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Biosynthesis-Inspired Intramolecular Oxa-Conjugate Cyclization of α,β-Unsaturated Thioesters: Stereoselective Synthesis of 2,6-*cis*-Substituted Tetrahydropyrans

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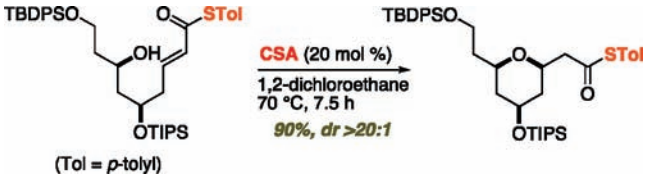
ABSTRACT



Intramolecular oxa-conjugate cyclization of α,β-unsaturated thioesters under Brønsted acid catalysis, inspired by biosynthesis of polyketide natural products, provides a variety of 2,6-*cis*-substituted tetrahydropyran derivatives with excellent diastereoselectivities. An added bonus of this methodology is that the product tetrahydropyrans could be readily elaborated to various derivatives by exploiting the unique reactivity of the thioester group.

Tetrahydropyrans are an important structural motif that can be widely found in a plethora of naturally occurring substances and as such represent valuable scaffolds for the design and synthesis of biologically active small molecules.[1] Accordingly, numerous methodologies have been developed for the synthesis of tetrahydropyran derivatives. Intramolecular oxa-conjugate cyclization (IOCC), often referred to as oxa-Michael cyclization, of α,β-unsaturated esters stands as one of the renowned methodologies for tetrahydropyran synthesis, and the products of this reaction have served as important intermediates in the total synthesis of complex natural products.[2,3] In general, the stereoselectivity of base-catalyzed IOCC of α,β-unsaturated esters depends on the reaction conditions.[4,5] It is known that the reaction provides 2,6-*trans*-substituted tetrahydropyrans under kinetic control, while 2,6-*cis*-substituted tetrahydropyrans are formed only when 2,6-*trans* and 2,6-*cis* isomers are in thermodynamic equilibrium.[6] Unfortunately, despite the fact that the majority of tetrahydropyran-containing natural products have 2,6-*cis* stereochemistry, the reaction sometimes results in poor diastereoselectivity under thermodynamic conditions.[7] It has

(1) For recent reviews on the synthesis of tetrahydropyrans, see: (a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

(2) For a recent review on oxa-conjugate addition, see: Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218.

(3) Our group has reported the total synthesis of tetrahydropyran-containing natural products relying on IOCC. See: (a) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3041. (b) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Tetrahedron* **2010**, *66*, 7492. (c) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1848. (d) Fuwa, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 584. (e) Fuwa, H.; Noto, K.; Sasaki, M. *Heterocycles* **2010**, *82*, 641.

(4) (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570. (b) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584.

(5) Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73.

(6) In some special cases, the stereoselectivity would depend on the local structure of substrates. For example, IOCC of α,β-unsaturated esters having a pro-axial δ-substituent favors 2,6-*cis*-substituted tetrahydropyrans under kinetic control; see: (a) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173. (b) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641. (c) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983.

(7) For recent examples, see: (a) Wang, B.; Hansen, T. M.; Wang, T.; Wu, D.; Weyer, L.; Ying, L.; Engler, M. M.; Sanville, M.; Leitheiser, C.; Christmann, M.; Lu, Y.; Chen, J.; Zunker, N.; Cink, R. D.; Ahmed, F.; Lee, C.-S.; Forsyth, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1484. (b) Bates, R. W.; Song, P. *Synthesis* **2010**, 2935. (c) Uenishi, J.; Iwamoto, T.; Tanaka, J. *Org. Lett.* **2009**, *11*, 3262. (d) Ferrié, L.; Boulard, L.; Pradaux, F.; BouzBouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864.

