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Diastereoselective Reductive Ring Expansion of Spiroketal Dihydropyranones to *cis*-Fused Bicyclic Ethers

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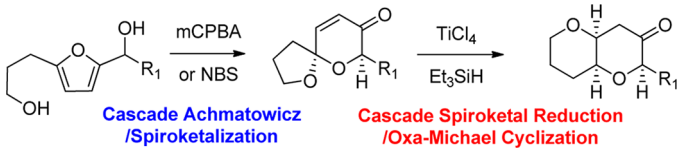
ABSTRACT



A novel double cascade synthetic strategy was developed for the diastereoselective syntheses of *cis*-fused bicyclic ethers, featuring cascade Achmatowicz rearrangement/spiroketalization and cascade spiroketal reduction/oxa-Michael cyclization. Especially, the chemo-, regio-, and diastereoselective reduction of densely functionalized spiroketal dihydropyranones, followed by oxa-Michael cyclization in a one-pot fashion, was achieved.

Achmatowicz Rearrangement (AR),[1] an oxidative rearrangement process of substituted furfuryl alcohol to pyranone acetals, has found wide application in organic synthesis,[2] particularly in the Targeted Oriented Synthesis (TOS) of natural products where the pyranone acetals derived from AR have been utilized as building blocks to construct substituted tetrahydropyrans, spiroketals, and Oxa-bridged bicycles (Scheme 1).[3] For example, DeShong[3b] et al. used the AR to build the 2,9-dioxabicyclononane core structure of tirandamycin A; Wender[3d] developed a strategy exploiting [5 + 2] cycloaddition[3a] of an AR adduct for the total synthesis of phorbol; and Nicolaou[3e] and Phillips[3f,g] employed AR to make highly functionalized tetrahydropyrans as the building blocks for maitotoxin and norhalichondrin B, respectively. Recently, Schreiber[4] et al. took advantage of the skeletal transformations of AR and developed a diversity-oriented synthesis (DOS) strategy to provide ~1260 more complex and diverse products. Nevertheless, the fundamental transformations based on AR adducts are still very limited[5] (Scheme 1): reductive etherification, cyclo- and/or spiroketalization, [5 + 2] cycloaddition, and a few others (glycosylation).[2] Apparently, the synthetic utilities of these densely functionalized dihydropyranones are underdeveloped, and some new reaction patterns should be further uncovered. In the course of our studies directed toward exploration of new reactivity patterns of AR adducts

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(2) For a review, see: (a) Harris, J. M.; Li, M.; Scott, J. G.; O'Doherty, G. A. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: 2004; Vol. 5, pp 221–253. For selected applications, see: (b) Al-Tel, T. H.; Semreen, M. H.; Voelter, W. *Org. Biomol. Chem.* **2010**, *8*, 5375. (c) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (d) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 3899. (e) Arrayas, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026. (f) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029. (g) Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591. (h) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (i) Herrmann, A. T.; Martinez, S. R.; Zakarian, A. *Org. Lett.* **2011**, *13*, 3636.

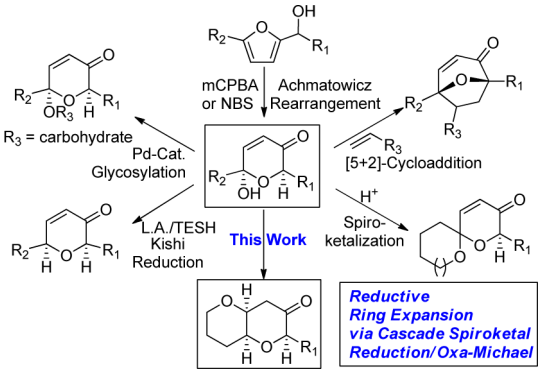
(3) For a review, see: (a) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189. For selected papers, see: (b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219. (c) Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873. (d) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (e) Nicolaou, K. C.; Baker, T. M.; Nakamura, T. *J. Am. Chem. Soc.* **2011**, *133*, 220. (f) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346. (g) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299.

(4) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095.

