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Efficient Chirality Transfer in the SmI_2-Mediated Cyclization of Aldehydo β-Alkoxyvinyl Sulfoxides: Asymmetric Synthesis of 3-Hydroxyoxanes

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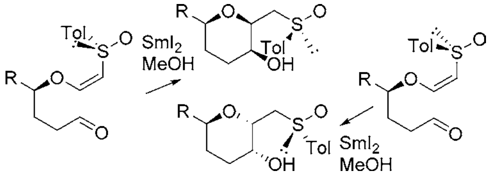
ABSTRACT



Stereoselective syntheses of 3-hydroxyoxanes were achieved via efficient chirality transfer in the SmI_2-mediated cyclization reactions of aldehydo β-alkoxyvinyl sulfoxides.

Chiral sulfoxides are important intermediates in modern asymmetric synthesis.[1] Diastereoselective intermolecular β-addition of alkyl radicals to chiral vinyl sulfoxides was reported by Toru and co-workers.[2] Malacria and co-workers reported successful examples of asymmetric carbocycle synthesis via diastereoselective intramolecular radical addition reactions of chiral vinyl sulfoxides.[3] Stereochemical aspects of asymmetric oxacycle synthesis via radical cyclization of chiral β-alkoxyvinyl sulfoxides prepared from primary alcohols have been discussed by Malacria and co-workers.[4] In the radical cyclization of chiral β-alkoxyvinyl sulfoxides prepared from secondary alcohols, the intrinsic preference for formation of *cis*-2,5-disubstituted oxolanes predominated, the sulfoxide chirality playing a secondary role. Double stereoselection in this type of radical cyclization provided a viable route for the stereoselective synthesis of oxolanyl allyl carbinols when coupled with subsequent Pummerer rearrangement and allylstannane reaction.[5] This protocol was used for the stereoselective synthesis of rolliniastatin 1 and jimenezin.[6]

Cyclization of aldehydo β-alkoxyvinyl sulfoxides under reductive conditions offers opportunities of controlling two stereocenters in 3-hydroxyoxane products via sulfoxide chirality transfer. We report in this communication results of the SmI_2-mediated cyclization reactions of aldehydo β-alkoxyvinyl sulfoxides, which led to stereoselective and stereospecific preparation of 3-hydroxyoxanes (Scheme 1).

The reaction of the prototype aldehydo β-alkoxyvinyl sulfoxide **1** with SmI_2 in the presence of methanol proceeded smoothly to yield a single 3-hydroxyoxane product **3** in 93% yield (Scheme 2). Reaction of the (*Z*)-(*S*)-isomer **2** also produced a single cyclization product **4**.[7] Dess−Martin

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(1) (a) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651−3706. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559−5601.

(2) Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794−7800.

(3) (a) Delouvriė, B.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11395−11401. (b) Brebion, F.; Vitale, M.; Fensterbank, L.; Malacria, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2889−2896.

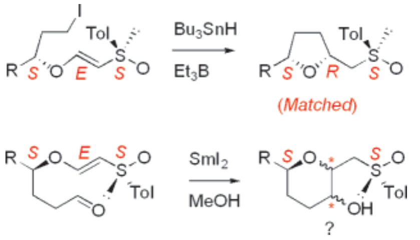
(4) Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366−368.

(5) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895−1897.

(6) (a) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396−10399. (b) Hwang, C. H.; Keum, G.; Sohn, K. I.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621−6623.

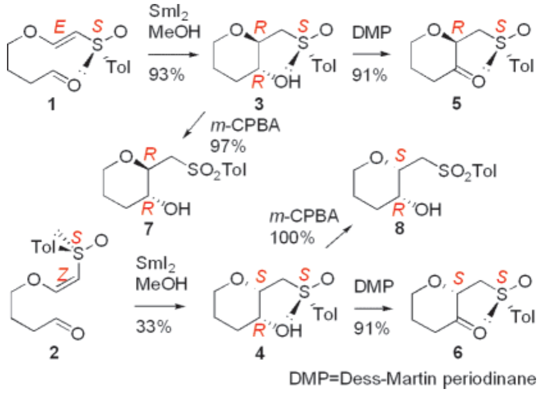
10.1021/ol071176+ CCC: $37.00

Scheme 1. Reactions of β-Alkoxyvinyl Sulfoxides



oxidation of **3** led to a ketone product **5**, which was identified unambiguously as the (*S*,*R*) product.[8] The alternative (*S*,*S*) ketone **6** was obtained from **4**. On the other hand, *m*-CPBA oxidation of **3** and **4** produced two sulfone diastereomers **7** and **8**, confirming the structural assignments.

