Efficient Chirality Transfer in the SmI$_2$-Mediated Cyclization of Aldehydo β-Alkoxyvinyl Sulfoxides: Asymmetric Synthesis of 3-Hydroxyoxanes

Jae Hoon Jung, Yong Wook Kim, Min Ah Kim, Soo Young Choi, Young Keun Chung, Tae-Rae Kim, Seokmin Shin, and Eun Lee*

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea
eunlee@snu.ac.kr

Received May 19, 2007

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. Diastereoselective intermolecular β-addition of alkyl radicals to chiral vinyl sulfoxides was reported by Toru and co-workers. Malacria and co-workers reported successful examples of asymmetric carbocycle synthesis via diastereoselective intramolecular radical addition reactions of chiral vinyl sulfoxides. 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. This protocol was used for the stereoselective synthesis of rolliniastatin 1 and jimenezin.

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 with SmI$_2$ in the presence of methanol proceeded smoothly to yield a single 3-hydroxyoxane product in 93% yield (Scheme 2). Reaction of the (Z)-(S)-isomer also produced a single cyclization product.

oxidation of 3 led to a ketone product 5, which was identified unambiguously as the (S,R) product. 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.

The SmI₂-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” 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 SmI₂-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.

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
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).

The results may be summarized as follows.

(1) In the 6-exo cyclization of aldehyde (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 aldehyde (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 aldehyde (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).

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.

**Scheme 8.** Formal Synthesis of Epimuscarine

Acknowledgment. This work was supported by a grant from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea, and by a grant from the Korea Research Foundation (MOEHRD) (KRF-2005-070-C00073). Brain Korea 21 graduate fellowship grants to J. H. Jung, Y. W. Kim, and M. A. Kim and a Seoul Science Fellowship grant to J. H. Jung are gratefully acknowledged.

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. OL071176+