**27** (81)
8	**10d**	**28** (30)
9	**11b**	**29** (40)
10	**11c**	**30** (52) + **31** (26)
11	**32**	**33** (50)
12	**34**	**35** (50)

[a] Conditions: $Sc(OTf)_3$ (20 mol %), Bu_4NPF_6 (20 mol %), CH_3NO_2, 0 °C to rt, 30 min. [b] Isolated yield and ratio.

Scheme 4. Rearrangements of Substituted Allyl Ethers and Mechanistic Rationale



tions. Under the optimized conditions, α-styrenyl ether **11d** afforded the dioxabicyclo[2.2.2]-octane **38** in 63% yield. Presumably, this reaction proceeds through trapping of the stabilized tertiary carbocation, arising from a cation-olefin cyclization, by the newly formed secondary metal-alkoxide (**37**). Interestingly, rearrangement of the related 2-methallyl ether substrate **11e** resulted in formation of an unexpected product which was characterized as the dioxabicyclo[3.2.1]-octane **40**. The structure of **40** was confirmed by X-ray analysis of a crystalline 2,4-dinitrophenylhydrazone derivative.[7] In this case, the tertiary carbocation **39** apparently undergoes a 1,2-hydride shift (migration of the appropriately aligned H_1 provides the major diastereomer observed) resulting in formation of an oxocarbenium ion, which is trapped by the metal alkoxide leading to **40**.

In summary, we have demonstrated divergent rearrangements of glycal-derived dihydropyrans to afford a series of structurally distinct frameworks. Isochroman skeletons were obtained by Friedel−Crafts trapping of allylic cations generated from the acid-catalyzed opening of a dihydropyran. Dioxabicyclo[2.2.2]- and dioxabicyclo[3.2.1]octanes have been accessed in a process involving nucleophilic attack on the cation generated from olefin cyclizations. Expansion of the rearrangement chemistry to cascade processes, as well as library synthesis applications, is currently underway and will be reported in future publications.

Acknowledgment. We gratefully acknowledge the NIGMS CMLD initiative (P50-GM067041) for financial support and the National Science Foundation for the purchase of the Waters high resolution mass spectrometer (CHE-0443618) used in this work. We also thank Dr. Paul Ralifo (Boston University) for NMR assistance and Dr. Jeff Bacon (Boston University) for X-ray crystallographic analysis.

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

OL101144K

(8) For select syntheses of isochromans *via* intramolecular Friedel−Crafts-type reactions see: (a) Martin, O. R. *Carbohydr. Res.* **1987**, *171*, 211. (b) Ahmer, M.; Bloch, R. *Synth. Commun.* **1992**, *22*, 1417. (c) Fearnly, S. P.; Tidwell, M. W. *Org. Lett.* **2002**, *4*, 3797. (d) Chandrasekhar, S.; Khatun, S.; Rajesh, G.; Reddy, R. *Tetrahedron Lett.* **2009**, *50*, 6693.

(9) For applications of lanthanide triflates to Friedel−Crafts reactions, see: (a) Walker, M. U.S. Patent 6,362,375, March 26, 2002. (b) Yoon, M. Y.; Kim, J. H.; Choi, D. S.; Shin, U. S.; Lee, J. Y.; Song, C. E. *Adv. Synth. Catal.* **2007**, *349*, 1725. (c) Dzuda, A.; Marks, T. J. *J. Org. Chem.* **2008**, *73*, 4004. (d) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, No. 6.

(10) (a) Hayashi, E.; Takahashi, Y.; Itoh, H.; Yoneda, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3520. (b) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.

(11) (a) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5664. (b) Kim, J. H.; Lee, J. W.; Shin, U. S.; Lee, J. Y.; Song, C. E. *Chem. Commun.* **2007**, *44*, 4683.

(12) (a) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653. (b) Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* **2004**, 825. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

(13) For select examples of Friedel−Crafts alkylation of allylic cations, see: (a) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364. (b) Mitchell, W. L.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2751. (c) Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 5308. (d) Huang, J.-W.; Shi, M. *Tetrahedron Lett.* **2003**, *44*, 9343. (e) Li, J.-H.; Liu, W.-J.; Yin, D.-L. *Synth. Commun.* **2004**, *34*, 3161. (f) Bandini, M.; Eichholzer, A.; Kotrusz, P.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2008**, *350*, 531. (g) Hu, B.; Xing, S.; Wang, Z. *Org. Lett.* **2008**, *10*, 5481.

(14) For a review of polyolefin cyclizations, see: Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.