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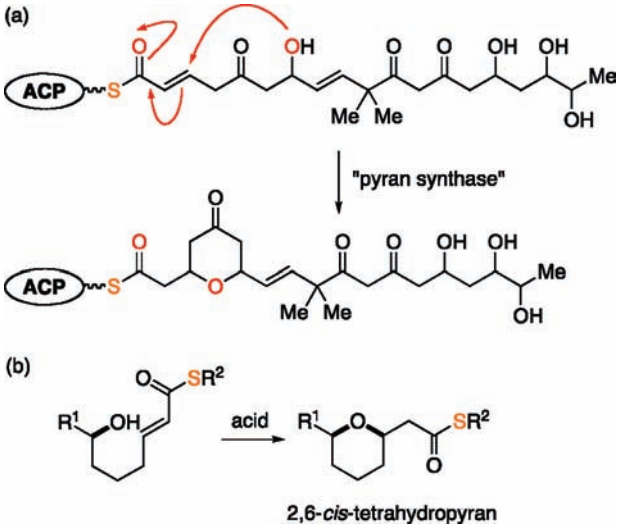
also been reported that strongly basic, harsh conditions and/or prolonged reaction times are in some cases necessary for the selective formation of 2,6-*cis*-substituted tetrahydropyrans.[3a−c,8] On the other hand, acid-catalyzed IOCC of α,β-unsaturated esters normally does not take place presumably because of the low nucleophilicity of alcohols and the low reactivity of α,β-unsaturated esters as conjugate acceptors.[6b,9,10]

Recent biosynthetic studies have postulated that the tetrahydropyrans of several polyketide natural products would be formed via IOCC catalyzed by pyran synthase (PS).[11] As illustrated in Scheme 1a, the reaction is thought to

Scheme 1. (a) Postulated Biosynthesis of Tetrahydropyrans of Polyketide Natural Products and (b) Biomimetic Methodology for Synthesis of 2,6-*cis*-Substituted Tetrahydropyrans

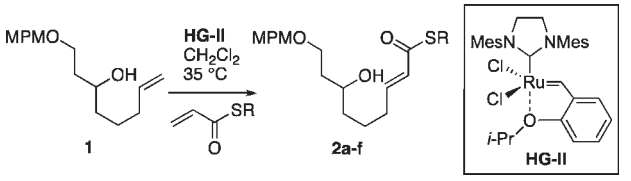


occur during their polyketide biosynthesis; an α,β-unsaturated thioester bound to an acyl carrier protein (ACP) would be activated by a PS probably through hydrogen bonding(s) and serve as an acceptor for the proximal hydroxy group. We thought that the feasibility of the biosynthetic formation of tetrahydropyrans would partly stem from the enhanced reactivity of α,β-unsaturated thioesters when compared with the corresponding oxoesters.[12]

Inspired by the biosynthetic origin of tetrahydropyrans, we envisioned that IOCC of α,β-unsaturated thioesters based on carbonyl activation under acid catalysis would represent a biomimetic methodology for the synthesis of 2,6-*cis*-substituted tetrahydropyran derivatives (Scheme 1b). We thought that this reaction would favor the formation of synthetically useful 2,6-*cis*-substituted tetrahydropyrans because its diastereoselectivity would depend on a late transition model (vide infra). In addition, we expected that the products of this reaction could be readily transformed into a series of derivatives by exploiting the unique reactivity of thioesters.

To test the viability of our idea, we first prepared a variety of α,β-unsaturated thioesters **2a**−**f** by exploiting the olefin cross-metathesis reaction[13,14] (Table 1). Treatment

Table 1. Preparation of α,β-Unsaturated Thioesters



entry	R	yield/%
1	Et	**2a**: 93
2	Ph	**2b**: 94
3	*p*-MeC_6H_4	**2c**: 92
4	*p*-$MeOC_6H_4$	**2d**: 82
5	*p*-$NO_2C_6H_4$	**2e**: 94
6	1-naphthyl	**2f**: 87

of hydroxy olefin **1** with an appropriate thioacrylate in the presence of the Hoveyda−Grubbs second-generation catalyst (**HG-II**)[15] in CH_2Cl_2 at 35 °C provided **2a**−**f** in high yields. A brief investigation on the cyclization promoter indicated that Brønsted acids, such as CSA, *p*-TsOH•H_2O, TFA, and CH_3SO_3H, were able to catalyze the cyclization, while Lewis acids (e.g., $MgBr_2$•OEt_2, $InCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$) were uniformly ineffective (no reaction or decomposition of the material).[16] To probe the reactivity of thioesters, **2a**−**f** were individually exposed

(8) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730.

(9) In contrast, IOCC of α,β-unsaturated ketones proceeds under acidic conditions due to their high reactivity. For examples, see: (a) Reddy, C. R.; Rao, N. N. *Tetrahedron Lett.* **2010**, *51*, 5840. (b) Bates, R. W.; Song, P. *Tetrahedron* **2007**, *63*, 4497. (c) Liu, J.; Yang, J. H.; Ko, C.; Hsung, R. P. *Tetrahedron Lett.* **2006**, *47*, 6121. (d) Chandrasekhar, S.; Prakash, S. J.; Shyamsunder, T. *Tetrahedron Lett.* **2005**, *46*, 6651. See also ref 7b.

