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Enantioselective Synthesis of 2,2,5-Tri- and 2,2,5,5-Tetrasubstituted Tetrahydrofurans *via* [4 + 2] Cycloaddition and Ring-Opening Cross-Metathesis

Noah M. Benjamin and Stephen F. Martin*

Department of Chemistry & Biochemistry, The University of Texas at Austin, Austin, Texas 78712, United States

sfmartin@mail.utexas.edu

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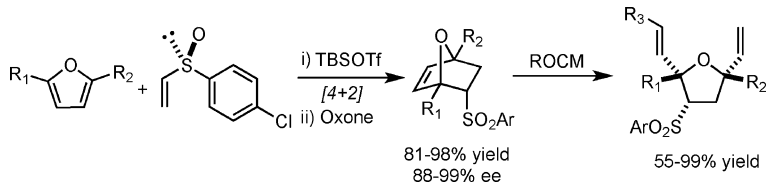
ABSTRACT



A chiral vinyl sulfoxide has been developed that undergoes highly diastereoselective Diels−Alder cycloadditions with various substituted furans in excellent yield. The cycloadducts can be stereoselectively transformed into 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans, which are structural subunits of many natural products, *via* regioselective ring-opening metathesis/cross-metathesis or oxidative cleavage/refunctionalization.

The 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofuran substructure **1** is a common motif found in a number of biologically active natural products such as cortistatin A,[1] (+)-davanone,[2] and caruifolin A[3] (Figure 1). In the context of several ongoing projects, we were confronted with the challenge of the enantioselective synthesis of substructures related to **1** (Z = H). A survey of the literature[4] revealed that available methodology for such constructions is limited largely to cyclizations of unsaturated or epoxy alcohols, and more general entries to these important substructures are lacking.

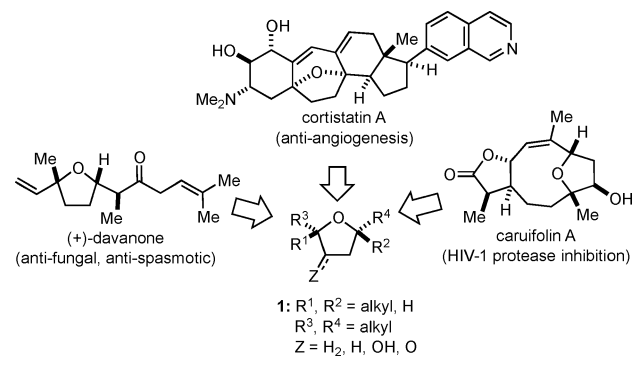


Figure 1. Natural products related to **1**.

(1) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.
(2) Sipma, G.; Van der Wal, B. *Recl. Trav. Chim. Pays-Bas.* **1968**, *87*, 715–720.
(3) Ma, C.; Nakamura, N.; Hattori, M.; Zhu, S.; Komatsu, K. *J. Nat. Prod.* **2000**, *63*, 1626–1629.
(4) (a) Figadere, B.; Harmange, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754. (b) Hay, M. B.; Wolfe, J. P. *Tetrahedron* **2007**, *63*, 261–290. (c) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866. (d) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2538–2541. (e) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1268–1271. (f) Marshall, J. A.; Griot, C. A.; Chobanian, H. R.; Myers, W. H. *Org. Lett.* **2010**, *12*, 4328–4331.

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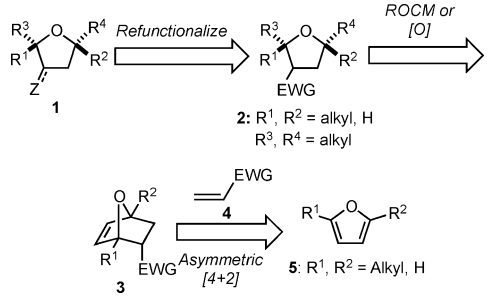
Various enantioselective [4 + 3][5] and [4 + 2][6,7] cycloadditions involving furan itself to give bridged bicyclic adducts are known, but the application of such tactics for elaboration to 2- and 2,5-substituted furans is not well established. Moreover, tactics for elaborating the products of these cycloadditions into monocyclic, substituted tetrahydrofurans are not well developed.[8,9] In view of the current state of the art, we recognized the significant opportunity to develop an efficacious entry to highly substituted tetrahydrofurans related to **1**, and we now report the results of some of our findings.