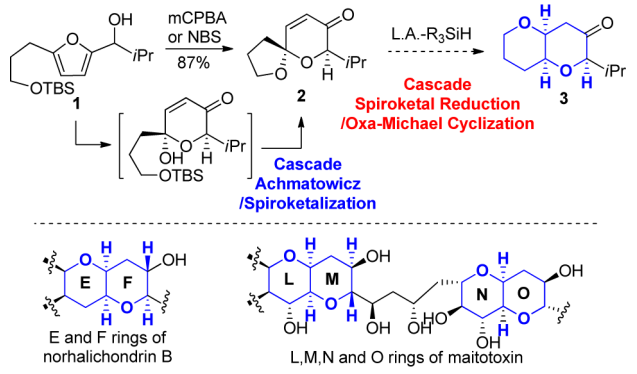
(5) Only 81 hits from Scifinder database for "Achmatowicz" keyword search (Sept, 2012).

10.1021/ol302813e

Scheme 1. Representative Transformations of Achmatowicz Rearrangement Adducts



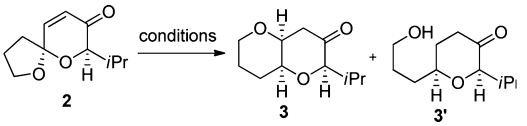
Scheme 2. Synthetic Plan for Exploration of Spiroketal Dihydropyranone



and potential applications in the total synthesis of natural products, we observed spontaneous spiroketalization of AR adducts tethered to *tert*-butyldimethylsilyl ether (TBSO, **1**) (Scheme 2). In order to make full use of these easily accessible, densely functionalized spiroketal dihydropyranones,[2b] we set forth to explore their reactivity and thus expand the syntheic utilities of AR adducts. Herein, we disclose our findings on an unprecedented reductive ring expansion of spiroketal dihydropyranone derived from AR, which involved cascade spiroketal reduction/oxa-Michael cyclization, leading to diastereoselective formation of *cis*-fused bicyclic ethers. Interestingly, the *cis*-fused bicyclic pyrans were thought to be an "abnormal" unit in maitotoxin[6] and halichondrins[7] (Scheme 2) and only a few synthetic methods have been exclusively developed.[8] The double cascade processes described here, therefore, would provide a concise route to diastereoselective synthesis of *cis*-fused cyclic ethers present in halichondrins and other (non-) natural products.

Our studies started with finding appropriate conditions for chemo-, regio- and diastereoselective reduction of spiroketal in the presence of enone. However, there is no precedence that documented this type of selective reduction. Given the facts that ketones or enones are readily reduced by conventional hydrides such as $LiAlH_4-AlCl_3$ or diisobutylaluminium hydride (DIBAL-H) that were used for spiroketal reduction,[8] we devoted our efforts on screening a variety of combinations of Lewis (or Brønsted) acids and silanes.[9] As shown in Table 1, Kishi reduction[10] (entries 1 and 3), a widely used reduction protocol for AR adducts to prepare the *cis*-disubstituted pyrans,[3e–g] unfortunately, gave only a trace amount of the desired product (**3**) after 48 h at rt. Amberlyst-15 and triethylsilane (TES) (entry 2) led sluggishly to saturation of the olefin. The TMSOTf-TES and $FeCl_3$-TES (entries 4 and 6) did not result in the ring opening at −78 °C while decomposition was observed at elevated temperatures. Interestingly,

Table 1. Lewis Acid–Silane Reduction of Spiroketal[a]



entry	Lewis acid (equiv)	silane (equiv)	temp (°C)	time (h)	conv (%)[a]	yield (**3**, %)[b]
1	TFA (10)	TES (5)	−78→25	72	100	0
2	A-15 (2)	TES (1.2)	25	48	40	<5
3	BF_3-Et_2O (1.2)	TES (1.2)	−78→25	48	20	<10
4	TMSOTf (1.2)	TES (1.2)	−78→25	24	10	<5
5	$Sc(OTf)_3$ (1.2)	TES (1.5)	−78→25	2	80	0
6	$FeCl_3$ (1.2)	TES (1.2)	−78→25	24	<5	0
7	$SnCl_4$ (1.2)	TES (1.2)	−78→25	1	100	27
8	$TiCl_4$ (1.2)	DPS (1.2)	−78	1	100	50
9[c]	**$TiCl_4$ (1.2)**	**TES (1.2)**	**−78**	**1**	**100**	**65**
10[d]	**$TiCl_4$ (1.2)**	**TES (2.5)**	**−78**	**1**	**100**	**35**

[a] Reaction progress was monitored by TLC. [b] Isolated yields. [c] 4 Å molecular sieves or 2,6-di-*tert*-butyl-4-methylpyridine was added, but did not improve the yield significantly. [d] The side products derived from conjugated reduction. TFA: trifluoroacetic acid. TMSOTf: trimethylsilyl trifluoromethanesulfonate. A-15: Amberlyst-15. TES: triethylsilane. DPS: diphenylsilane.