(10) A single example of acid-catalyzed IOCC of an α,β-unsaturated ester, presumably promoted by the *gem*-dimethyl substitution effect, has recently been reported. See: Hajare, A. K.; Ravikumar, V.; Khaleel, S.; Bhuniya, D.; Reddy, D. S. *J. Org. Chem.* **2011**, *76*, 963.

(11) (a) Irschik, H.; Kopp, M.; Weissman, K. J.; Buntin, K.; Piel, J.; Müller, R. *ChemBioChem* **2010**, *11*, 1840. (b) Sudek, S.; Lopanik, N. B.; Waggoner, L. E.; Hildebrand, M.; Anderson, C.; Liu, H.; Patel, A.; Sherman, D. H.; Haygood, M. G. *J. Nat. Prod.* **2007**, *70*, 67. (c) Julien, B.; Tian, Z.-Q.; Reid, R.; Reeves, C. D. *Chem. Biol.* **2006**, *13*, 1277. (d) Piel, J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14002.

(12) There are only limited reports that describe the use of α,β-unsaturated thioesters as conjugate acceptors. See: (a) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798. (b) Mazery, R. D.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753. (d) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (e) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687. (f) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

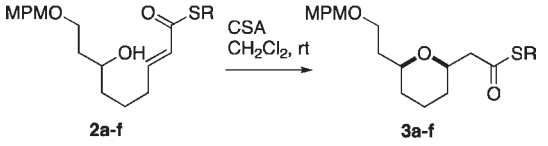
(13) For a review on the olefin cross-metathesis reaction, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(14) Van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 5651.

(15) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(16) Spencer et al. have reported that hetero-Michael reactions are actually catalyzed by protons. See: Wabnitz, T. C.; Yu, J,-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484.

Table 2. Brønsted Acid Catalyzed Cyclization of α,β-Unsaturated Thioesters[a]



2a-f **3a-f**

entry	2	R	time/h	yield/% (rsm)	*cis*/*trans*[b]
1[c]	**2a**	Et	21	**3a**: 43 (26)	15:1
2	**2b**	Ph	40	**3b**: 56 (41)	>20:1
3	**2c**	*p*-MeC_6H_4	40	**3c**: 72 (12)	>20:1
4	**2d**	*p*-$MeOC_6H_4$	44	**3d**: 69 (16)	>20:1
5	**2e**	*p*-$NO_2C_6H_4$	45	**3e**: 29 (65)	>20:1
6	**2f**	1-naphthyl	73	**3f**: 56 (35)	>20:1

[a] All reactions were performed using 20 mol % of CSA in CH_2Cl_2 at room temperature unless otherwise noted and quenched when cleavage of the MPM group was observed by TLC analysis. [b] The ratio of 2,6-*cis* and 2,6-*trans* isomers was estimated by 600 MHz ^{1}H NMR analysis. [c] The reaction was performed using 70 mol % of CSA.

to CSA in CH_2Cl_2 at room temperature to deliver the 2,6-*cis*-substituted tetrahydropyrans **3a**−**f**, respectively, in moderate to good yields (Table 2). Since **2c** showed the highest reactivity among others in these preliminary experiments (entry 3), further investigations were carried out using *S*-(*p*-tolyl) thioesters as the substrate.