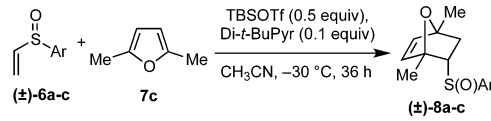
Based upon a survey of the literature, we reasoned that processing enantiomerically pure oxabicycloheptenes **3** *via* regioselective ring-opening cross-metathesis (ROCM) or oxidative cleavage would lead to tetrahydrofurans **2**;[8,9] removal or refunctionalization of the electron-withdrawing group (EWG) in **2** would then deliver the desired tetrahydrofurans **1** (Scheme 1). Access to enantiomerically pure **3** would require

Scheme 1. Retrosynthetic Analysis of **1**



the development of a highly enantioselective or diastereoselective Diels−Alder reaction of substituted furans **5** with a dienophile **4** wherein the EWG could be easily transformed into a hydrogen atom or an oxygen function. Namely, we required that **4** serve as an ethylene, vinyl alcohol, or ketene equivalent. We were thus attracted to the use of sulfoxides as the preferred activating groups because this moiety can be more readily removed and/or refunctionalized than carboxylic acid derivatives.[10] *p*-Tolyl vinyl sulfoxide (**6a**) was known to undergo [4 + 2] cycloaddition with furan, but not substituted furans, in the presence of a Lewis acid promoter in good yield and de,[7] so we initiated our studies by examining the reaction of **6a** with 2,5-dimethylfuran (**7c**). After screening a series of Lewis acids, we found TBSOTf to be the optimal promoter for this cycloaddition giving oxabicycle **8a** in 68% yield (Table 1). In an effort to improve

Table 1. Development of Dienophile **6c**



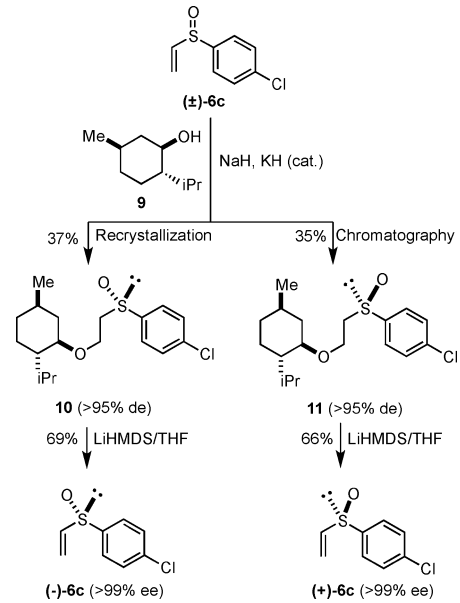
entry	Ar	isolated yield (%)[a]
a	Tolyl	68
b	Phenyl	81
c	4-Chlorophenyl	94

[a] All cycloadditions proceeded with greater than >20:1 endo/exo selectivity.

the yield in this reaction, we explored other aryl vinyl sulfoxides as dienophiles and discovered that cycloadditions of **7c** with phenyl vinyl sulfoxide (**6b**) and *p*-chlorophenyl vinyl sulfoxide (**6c**) proceeded to give **8b** and **8c** in 81% and 94% yields, respectively.

Having established that **6c** was the preferred dienophile, it was necessary to develop an efficient means to prepare both enantiomers in pure form. Fortunately, we were able to adapt a procedure that had been developed by Maignan for the preparation of both enantiomers of **6a**[11] (Scheme 2).