(6) (a) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (b) Sasaki, M.; Matsumori, N.; Muruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672. (c) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675.

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(8) (a) Fearnley, S. P.; Lory, P. *Org. Lett.* **2007**, *9*, 3507. (b) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263. (c) Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253. (d) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863. (e) Martin, V. S.; Palazon, J. M. *Tetrahedron Lett.* **1992**, *33*, 2399. (f) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. (g) Takemoto, Y.; Furuse, S.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T.; Ibuka, T. *Chem. Commun.* **1999**, 2515. (h) Sarang, P.; Bhalerao, P.; Mobin, S. M. *Synlett* **2011**, 386.

(9) (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089.

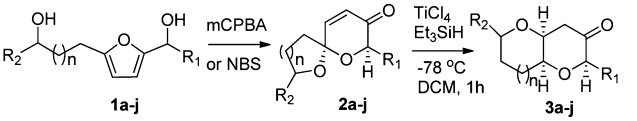
(10) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

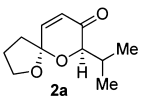
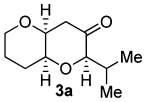
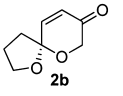
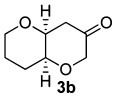
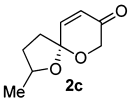
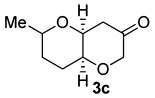
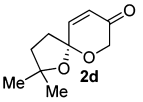
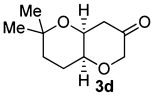
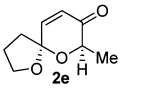
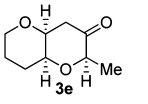
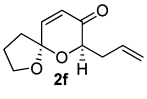
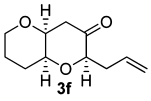
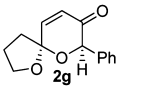
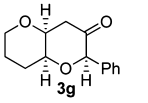
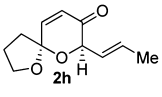
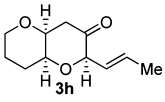
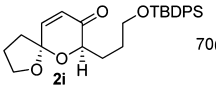
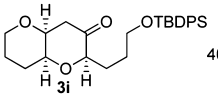
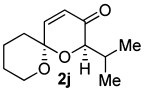
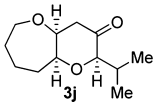
$Sc(OTf)_3$-TES (entry 5) cleanly promoted both reductive ring opening of the spiroketal and conjugated reduction, leading to only γ-hydroxytetrahydropyran-3-one (**3′**) in 70% yield. Fortunately, $SnCl_4$-TES was found for the first time to deliver the desired bicyclic ether product in 27% yield (entry 7), along with some side products due to saturation of olefin and/or reduction of the ketone. Further experimentation revealed that the reductive ring expansion proceeded smoothly with $TiCl_4$-TES to give the bicyclic ether as a single diastereomer in 65% yield (entry 9), through chemo-, regio-, and diastereoselective reduction of spiroketal dihydropyranone followed by oxa-Michael cyclization. Note that 2.5 equiv of triethylsilane with $TiCl_4$ (1.2 equiv) led to partial reduction of bicyclic ketone to the corresponding alcohol (entry 10).