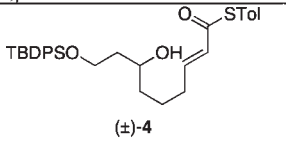
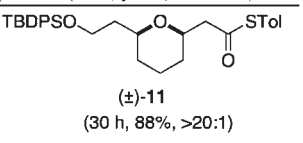
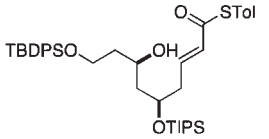
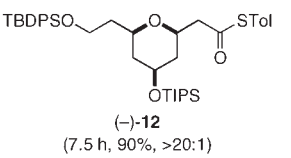
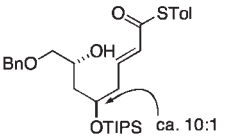
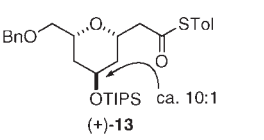
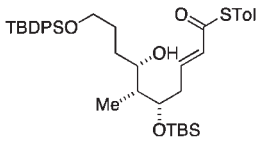
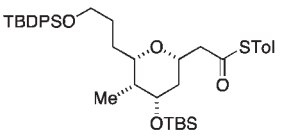
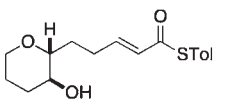
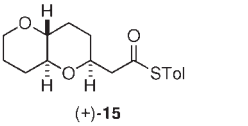
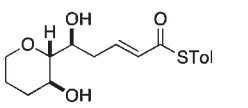
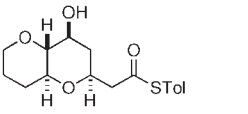
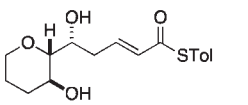
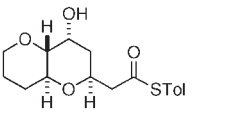
To probe the scope of the reaction, we next examined a series of α,β-unsaturated thioesters **4**−**10** (Table 3). Although the cyclization of **4** only proceeded slowly at room temperature, the reaction was complete in a reasonable time simply by running the reaction in 1,2-dichloroethane (DCE) at 70 °C, giving **11** in 88% yield as a single stereoisomer. In a similar manner, thioesters **5**−**10** were treated with 20 mol % of CSA (DCE, 70 °C) to afford the 2,6-*cis*-substituted tetrahydropyrans **12**−**17**, respectively, in excellent yields with high diastereoselectivity.[17] Interestingly, we found that δ-substituted α,β-unsaturated thioesters (i.e., **5**, **6**, **7**, **9**, and **10**) cyclized more rapidly than unsubstituted ones (i.e., **4** and **8**). For each product, the 2,6-*cis* stereochemistry was confirmed by NOE experiment(s) and/or $^3J_{H,H}$ values.[18]

The observed stereoselectivity of the Brønsted acid catalyzed IOCC of α,β-unsaturated thioesters can be explained by considering a late transition state model, wherein unfavorable steric interactions between substituents are avoided as much as possible (Scheme 2). The possibility that the preferential formation of 2,6-*cis* isomers is due to thermodynamic equilibration was ruled out because isomerization of *trans*-**14** to the thermodynamically more stable *cis*-**14** was not observed under the cyclization conditions (CSA, DCE, 70 °C, 6 h).

(17) Here, we confirmed that treatment of the corresponding oxoester of **5** with CSA resulted only in decomposition of the material. This clearly demonstrates that thioesters are more reactive toward the conjugate addition of oxygen nucleophiles than the corresponding oxoesters.

(18) See the Supporting Information for details.

Table 3. Application to Various Substrates (Tol = *p*-tolyl)[a]

α,β-unsaturated thioester	product (time, yield, *cis*/*trans*)
 (±)-**4**	 (±)-**11** (30 h, 88%, >20:1)
 (−)-**5**	 (−)-**12** (7.5 h, 90%, >20:1)
 (−)-**6**	 (+)-**13** (6 h, 96%, >20:1)
 (+)-**7**	 (−)-*cis*-**14** (4.5 h, 92%, 14:1)
 (+)-**8**	 (+)-**15** (23 h, 92%, >20:1)
 (+)-**9**	 (+)-**16** (10.5 h, 91%, >20:1)
 (−)-**10**	 (+)-**17** (10 h, 97%, >20:1)

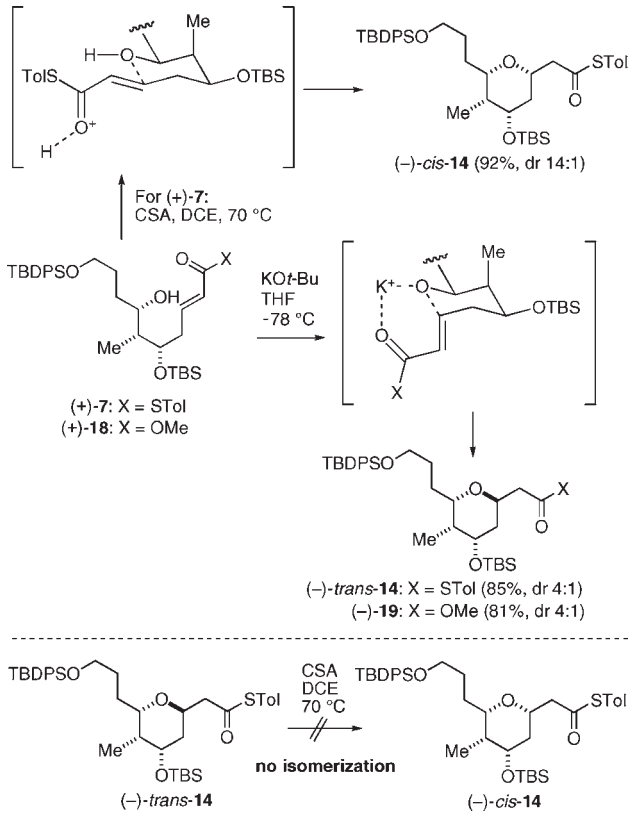
[a] All reactions were performed using 20 mol % of CSA in DCE at 70 °C. [b] The ratio of 2,6-*cis* and 2,6-*trans* isomers was determined by 600 MHz ^{1}H NMR analysis.