Scheme 2. Enantioselective Synthesis of (+)-**6c** and (−)-**6c**



(5) (a) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353–3356. (b) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694–1295. (c) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059. (d) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50–51. (e) Harmata, M.; Brackley, J. A.; Barnes, C. L. *Tetrahedron Lett.* **2006**, *47*, 8151–8155. (f) Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573–576. (g) Xu, J.; Caro-Diaz, E. J. E.; Theodorakis, E. A. *Org. Lett.* **2010**, *12*, 3708–3711.

(6) (a) Fraile, J. M.; Garcia, J. I.; Gracia, D.; Mayoral, J. A.; Pires, E. *J. Org. Chem.* **1996**, *61*, 9479–9482. (b) Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079–4082. (c) Ryu, D. H.; Kim, K. H.; Sim, J. Y.; Corey, E. J. *Tetrahedron Lett.* **2007**, *48*, 5735–5737.

(7) Ronan, B.; Kagan, H. B. *Tetrahedron: Asymmetry* **1991**, *2*, 75–90.

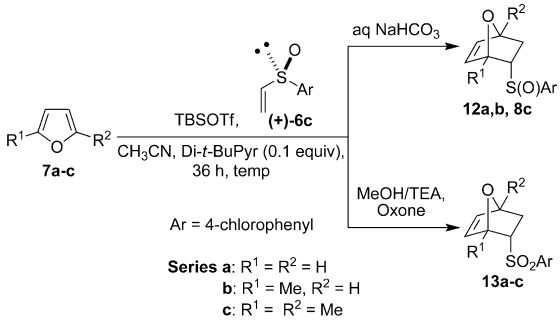
(8) For examples, see: (a) Ager, D. J.; East, M. B. *J. Chem. Res. Synop.* **1986**, 4622–463. (b) Klein, L. L.; Shanklin, M. S. *J. Org. Chem.* **1988**, *53*, 5202–5209.

(9) (a) Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 9739–9741. (b) Usher, L. C.; Estrella-Jimenez, M.; Ghiviriga, I.; Wright, D. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4560–4562. (c) Arjona, O.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611–622. (d) Rainier, J. D.; Liu, Z. *Org. Lett.* **2005**, *7*, 131–133. (e) Ikoma, M.; Oikawa, M.; Gill, M. B.; Swanson, G. T.; Sakai, R.; Shimamoto, K.; Sasaki, M. *Eur. J. Org. Chem.* **2008**, 5215–5220.

In the event, racemic **6c** underwent base-induced, conjugate addition of (−)-menthol (**9**) giving the easily separable diastereomers **10** and **11**; the structure of **10** was determined by X-ray crystallographic analysis. Elimination of mentholate ion was then promoted using LiHMDS, giving both **(−)-6c** and **(+)-6c** in >99% *ee* and good yield. Unlike a previous report of a similar reaction,[11] our procedure does not rely upon methylation of the intermediate alkoxide, thereby allowing facile recovery of menthol in about 90% yield.

We then examined the diastereoselectivities of the cycloadditions of enantiopure **(+)-6c** with furans **7a−c** in the presence of TBSOTf, and the results of the optimized reactions are collected in Table 2. Two workup procedures

Table 2. Diels−Alder Cycloaddition with Substituted Furans



furan	product	L.A. equiv	furan equiv	temp (°C)	yield (%)	endo/exo[a]	endo de/ee (%)[b]
7a	**12a**	1	5	0	98	1.8/1	90
7a	**13a**	1	5	0	98	-	88
7b	**12b**	0.75	2	–30	89[c]	25/1	99
7b	**13b**	0.75	2	–30	81[c]	-	99
7c	**8c**	0.50	2	–30	94	25/1	98
7c	**13c**	0.50	2	–30	88	-	98

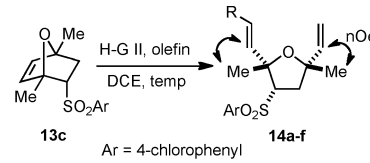
[a] Determined by NMR. [b] Determined by chiral HPLC. [c] Cycloaddition proceeded with complete regioselectivity and with the methyl substituent proximal to the sulfoxide/sulfone.

were developed that enabled the direct and facile synthesis of either sulfinyl substituted cycloadducts **12a−c** or sulfonyl substituted adducts **13a−c**.

