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Published on Web 12/20/2006

# Lewis Acid-Promoted Intermolecular Acetal-Initiated Cationic Polyene Cyclizations

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The intramolecular acetal-initiated cationic polyene cyclization reaction was first introduced by W. S. Johnson.[1,2] Since then, this method has been extensively developed to afford bicyclic,[2,3] tricyclic,[2,3] tetracyclic,[2,3] and even pentacyclic[2,3] products in respectable to good yields. Asymmetric induction has also been achieved using chiral acetal templates, providing enantiomeric excess of up to 90%.[2] However, there exist some disadvantages in using acetals for intramolecular polyene cyclizations. The need to incorporate the required acetal into the acyclic precursor introduces added synthetic complexity. In addition, the accommodation of the acetal moiety also diminishes the structural flexibility in the acyclic precursor. These two problems, though minor, could reduce the scope and applicability of the method substantially. In order to overcome these issues and yet retain the advantages of using acetals as initiators, we devise the *intermolecular* acetal-initiated polyene cyclization reaction.

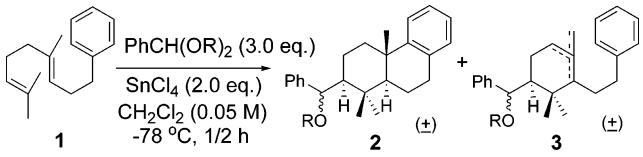
Initial efforts to develop the intermolecular reaction were focused on selecting a suitable acid to mediate the cyclization. Tin(IV) chloride[1,3] showed the most promising results when used in the intermolecular method (Table 1, entry 1). Upon optimization, (*3E*)-4,8-dimethyl-1-phenyl-nona-3,7-diene (**1**) was cyclized in the presence of benzaldehyde dimethyl acetal and tin(IV) chloride to give **2a** in high yield (87%) (Table 1, entry 1).

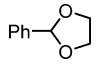
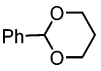
With this optimization conditions, the intermolecular polyene cyclization was carried out with different acetals and the results are shown in Table 1. In all cases, the cyclized products were obtained in good to excellent yields. Small amounts of monocyclized products were obtained in some cases (Table 1, entries 1 to 4). The highly acidic environment generated by tin(IV) chloride probably facilitated deprotonation of intermediate species to form these monocyclized products. Increasing bulkiness of acetals did not affect the excellent reaction rates and yields of the intermolecular reactions (Table 1, entry 4). Especially noteworthy, reactions using benzaldehyde cyclic acetals (Table 1, entries 5 to 6) proceeded smoothly to give the desired products in good to excellent yields without detection of the monocyclization products.

These encouraging results set the stage for examination of the asymmetric version of this methodology (Table 2). After screening various chiral acetal templates, the cyclization reaction using (4*S*,6*S*)-4,6-dimethyl-2-phenyl-1,3-dioxane (Table 2, entry 2) was most promising, providing the desired products in high yield and moderate selectivity[4] (89% yield, 64% de). The generality of asymmetric induction was further demonstrated by applying the protocol to a series of benzene-substituted substrates (Table 2, entries 3 to 7). Good yields and moderate diastereomeric excesses were achieved. These results clearly showed that asymmetric induction could be very efficiently achieved through intermolecular acetal-initiated polyene cyclizations.

To rationalize the stereoinduction observed with the use of chiral cyclic acetals, we set out to determine the absolute stereochemistry of the cyclization products. The absolute stereochemistry of the

***Table 1.*** $SnCl_4$-Mediated Intermolecular Acetal-Initiated Cationic Polyene Cyclization Using Various Acetals[a]




| entry | acetal | product | yield (%) (**2**[b]+**3**)[c] | ratio (**2**:**3**)[d] |
|---|---|---|---|---|
| 1 | $PhCH(OMe)_2$ | **2a** | 87 | 88:12 |
| 2 | $PhCH(OEt)_2$ | **2b** | 90 | 86:14 |
| 3 | $PhCH(OAlly)_2$ | **2c** | 84 | 97:03 |
| 4 | $PhCH(OiPr)_2$ | **2d** | 94 | 84:16 |
| 5 |  | **2e** | 72 | >99:01 |
| 6 |  | **2f** | 76 | >99:01 |

[a] All reactions were performed with **1** (0.1 mmol), acetal (0.3 mmol), and $SnCl_4$ (0.2 mmol, 1.0 M in $CH_2Cl_2$) in dichloromethane (2 mL) at −78 °C unless otherwise stated. $SnCl_4$ was added to the reaction mixture at −78 °C after **1** and acetal were mixed in dichloromethane at room temperature. [b] Isomers diastereomeric at the benzylic CH were obtained for **2** in ratios from 80:20 to 100:0. [c] Combined yield. [d] Determined by $^1H$ NMR.

major isomer **2h** was determined by X-ray crystallography analysis of the corresponding ketone derivative **4h**. Therefore, PCC oxidation of cyclization product mixture **2h**/**2h′**/**2h″** followed by recrystallization of the corresponding ketone mixture gave the major isomer **4h** in overall 24% yield. The X−ray crystal structure showed the absolute stereochemistry of **4h** (*S* (template), *R* (benzyl), *S* (ring))[4] in Scheme 1.