Scheme 2. SmI$_2$-Mediated Cyclization of β-Alkoxyvinyl Sulfoxides **1** and **2**

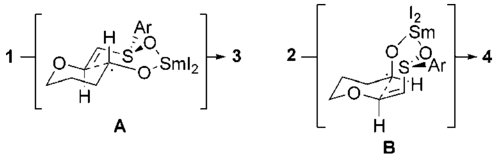


DMP=Dess-Martin periodinane

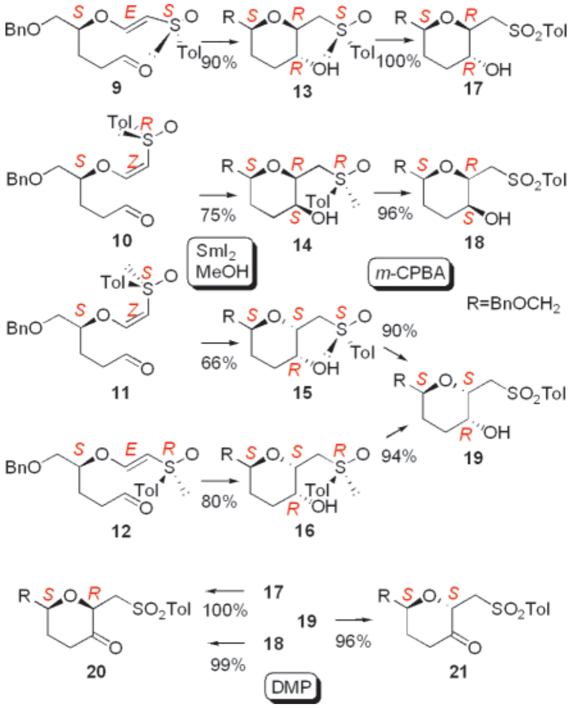
The SmI$_2$-mediated 6-*exo* cyclization reactions of aldehydo β-alkoxyvinyl sulfoxides were indeed stereoselective and stereospecific. The observed stereoselectivity may be explained by proposing the "eclipsed lone pair"[3a] transition states **A** and **B**, in which the sulfoxide oxygen-coordinated samarium ketyl group necessarily approaches the double bond opposite from the bulky aryl group (Scheme 3).[9,10]

Reactions of four β-alkoxyvinyl sulfoxides, **9**−**12**, were then investigated. A single product **13** was obtained from SmI$_2$-mediated cyclization of **9** in 90% yield. Likewise, diastereomeric 3-hydroxyoxane derivatives **14**−**16** were obtained from the reaction of **10**−**12** (Scheme 4). *m*-CPBA oxidation of **13** and **14** produced a diastereomeric pair of sulfones **17** and **18**, both of which were converted into a single keto sulfone **20**. A single sulfone **19** was obtained from *m*-CPBA oxidation of **15** and **16**. A second keto sulfone **21** was obtained via Dess−Martin oxidation of **19**, which confirms the *trans*-2,6-disubstitution pattern in the products **15** and **16**.

Scheme 3. Transition State Structures for Reactions of **1** and **2**



Scheme 4. Synthesis of 3-Hydroxyoxanes from β-Alkoxyvinyl Sulfoxides **9**−**12**



The transition state structures **C** and **D** for the reaction of **9** and **10** may be proposed following the rationale already used for structures **A** and **B** (Scheme 5). In the transformation of **11** into the product **15**, the transition state structure **E** appears to play an important role. It is more difficult to propose a transition state structure for the **12**−**16** conversion; in fact, the expected product would be **22** via the transition state structure **G**. A possible transition state structure **F** for conversion of **12** into **16** does not adopt the familiar chairlike conformation through sulfoxide oxygen−samarium coordination.

