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# Stereoselective Synthesis of *cis*-2,5-Disubstituted THFs: Application to Adjacent Bis-THF Cores of Annonaceous Acetogenins

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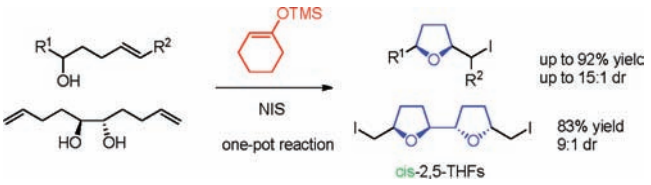
## ABSTRACT




**The iodocyclization of γ,δ-unsaturated alcohols in the presence of a silyl enol ether produced *cis*-2,5-disubstituted tetrahydrofurans in one pot via siloxy intermediates. *N*-Iodosuccinimide (NIS) effectively worked as an activator of the double bonds in the substrates and the silyl enol ether. Application to an expedient synthesis of the adjacent bis-tetrahydrofuran core of Annonaceous acetogenins with a *cis/threo/cis* relative stereochemistry is also described.**

2,5-Disubstituted tetrahydrofurans (THFs) are found in many biologically active molecules including Annonaceous acetogenins,[1] polyether antibiotics,[2] macrodiolides,[3] and others. For the preparation of such valuable skeletons, several elegant approaches have already been developed by many synthetic chemists.[4] Among them, the electrophilic halocyclization of γ,δ-unsaturated alcohols is an attractive method to construct 2,5-disubstituted THF ring systems because the starting alcohols are easily prepared[5] and the halogenated product lends itself to further useful synthetic transformations. In general, the halocyclization of the γ,δ-unsaturated alcohols favorably produces *trans*-2,5-THFs because *trans* isomers are thermodynamically more stable than *cis* isomers.[6,7] However, *cis*-2,5-THF moieties widely occur in many natural products. In the early 1980s, Bartlett et al. reported the stereoselective iodocyclization of benzyloxy derivatives leading to *cis*-2,5-THFs.[7] They showed that steric repulsion between the protective group on the hydroxyl function and the substituents at the 2 or 5 positions were critical for the *cis*-selective fashion. Other groups also reported synthesis of *cis*-2,5-THFs based on a similar strategy,[8] although protection of the hydroxyl group was necessary. The preparation of protected alcohols is usually conducted under acidic or basic conditions. Aiming at complex natural product synthesis, the regiocontrolled

(1) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.

(2) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(3) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.

(4) (a) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (b) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (c) Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537.

(5) For the preparation of some γ,δ-unsaturated alcohols, see references in the Supporting Information.

(6) (a) Wiley, A. R.; Harris, T. W.; Brungardt, C.; Marx., M. *J. Med. Chem.* **1982**, *25*, 121. (b) Baldwin, S. W.; McIver, J. M. *J. Org. Chem.* **1987**, *52*, 322. (c) Miura, K.; Hondo, T.; Okajima, S.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 487. (d) Harrowven, C. D.; Sibley, E. M. G. *Tetrahedron Lett.* **1999**, 8299.

(7) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(8) (a) Marek, I.; Lefrançois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* **1992**, *33*, 1747. (b) Zhang, H.; Weifang, S.; Ruan, Z.; Mootoo, D. R. *Tetrahedron Lett.* **1995**, *36*, 649. (c) Ruan, Z.; Dabideen, D.; Blumenstein, M.; Mootoo, D. R. *Tetrahedron* **2000**, *56*, 9203. (d) Kim, S.-W.; Choi, M.-S.; Park, G.; Kim, Y. S.; Cho, S. G. *Bull. Korean Chem. Soc.* **2001**, *22*, 626.

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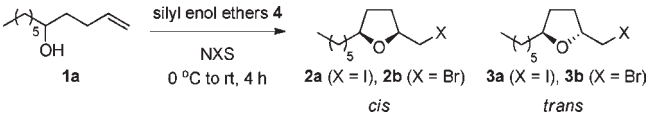
protection of poly hydroxyl compounds is sometimes problematic. Furthermore, a wide substrate scope has also not been fully examined to date. In this paper, we describe a novel diastereoselective iodocylization to give *cis*-2,5-THFs from the $\gamma,\delta$-unsaturated alcohols in a one-pot procedure using silyl enol ethers for the in situ silylation.