The stereochemistry of the other minor isomers was confirmed by chiral HPLC, $^1H$ NMR, and $^{13}C$ NMR analyses after converting **2** to **5** (Scheme 2). The conversion of **2h**/**2h′**/**2h″** to **5** or **7** gave a mixture of isomers in an enantiomeric ratio of 76 (*S*):24 (*R*), which is in agreement with our stereochemical observation. Therefore, the absolute configuration of **2h″** must be *S* (template), *S* (benzyl), *S* (ring)[4] (Scheme 3).

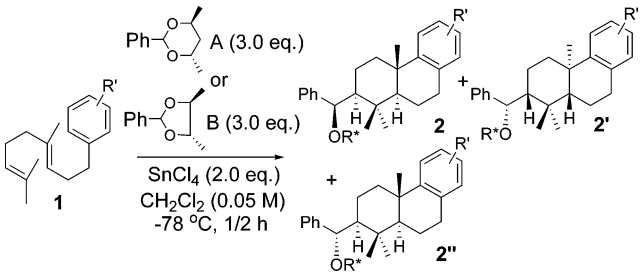
Acetal-initiated cyclization products are very versatile and can easily be converted into various optically active tricyclic terpene compounds[5] (Scheme 2).

The observed absolute stereochemical preference is rationalized as shown in Scheme 3. $SnCl_4$-assisted acetal ring opening can proceed via path A or B. Ring opening through path A eliminates the pre-existing axial stereorepulsion in the cyclic acetal and hence is more favorable.[4,6] The resulting oxonium ion is subsequently attacked on the less hindered *Re* face by the polyene via antiperiplanar, open-chain transition states (path A1 and A2). The transition state leading from path A1 is presumed to be much less sterically demanding and lower in energy compared to that from path A2, thereby affording the major isomer **2h** as determined by



**10.1021/ja067660+ CCC: $37.00** 

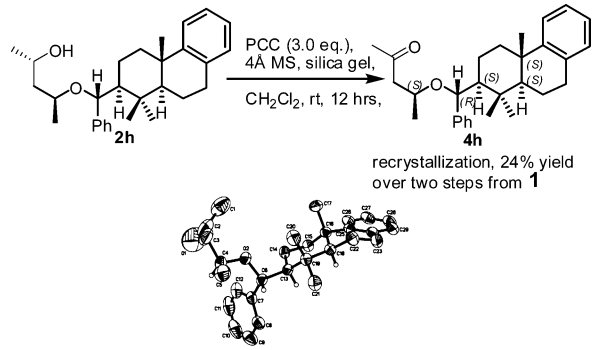
***Table 2.*** $SnCl_4$-Mediated Asymmetric Intermolecular Acetal-Initiated Cationic Polyene Cyclization Using Different Benzene-Substituted Substrates



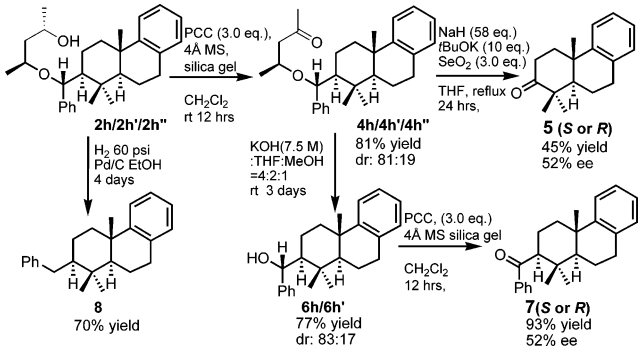

| entry | R′ | products | acetal | yield (%) (**2** + **2′** + **2″**)[a,b] | ratio[c] (**2**:**2′**:**2″**) | dr[d] (**2** + **2″**:**2′**) |
|---|---|---|---|---|---|---|
| 1[e] | | **2g/g′/g″** | B | 58 | 76:8:13:3 | 89:11 |
| 2 | | **2h/h′/h″** | A | 89 | 66:18:16 | 82:18 |
| 3 | 4-*i*Pr | **2i/i′/i″** | A | 88 | 73:14:13 | 86:14 |
| 4 | 4-OMe | **2j/j′/j″** | A | 75 | 72:16:12 | 84:16 |
| 5[f] | 3-OMe | **2k/k′/k″** | A | 65 | 66:19:15 | 81:19 |
| 6 | 4-Me | **2l/l′/l″** | A | 87 | 66:17:17 | 83:17 |
| 7 | 3-Me | **2m/m′/m″** | A | 85 | 71:18:11 | 82:18 |

[a] Combined yield. [b] The fourth possible isomeric product was not detected by $^1$H NMR except entry 1. [c] Determined by $^1$H NMR. [d] dr = diastereoisomer ratio, reported as (**2** + **2″**:**2′**). Major isomer **2h** is believed to have the same absolute ring stereoconfiguration compared to **2h″** (see text and ref 4). [e] Side products **6h/6h′** were obtained in 25% yield. [f] Product with benzene ring cyclized at meta position to OMe was obtained in 15% yield as well.