Having identified the optimal conditions for the cascade reductive ring expansion of spiroketal dihydropyranone to *cis*-fused bicyclic ethers, we set out to examine the scope of substrates for both cascade processes: Achmatowicz/spiroketalization and spiroketal reduction/oxa-Michael cyclization (Table 2). A series of substituted furfuryl diols (**1a**−**j**) were prepared by following modified literature methods.[11] Pleasingly, the first stage cascade reactions, Achmatowicz/spiroketalization proceeded smoothly for almost all substrates to afford the spiroketal pyranones (**2a**−**2i**) in good to excellent yields (54−93%) with good diastereoselectivity due to anomeric effects. Notably, Achmatowicz adducts tethered to γ-secondary (R_2 = Me) or γ-tertiary (R_2 = Me_2) alcohols (entries 3 and 4) could also efficiently cyclize to form spiroketals. Although the [6,6] spiroketal dihydropyranone was not generated spontaneously during the AR, subjection of the crude AR adduct to Amberlyst-15 in CH_2Cl_2 gave the desired product **2j** with excellent yields (entry 10). Most importantly, we first demonstrated that the allyl, alkenyl, and phenyl substituted furfuryl alcohols (entries 6−8) are competent substrates for AR in good yields. For the second stage cascade reactions, reductive ring expansion proceeded smoothly with most substrates (even a diastereomeric mixture), except **2d**, to afford the corresponding bicyclic ethers in an exclusive *cis*-fused fashion in moderate to good yields (32%−65%). The relative stereochemistry of **3a** was established by nuclear Overhauser enhancement (NOE) experiments.[11] As shown in Table 2, the unsuccessful reductive ring expansion of **2d** (entry 4) suggested the bulky group at tetrahydrofuran could prevent the reduction of spiroketal, while the substituents on pyranone have less effects on the reductive ring expansion (entries 1 and 2). Noteworthy is that when R_1 was an allyl (entry 6), alkenyl (entry 8), or *tert*-butyldiphenylsilyl ether group (entry 9), reductive ring expansion produced bicyclic ethers with the functional groups at the positions (**3f**, **3h** and **3i**) that could be further elaborated for fusion of (an)other ring(s). It was also noted that the reductive ring-opening intermediate of [6,6]-spiroketal pyranone **2j** (entry 10) undergoes slow 7-*exo*-*trig* oxa-Michael cyclization, which could be accelerated by addition of Amberlyst-15 to provide **3j** in 35% combined yields.

Next, we were interested in the stereochemical outcomes and possible mechanisms of the reductive ring expansion. As outlined in Scheme 3, there are two possible pathways leading to bicyclic ethers but with different stereochemistry. If the Lewis acid coordinates with carbonyl (*path b*), ring expansion (**4b**→**5b**) might occur stereospecifically to generate an oxonium ion, followed by hydride reduction, to provide **3a′** with a 2,5-*anti* configuration. On the other

Table 2. Cascade Achmatowicz−Spiroketalization and Cascade Spiroketal Reduction-Oxa-Michael Cyclization

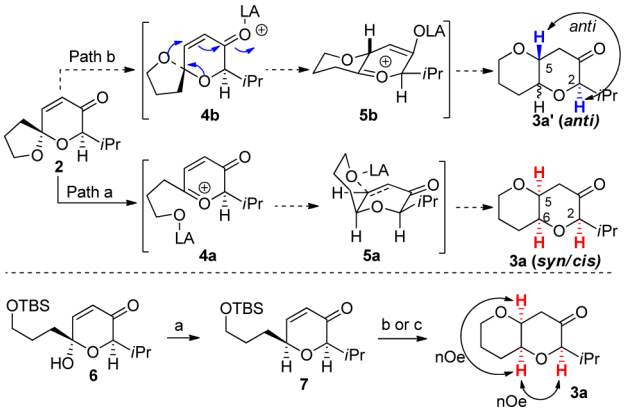


entry	spiroketal	yield (**2**, dr)[a,c]	bicyclic ether	yield (**3**, dr)[b,c]
1	 **2a**	87(7:1)	 **3a**	65 (1:0)
2	 **2b**	81	 **3b**	62 (1:0)
3	 **2c**	78(3:1)	 **3c**	53 (3:1)
4	 **2d**	92	 **3d**	0[d]
5	 **2e**	74(6:1)	 **3e**	54 (1:0)
6	 **2f**	93(5:1)	 **3f**	55 (1:0)
7	 **2g**	56(4.5:1)	 **3g**	59 (4:1)
8	 **2h**	54(6:1)	 **3h**	32 (10:1)
9	 **2i**	70(4:1)	 **3i**	40 (1:0)
10	 **2j**	84(15:1)	 **3j**	35 (1:0)

[a] Isolated yields of cascade Achmatowicz-spiroketalization. [b] Isolated yield of spiroketal reduction/oxa-Michael cyclization. [c] Diastereomeric ratio was determined by ^1H NMR of crude mixture. [d] Decomposition was observed. mCPBA: 3-chloroperbenzoic acid. NBS: *N*-bromosuccinimide.