On the other hand, IOCC of **7** under basic conditions (KO*t*-Bu, THF, −78 °C) gave the cyclization product as a 4:1 mixture of diastereomers favoring *trans*-**14** (Scheme 2). The diastereoselectivity of the cyclization was exactly the same as that of the corresponding oxoester **18**. The preferential formation of 2,6-*trans* isomers under these conditions could be reasoned by the chelation-controlled model.[4]

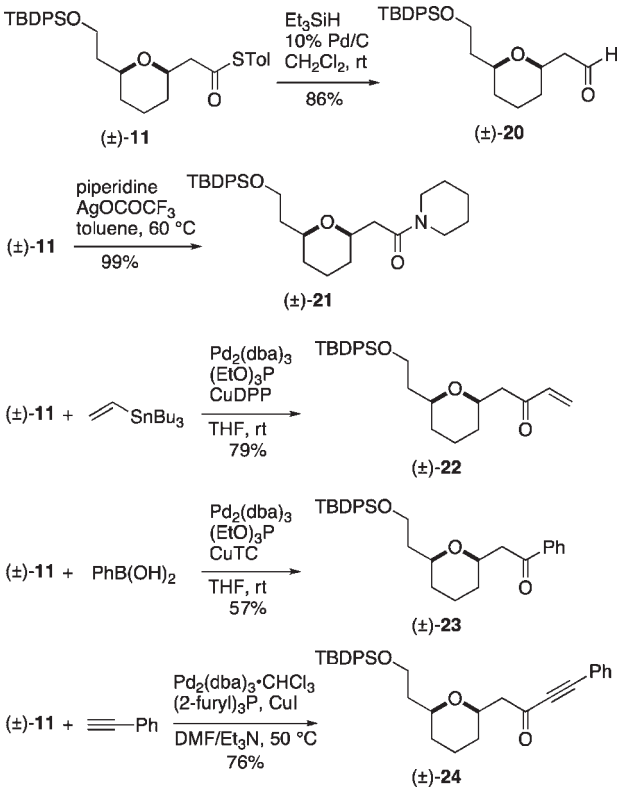
Finally, we examined derivatization of the tetrahydropyran **11** as summarized in Scheme 3. Reduction of **11** under the Fukuyama conditions (Et_3SiH, 10% Pd/C)[19] gave aldehyde **20** in 86% yield. Amidation of **11** with piperidine in the presence of $AgOCOCF_3$[20] proceeded smoothly to provide amide **21** in 99% yield. Moreover,

(19) Fukuyama, T.; Lin, S. C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

Scheme 2. Mechanistic Considerations



Scheme 3. One-Step Derivatization of Thioester **11**



palladium-catalyzed reactions of thioesters enabled unsymmetric ketone synthesis from **11**.[21] Coupling of **11** with tri(*n*-butyl)vinylstannane under the Liebeskind conditions[22] gave enone **22** in 79% yield. Coupling of **11** with phenylboronic acid[23] afforded phenyl ketone **23** in 57% yield. A Sonogashira-type reaction[24] of **11** with phenylacetylene under our previously optimized conditions[25] delivered ynone **24** in 76% yield.

In conclusion, we have shown that Brønsted acid catalyzed IOCC of α,β-unsaturated thioesters represents a biomimetic methodology for the stereoselective synthesis of 2,6-*cis*-substituted tetrahydropyran derivatives. The ready availability of α,β-unsaturated thioesters via olefin cross-metathesis and the synthetic versatility of the cyclization products due to the unique reactivity of the thioester group are additional benefits of our methodology.

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

(20) Kurosu, M. *Tetrahedron Lett.* **2000**, *41*, 591.
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