***Scheme 1.*** Modification of Cyclization Product, Absolute Stereochemistry Determination of Cyclization Product **2h**, and Representation Structures of **4h** and Assignment of Stereochemistry



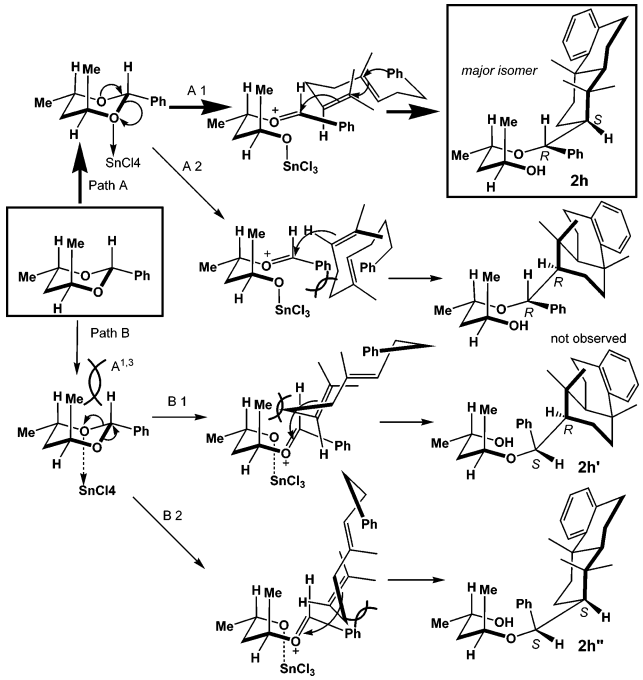

***Scheme 2.*** Functionalization of Cyclization Products to Various Terpenes




X-ray analysis. Cyclizations proceeding through equally unfavorable paths B1 and B2 provided minor isomers **2h′** and **2h″**, respectively.

Herein, we have reported an asymmetric Lewis acid-mediated intermolecular acetal-initiated cationic polyene cyclization to form tricyclic compounds. Optical active terpenes[5] can be synthesized in a two-step modification sequence. Optimizations of the chiral $PhCH(OR)_2/SnCl_4$ systems are in progress to achieve selectivities, and the application of this method in cyclizations to form tetracyclic products are in progress.

***Scheme 3.*** Proposed Rationale for Stereochemical Induction




**Acknowledgment.** This paper is dedicated to Professor E. J. Corey for his 79th birthday. We thank Prof. Kum-Fun Mok and Dr Yong-Xin Li for X-ray analyses. We gratefully acknowledge the Nanyang Technological University for the funding of this research.

**Supporting Information Available:** Additional experiment procedures and spectrum data for reactions products (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861−3862.
(2) For reviews of acetal initiating polyene cyclization, see: (a) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi−1. (b) Johnson, W. S. *Angew. Chem., Int. Ed.* **1976**, *15*, 9−16. (c) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1−8.
(3) For some recent examples of non-enzymatic polyene cyclization, see: (a) Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272−6273. (b) Yamamoto, H.; Ishihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122−11123. (c) Yamamoto, H.; Ishihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647−3655 and references therein. (d) Corey, E. J.; Schreiber, J. V.; Mi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11290−11291. (e) Corey, E. J.; Huang, A. X.; Xiong, Z. M. *J. Am. Chem. Soc.* **1992**, *121*, 9999−10003 and references therein. (f) Zoretic, P. A.; Zhang, Y. H. *Tetrahedron Lett.* **1996**, *37*, 1751−1754. (g) Sen, S. E.; Zhang, Y. Z.; Roach, S. L. *J. Org. Chem.* **1996**, *61*, 9534−9537. (h) Livinghouse, T.; Harring, S. R. *Tetrahedron* **1994**, *50*, 9229−9254. (i) Fish, P. V. *Tetrahedron Lett.* **1994**, *35*, 7181−7184. (j) Demuth, M.; Hoffmann, U.; Gao, Y. M.; Pandey, B.; Klinge, S.; Warzecha, K. D.; Krüger, C.; Roth, H. D. *J. Am. Chem. Soc.* **1993**, *115*, 10358−10359. (k) Snowden, R. L. *J. Org. Chem.* **1992**, *57*, 955−960.
(4) The three new chiral centers formed are considered as a chiral group (fixed relative configuration within the group) based on the Stork−Eschenmoser postulate. See: (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(5) (a) Mori, K.; Waku, M. *Tetrahedron* **1985**, *41*, 5653−5660. (b) Müller, R.; Rüedi P. *Helv. Chim. Acta* **2003**, 439−456.
(6) (a) Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3253−3257. (b) Johnson, W. S.; Choi, V. M. F.; Elluott, John D. *Tetrahedron Lett.* **1984**, *25*, 591−594.

JA067660+