The ability to access both cycloadducts with equal ease enhances the versatility of the method. It is noteworthy that the yield and diastereoselectivity observed for the reaction of **(+)-6c** with furan (**7a**) compare favorably with the report of Kagan for the reaction of **7a** with (−)-tolyl vinyl sulfoxide. The stereoselectivity of the cycloaddition improves significantly when the substituted furans **7b,c** are employed as dienes. The structures of **12a**, **12b**, and **13c** were established by X-ray crystallography.

Having developed the highly stereoselective cycloadditions of various furans with the chiral vinyl sulfoxide **6c**, it was then necessary to identify ring-opening transformations that would provide 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans related to **1**. Toward this end, we were attracted to the possibility that regioselective, ring-opening/cross-metathesis (ROCM) of the oxabicyclic systems **13a−c** might lead to 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans of the general form **1**. This premise was founded on the knowledge that regioselective ROCM reactions had been applied to unsymmetrically substituted norbornene derivatives bearing electron-withdrawing groups.[9,12] Consistent with our expectations, reaction of enantiomerically pure **13c** with excess allyltrimethylsilane in the presence of Hoveyda−Grubbs second generation catalyst[13] led to a completely regioselective ROCM reaction to furnish **14a** as the only observable product in 94% yield (Table 3). In order to expand the scope

Table 3. Ring-Opening/Cross-Metathesis of **13c**



entry	R[a,b]	cat. loading (mol %)	temp (°C)	product	yield (%)
a	TMS	2.5	25	**14a**	94
b	Ph	5	25	**14b**	93
c	Ph	5	0	**14c**	89
d	$(OAc)_2$	10	25	**14d**	55[c]
e	nBu	2.5	25	**14e**	82
f		5	25	**14f**	78

[a] 6−10 equiv of olefin. [b] Reaction performed with enantiomerically pure **13c** for entry a and racemic **13c** for entries b−f. [c] Reaction only proceeds under an atmosphere of ethylene.

of this ROCM, a number of monosubstituted alkenes were allowed to react with racemic **13c** to give racemic **14b−f** as the only observed products in yields ranging from 55% to 93%. The structure of **14a** was determined by X-ray analysis, whereas those of **14b−f** were assigned by a characteristic NOE signal between the vinylic protons and the proximal methyl substituents. Although several of these ROCM reactions proceeded with identical regioselectivity using the sulfoxide **8c**, >10% catalyst loadings were required, and the yields were generally ∼30% lower.

We then queried whether regioselective ROCM reactions could be applied to **13b**. Reaction of enantiomerically pure **13b** with allyltrimethylsilane in the presence of Hoveyda−Grubbs second generation catalyst at 70 °C proceeded regioselectively to give a mixture (12:1) of **15a** and **16a** in 76% yield (Table 4). Interestingly, when the reaction was performed

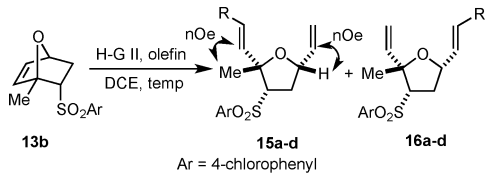
(10) (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019–2045. (b) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749–1750. (c) Becker, S.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1990**, *55*, 6194–6198. (d) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547–10658. (e) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831–834.

(11) Alexandre, C.; Guillot, C.; Hayes, P.; Maignan, C. *Tetrahedron Lett.* **1998**, *39*, 5769–5770.

(12) (a) Carreras, J.; Avenoza, A.; Busto, J. H.; Peregrina, J. M. *J. Org. Chem.* **2009**, *74*, 1736–1739. (b) Weeresakare, G. M.; Liu, Z.; Rainier, J. D. *Org. Lett.* **2004**, *6*, 1625–1627.