Extension of this method for synthesis of hydroxyoxolanes was not straightforward. In practice, the unstable aldehyde substrates obtained from the primary alcohol precursors via

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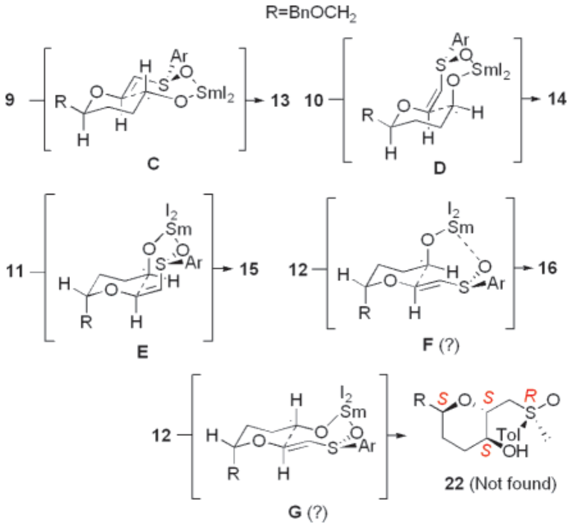
(7) In this case, the product **4** was obtained in low yield; a large quantity of the retro hetero-Michael product was obtained.

(8) CCDC-645184 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) For results of an ab initio study on the conformations of methyl vinyl sulfoxide, see: Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952−7958.

(10) Results of ab initio calculations on (*E*)-(*S*)- and (*Z*)-(*S*)-phenyl β-methoxyvinyl sulfoxides are presented in the Supporting Information. In both cases, global minimum structures were obtained with the sulfur lone pair electrons syn coplanar with respect to the double bonds.

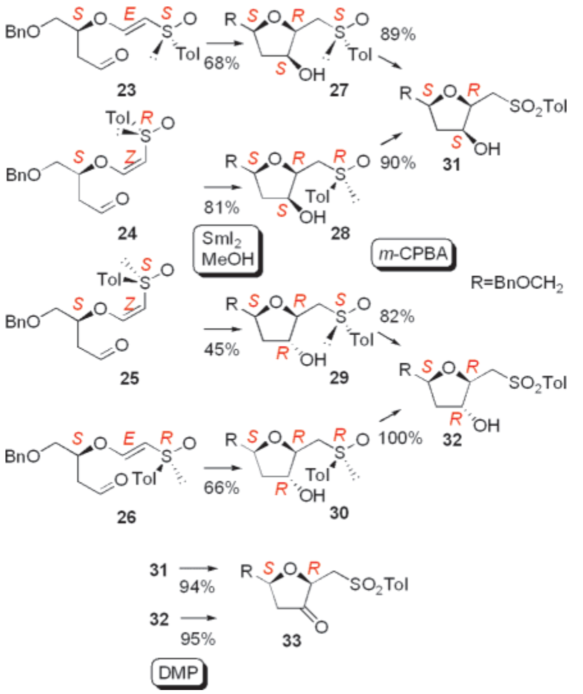
Scheme 5. Transition State Structures for Reactions of **9**−**12**