(11) For details, see Supporting Information.

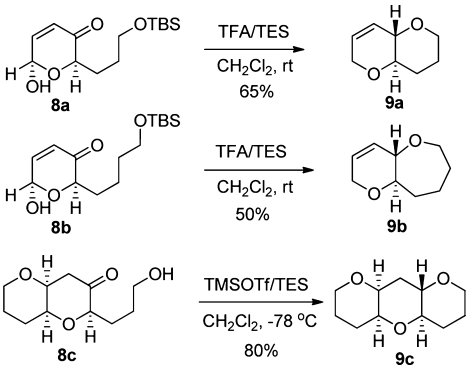
Scheme 3. Stereochemical Outcomes on Reductive Ring Expansion of Spiroketal Dihydropyranone[a]



[a] Conditions: (a) TFA (5 equiv), Et_3SiH (5 equiv), CH_2Cl_2, −40 °C, 90%; (b) TBAF (1.2 equiv), THF, rt, 81%; (c) Amberlyst-15, MeOH/CH_2Cl_2, rt, 83%. mCPBA: 3-chloroperbenzoic acid. NBS: *N*-bromosuccinimide.

hand, when reductive opening of spiroketals[12] (**2**→**4a**→**5a**) via oxonium **4a** takes place first to afford the enone tethered to an alkyl alcohol, intramolecular oxa-Michael cyclization[13] of **5a** would follow to give *cis*-fused bicyclic ether **3a** with a 2,5,6-*syn*-*cis* configuration (*path a*). The high 2,6-*syn* diastereoselectivity of reduction in *path a* has been well established due to the conformation in which *i*Pr sits at the equatorial position and the planar oxacarbenium was attacked by hydride from the axial position.[14] In view of the all *syn* stereochemical outcomes obtained in Table 2, we proposed the reductive ring expansion operates via cascade spiroketal reduction/oxa-Michael cyclization (*path a*). In fact, a diastereomeric mixture of spiroketal pyranones (cf. **2a** and **2e**) may be employed for the reductive ring expansion and a single diastereomer product (**3a** and **3e**, respectively) could be obtained. To further support this mechanistic speculation, we performed a careful Kishi reduction of dihydropyranone acetal **6** to produce intermediate pyranone **7** (**5a** in *path a*), which was subjected to intramolecular oxa-Michael cyclization under both acidic and basic conditions. Remarkably, both Amberlyst-15 in CH_2Cl_2/MeOH and TBAF in THF efficiently promoted the cascade desilylation/oxa-Michael cyclization to give the single diastereomer **3a** with the exclusive *syn-cis* configuration.

Scheme 4. Kishi Reductive Cyclization of Dihydropyranones Acetal and Hydroxy Ketone[a]



[a] Isolated yield.

In order to utilize the ketone functional group that resulted from the AR, Kishi reduction was carried out for simple substrate **8a** (Scheme 4). To our delight, *trans*-fused [6,6]-bicyclic ether **9a** was obtained as the only major product in 65% yield. This comprises the first double Kishi reduction for Achmatowicz adducts with simultaneous removal of the silyl group. Analogously, [6,7]-bicyclic ether **9b** was achieved in 50% yield. Remarkably, the bicyclic ketone **8c** obtained from our double cascades could be efficiently transformed into the desired [6,6,6]-tricyclic ether **9c** in 80% yield with a *cis-anti-trans* configuration.[11]

In summary, we have developed a novel double cascade synthetic strategy for the diastereoselective syntheses of *cis*-fused bicyclic ethers through Achmatowicz/spiroketalization and spiroketal reduction/oxa-Michael cyclization. Significantly, we have achieved the chemo-, regio-, and diastereoselective reduction of the highly functionalized spiroketal dihydropyranone and subsequent oxa-Michael cyclization, which expands the current fundamental transformations of Achmatowicz adducts. Further exploration of Achmatowicz rearrangement adducts for natural product synthesis is ongoing in our laboratory.

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Supporting Information Available. Detailed experiments and ^1H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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