(13) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

Table 4. Ring-Opening/Cross-Metathesis of **13b**



entry	R[a,b]	cat. loading (mol %)	temp (°C)	yield (%)	15:16
a	TMS	1	70	76	12:1
b	CO_2Me	5	70	67[c]	0:1
c	Ac	1	84	59	1:0
d		2.5	25	99	-

[a] 6−10 equiv olefin. [b] Reaction performed with enantiomerically pure **13c** for entry a and racemic **13c** for entries b−d. [c] Reaction was run in neat methyl acylate in a sealed tube.

at room temperature, the selectivity eroded, and a mixture (3:1) of **15a** and **16a** was isolated. Several other olefins also engaged in efficient ROCM with **13b**, but the reaction with methyl acrylate proceeded in the opposite regiochemical sense. The origin of this difference is not clear, but the reversal of regiochemical preference in ROCM reactions based on the electronics of the metathesis cross-partner has been observed previously.[12] When **13a** was used as a substrate in these ROCM reactions, only mixtures were obtained.

Oxidative cleavage was then explored as a tactic to convert oxabicyclo[2.2.1]heptenes into substituted tetrahydrofurans. For example, we found that ozonolysis of **13c** in the presence of lutidine at −78 °C in acetone/H_2O (9:1),[14,15] followed by reduction of the crude product with excess sodium borohydride, furnished the diol **17** in 84% yield (Scheme 3). Alternatively, reaction of the intermediate obtained from ozonolysis with the Ohira−Bestmann reagent gave the diyne **18** in 53% yield as a mixture (4:1) of epimeric sulfones.[16]

In order to access substituted tetrahydrofurans of the general type **1**, it remained to establish a suitable protocol for removing the sulfonyl group. Although there are methods for converting sulfones into ketones by oxidative desulfonylation to give tetrahydrofurans related to **1** (Z = O, OH),[10d] we were primarily interested in targeting substituted tetrahydrofurans of the general type **1** (Z = H).

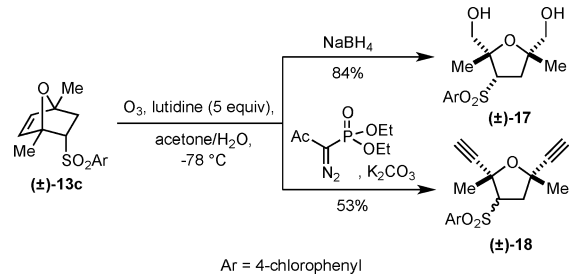
Accordingly, we found after extensive experimentation that the sulfonyl group in **14a** could be selectively removed

(14) The presence of tertiary amines is known to improve the yield of certain ozonolysis reactions. See: Smith, A. B.; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438–1449.

(15) Ozonolysis in the presence of water leads directly to aldehydes. See: Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688–4690.

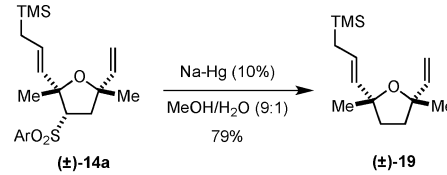
(16) Roth, G. J.; Liepold, B.; Muller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.

Scheme 3. Oxidative Cleavage Methods



without concomitant carbon−oxygen bond cleavage by the action of Na−Hg amalgam in aqueous methanol to deliver **19** in 79% yield (Scheme 4).

Scheme 4. Desulfurization of **14a**



In summary, we have developed the chiral vinyl sulfoxide **6c**, both enantiomers of which are readily available, that undergoes highly diastereoselective [4 + 2] cycloadditions with several substituted furans. These represent the first examples of the use of substituted furans in enantioselective [4 + 2] cycloadditions with vinyl sulfoxides. The cycloadducts obtained from the reaction of **6c** with furans may be further processed *via* several different refunctionalization manifolds to give facile access to 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans that comprise structural subunits in a broad array of biologically active natural products. We are also exploring other applications of **6c** as a chiral dienophile in other Diels−Alder reactions.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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