For the development of an alternative approach to *cis*-2,5-THFs, we proposed that halogenating reagents serve as an activator of silyl enol ethers to convert the $\gamma$, $\delta$-unsaturated alcohols into the siloxy derivatives and the successive intramolecular halocyclization, thus yielding *cis*-2,5-THFs in one operation.[9] We examined the reaction conditions using **1a** as a model substrate to demonstrate our concept (Table 1). First, the iodocyclization of **1a** with *N*-iodosuccinimide (NIS) (2.5 equiv) in dichloromethane produced the *trans* isomer **3a** as a major product, as expected (entry 1). The iodocyclization in the presence of various types of trimethylsilyl (TMS) enol ethers **4** was next examined. In entry 2, the addition of **4a** resulted in the reversal of the selectivity, i.e., a 3:1 preference for the *cis* isomer **2a**. This results indicated that the iodocyclization occurred via the corresponding silyl ether of **1a**. During the screening of silyl enol ethers (entries 2−5), trimethylsiloxy cyclohexene **4d** gave the best result with a 88% combined yield and 11:1 selectivity. For enhancement of the selectivity, more bulky triethylsilyl (TES) derivative **4e** was used.

**Table 1.** Optimization[a]



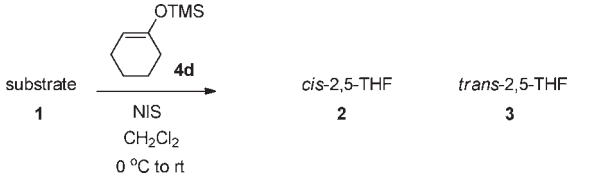

| entry | silyl enol ether **4** | solvent | yield (%)[b] | dr (**2**:**3**)[c] |
|---|---|---|---|---|
| 1[d] | none | $CH_2Cl_2$ | 85 | 1:3 |
| 2 |  **4a** | $CH_2Cl_2$ | 82 | 3:1 |
| 3 |  **4b** | $CH_2Cl_2$ | 96 | 1:1 |
| 4 |  **4c** | $CH_2Cl_2$ | 82 | 8:1 |
| 5 |  **4d** | $CH_2Cl_2$ | 88 | 11:1 |
| 6 |  **4e** | $CH_2Cl_2$ | 76 | 1:1 |
| 7 | **4d** | $CH_3CN$ | 94 | 2:1 |
| 8 | **4d** | THF | 45 | 1:2 |
| 9[e] | **4d** | $CH_2Cl_2$ | 65 | 1:2 |

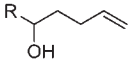
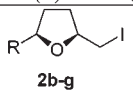
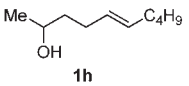
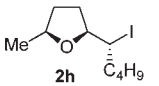
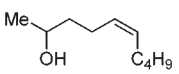
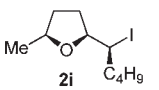
[a] Unless otherwise noted, reactions were performed using silyl enol ether (1.5 equiv) and NIS (2.5 equiv). [b] Total yields of **2** and **3**. [c] Dr was determined by $^1$H NMR. [d] 1.5 equiv of NIS was used. [e] NBS was used instead of NIS.

However, the selectivity was not improved (entry 6). The TMS group proved to be bulky enough for any steric effect on the present reaction. Other common solvents for the halocyclization, such as acetonitrile and THF, gave poor results (entries 7 and 8).[10] *N*-Bromosuccinimide (NBS) was not effective for this reaction because the siloxy intermediate was not formed (entry 9). Compounds **2b** and **3b** were formed directly from **1a** due to the low reactivity of NBS toward the silyl enol ether.