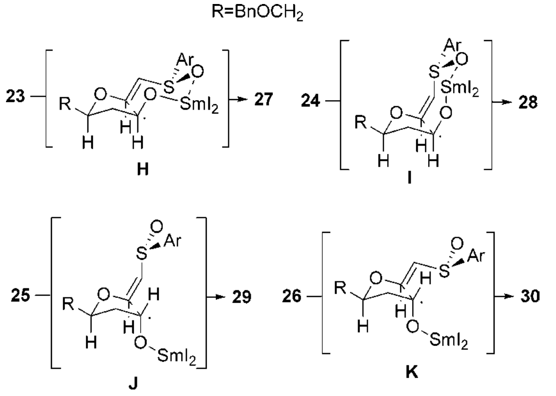
Dess−Martin oxidation were directly reacted with samarium iodide for 5-*exo* cyclization reactions. Adopting this protocol, a single hydroxyoxolane product **27** was obtained from aldehyde **23** in 68% (two steps) yield. The reaction of alternative aldehydes **24**−**26** afforded the products **28**−**30** stereoselectively. A single sulfone product **31** was obtained from the *m*-CPBA oxidation of sulfoxides **27** and **28**. A second sulfone **32** was obtained from sulfoxides **29** and **30**. Sulfones **31** and **32** were converted into a single keto sulfone **33** (Scheme 6).

It is to be emphasized that only *cis*-2,5-disubstituted 3-hydroxyoxolane products were obtained via 5-*exo* cyclization in contrast to the results in the 6-*exo* cyclizations. Presumably, sulfoxide oxygen−samarium coordination is less important in the 5-*exo* cyclization reactions, which should be much faster than the 6-*exo* cyclization. The intrinsic preference for formation of *cis*-2,5-disubstituted oxolanes prevails in these cases, and transition states **H**−**K** may be proposed for the conversion of **23**−**26** (Scheme 7).

Scheme 6. Synthesis of 3-Hydroxyoxolanes from β-Alkoxyvinyl Sulfoxides **23**−**26**



Scheme 7. Transition State Structures for Reactions of **23**−**26**



The results may be summarized as follows.

(1) In the 6-*exo* cyclization of aldehydo (*Z*)-β-alkoxyvinyl sulfoxides (**10** and **11**), sulfoxide chirality transfer through the sulfoxide oxygen−samarium coordination determines the stereochemistry of the newly generated stereogenic centers at C-2 and C-3 regardless of the carbinol chirality. The intrinsic preference for *cis*-2,6-disubstituted oxane may be overruled, and *trans*-2,6-disubstituted oxane **15** is formed from **11**.

(2) Concerning the 6-*exo* cyclization of aldehydo (*E*)-β-alkoxyvinyl sulfoxides, stereoselectivity may easily be predicted in the matched case (**9**), but it is difficult to suggest the correct transition state structure in the mismatched case (**12**). The importance of the sulfoxide oxygen−samarium coordination is not evident in the mismatched case.

(3) In the 5-*exo* cyclization of aldehydo (*E*)- and (*Z*)-β-alkoxyvinyl sulfoxides (**23**−**26**), the sulfoxide oxygen−samarium coordination is not important, and *cis*-2,5-disubstituted oxolanes are formed regardless of the sulfoxide chirality. The C-3 configuration of the 3-hydroxyoxolane products may be predicted by considering sterically less-hindered transition state structures.

The oxacyclic products obtained in the present studies may serve as precursors in further transformations. For example, sodium amalgam reduction of the sulfone functional group in **31** and reductive debenzylation by Raney nickel afforded the known diol **34**,[11] which constitutes a formal synthesis of (+)-epimuscarine (**35**)[12] (Scheme 8).

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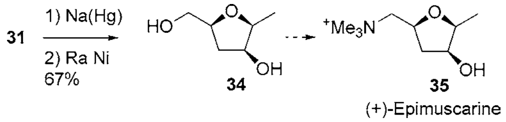
[11] (a) Mubarak, A. M.; Brown, D. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 809−813. (b) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608−3613.

[12] For more recent syntheses of **35**, see: (a) Hartung, J.; Kneuer, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3019−3031. (b) Popsavin, V.; Berić, O.; Popsavin, M.; Radić, L.; Csanádi, J.; Ćirin-Novta, V. *Tetrahedron* **2000**, *56*, 5929−5940.

Scheme 8. Formal Synthesis of Epimuscarine



The method described in this communication opens up new ways for the preparation of functionalized oxacycles, which will facilitate syntheses of complex natural products and bioactive molecules.

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Supporting Information Available: Experimental procedures (36 pages) and ^{1}H NMR and ^{13}C NMR spectra of the intermediates and products (48 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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