With the optimized conditions in hand, we then explored the generality and scope of the substrates using various $\gamma,\delta$-unsaturated alcohols **1** (Table 2). In entries 1−3, the reaction of alcohols **1b**−**d** smoothly proceeded to predominantly give the *cis* products **2b**−**d**. The alcohols with various functional groups **1e**−**g** were available for this reaction, and the corresponding products **2e**−**g** were obtained in high yields without any difficulty (entries 4−6). It is noteworthy that acid-labile *tert*-butyldimethylsilyl (TBS) and triphenylmethyl (Tr) groups were not affected under these conditions (entries 5 and 6). Even using the substrates with internal olefins **1h** and **1i**, the stereoselective cyclization proceeded diastereoselectively in high yields (entries 7 and 8).

**Table 2.** Iodocyclization of $\gamma,\delta$-Unsaturated Alcohol **1**[a]

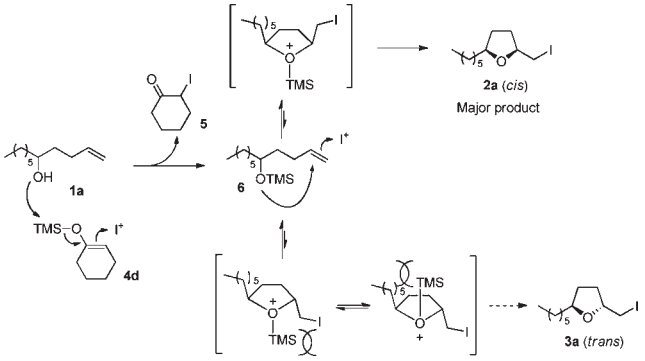



| entry | substrate (**1**) | product (**2**) | time (h) | yield (%) | dr (**2**:**3**)[b] |
|---|---|---|---|---|---|
| |  **1b-g** |  **2b-g** | | | |
| 1 | R = Me (**1b**) | **2b** | 4 | 82 | 6:1 |
| 2[c] | = *i*Pr (**1c**) | **2c** | 12 | 85 | 15:1 |
| 3[c] | = vinyl (**1d**) | **2d** | 8 | 87 | 9:1 |
| 4 | = $C_4H_8OBn$ (**1e**) | **2e** | 4 | 85 | 12:1 |
| 5 | = $C_4H_8OTBS$ (**1f**) | **2f** | 4 | 82 | 11:1 |
| 6 | = $C_3H_6OTr$ (**1g**) | **2g** | 4 | 89 | 9:1 |
| 7 |  **1h** |  **2h** | | | |
| | | **2h** | 4 | 92 | 11:1 |
| 8 |  **1i** |  **2i** | | | |
| | | **2i** | 4 | 85 | 11:1 |

[a] Unless otherwise noted, reactions were performed using **4d** (1.5 equiv) and NIS (2.5 equiv). [b] Dr was determined by $^1$H NMR. [c] Reactions were performed at −40 °C.

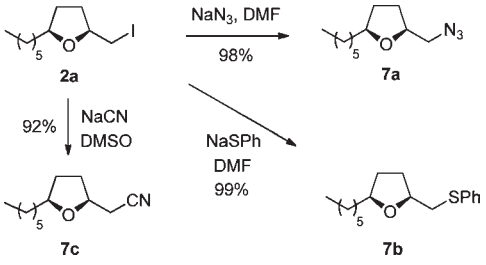
In accord with Bartlett's proposal,[7] a plausible explanation for the reaction mechanism of the present iodocyclization is exemplified in Scheme 1 using alcohol **1a** and silyl enol ether **4d**. Initially, **4d** was activated by NIS and reacted with **1a** to give the intermediate **6** and coproduct **5**.[11] The minor product **3a** should be generated through the high-energy transition states due to 1,2-steric interactions. As a result, *cis*-2,5-THF **2a** was favorably obtained.

**Scheme 1.** Plausible Reaction Mechanism



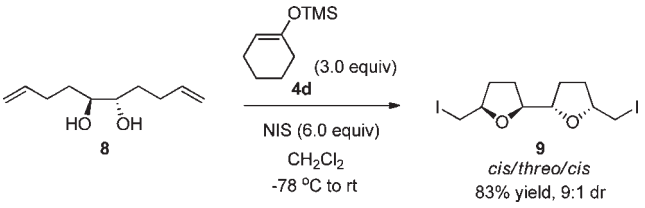

To demonstrate the utility of our products, we performed the substitution of the iodine atom in **2a**. Upon treatments of **2a** with sodium azide, sodium thiophenolate and sodium cyanide, the corresponding substituted compounds **7a**–**c** were obtained in good yields (Scheme 2).

**Scheme 2.** Derivatization of **2a**




Adjacent bis-THF fragments are essential components of Annonaceous acetogenins, which show a wide array of biological properties such as antitumor, immunosuppresive, antimicrobial and insecticidal activities.[1,12] Although many methods have been developed for the synthesis of the bis-THF cores of Annonaceous acetogenins, the approach to bis-THFs with a *cis*/*threo*/*cis* relative stereochemistry was rather limited.[13] We planned the one-pot synthesis of adjacent bis-THFs using our method. As illustrated in Scheme 3, the double iodocyclization of $C_2$-symmetric diol **8**, which is readily obtained from *trans*-1,5,9-decatriene by the regioselective Sharpless asymmetric dihydroxylation,[14] produced *cis*/*threo*/*cis* bis-THF **9** in an 83% combined yield with a 9:1 selectivity.[15] In the absence of **4d**, the double iodocyclization favorably produced the *trans*/*threo*/*trans* isomer.[16] These results indicated that the formation of the newly formed stereogenic centers can be controlled by the presence or absence of silyl enol ether **4d**.

**Scheme 3.** One-Pot Synthesis of *cis*/*threo*/*cis* Bis-THF **9**




Next, the obtained **9** was converted into the *cis*/*threo*/*cis* bis-THF cores of Annonaceous acetogenins, which are found in rolliniastatin 1, rollimembrin, and membranacin.[17] In a previous synthetic route to these natural products, the stereocenters in bis-THF cores are constructed in order and many reaction steps are required.[13c–f] Although Piccialli reported an elegant one-pot synthesis of bis-THF rings from linear polyenes by oxidative cyclization, the product yields were low.[13g,h] We aimed at the concise synthesis of Koert and Lee's common intermediate **13**[13c,e] for the synthesis of the set of natural products, rolliniastatin 1, rollimembrin, and membranacin (Scheme 4). The substitutions of two iodine atoms in **9** by sodium

(9) There are some reports for the iodocyclization of silyl ethers, though in rather low yields or low selectivity. (a) Reference 7. (b) Brimble, A. M.; Edmonds, K. M. *Tetrahedron* **1995**, *51*, 9995.

(10) Details of optimization are provided in the Supporting Information.

(11) We isolated compound **6** and coproduct **5** and confirmed their structures by $^1$H NMR (see the Supporting Information).

(12) For a recent review for total synthesis of Annonaceous acetogenins, see: Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* **2008**, *4*, 48.

(13) (a) Bruke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953. (b) Wysocki, L. M.; Dodge, M. W.; Voight, E. A.; Bruke, S. D. *Org. Lett.* **2006**, *8*, 5637. (c) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (d) Head, G. D.; Whittingham, W. G.; Brown, R. C. D. *Synlett* **2004**, 1437. (e) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396. (f) Morris, C. L.; Hu, Y.; Head, G. D.; Brown, L. J.; Whittingham, W. G.; Brown, R. C. D. *J. Org. Chem.* **2009**, *74*, 981. (g) Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2002**, *43*, 9265. (h) Piccialli, V.; Caserta, T.; Caruso, L.; Gomez-Paloma, L.; Bifulco, G. *Tetrahedron* **2006**, *62*, 10989.

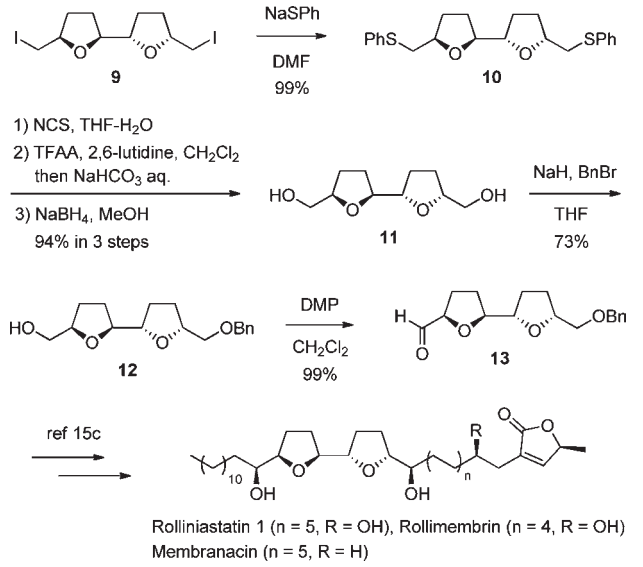
(14) Diol **8** was prepared from commercially available *trans*-1,5,9-decatriene in one step (57% yield).Tian, S.-K.; Wang, Z.-M.; Jiang, J.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2551.

(15) The ratio of two diastereomers was determined by $^1$H NMR. Two diasteromers were inseparable and **9** (9:1 dr) was used for further transformation in Scheme 4.

(16) The iodocyclization of ***ent*-8** with iodine gave *trans*/*threo*/*trans* bis-THF product as a major isomer with a 7:1 selectivity: Lee, S.; Lee, Y.-S.; Park, G.; Choi, S.; Yoon, S.-H. *Bull. Korean Chem. Soc.* **1998**, *19*, 115.

(17) (a) Pettit, G. R.; Cragg, G. M.; Polonsky, J.; Herald, D. L.; Goswami, A.; Smith, C. R.; Moretti, C.; Schmidt, J. M.; Weisleder, D. *Can. J. Chem.* **1987**, *65*, 1433. (b) González, M. C.; Tormo, J. R.; Bermejo, A.; Zafra-Polo, M. C.; Estornell, E.; Cortes, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1113. (c) Saez, J.; Sahpaz, S.; Villaescusa, L.; Hocquemiller, R.; Cavé, A. *J. Nat. Prod.* **1993**, *56*, 351. (d) Chávez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1999**, *62*, 1119. (e) González, M. C.; Lavaud, C.; Gallardo, T.; Zafra-Polo, M. C.; Cortes, D. *Tetrahedron* **1998**, *54*, 6079.

**Scheme 4.** Application to Natural Products Synthesis




thiophenolate gave **10**. Oxidation of thiol, Pummerer rearrangement of sulfoxide, and reduction of aldehyde afforded diol **11**. The expedient synthesis of compound **13** was achieved via the monoprotection of the hydroxyl groups and subsequent oxidation of the remained alcohol with Dess-Martin periodinane. Consequently, we accomplished the synthesis of the key intermediate **13** from the known diol **8** in seven steps with a 56% overall yield.[18]

In conclusion, we have described the efficient and concise synthesis of *cis*-2,5-disubstituted THFs from $\gamma,\delta$-unsaturated alcohols. Our report is the first example of the selective synthesis of a *cis*-2,5-THF stereoisomer from the alcohol precursors in a one-pot procedure by an iodocyclization strategy. The present method is applicable to various substrates with acid-sensitive functions and internal olefins. We have achieved the efficient formation of adjacent bis-THFs with a *cis*/*threo*/*cis* stereochemistry, which are an essential component of some Annonaceous acetogenins. We have also disclosed the useful utilization of a halogenating reagent in organic synthesis.

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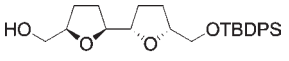
**Supporting Information Available.** Experimental details and detailed spectroscopic data of all new compounds including TBDPS-ether **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Aldehyde **13** was obtained as an inseparable mixture of two diastereomers (9:1 dr). The major diastereomer was identical with the Koert and Lee's common intermediate **13**. The undesired isomer is separable when the diol **11** is transformed into the corresponding TBDPS-ether **14** (see the Supporting Information).




**14**

The authors declare no competing financial interest.