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Communications

Stereoselective Cyclization Mediated by Samarium(II) Iodide Using Allyl Sulfides and Sulfones as Ketyl Radical Acceptors†

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Summary: This paper describes the new types of completely stereoselective cyclizations induced by samarium(II) iodide using allyl sulfides or sulfones as a ketyl radical acceptor.

The carbocyclic ring annulation process represents an extremely important transformation in organic synthesis, and for this reason, there has been much research on the stereoselective intramolecular carbon–carbon bond formation reactions. Samarium(II) iodide has evolved as a unique, single-electron reducing reagent for promoting reductive couplings, such as ketone–olefin and pinacol couplings, to effectively accomplish carbon–carbon bond formation under exceedingly mild conditions.[1] In particular, investigations of ketone–olefin coupling cyclizations induced by samarium(II) iodide have led to the development of useful and convenient methods for the construction of highly functionalized carbocycles.[2] However, poor diastereoselectivity resulted in several cases of the samarium(II) iodide promoted intramolecular couplings of α,β-unsaturated esters with aldehydes or ketones.[2e-i,m] Recently, we have found that such types of reductive cyclizations take place in a completely stereocontrolled manner using allyl sulfides or sulfones as a ketyl radical acceptor instead of α,β-unsaturated esters. In this paper, we would like to report these new types of highly stereoselective annulation reactions mediated by samarium(II) iodide.

Scheme 1 summarizes the results from a number of experiments. Treatment of (*E*)-7-(phenylthio)-5-heptenal (**1**)[3] and (*Z*)-7-(phenylthio)-5-heptenal (**4**)[3] with samarium(II) iodide in the presence of hexamethylphosphoramide (HMPA) at −10 °C exclusively (>99:1, 400 MHz ^{1}H-NMR) afforded the *trans*-cyclopentanol **3**.[4] The *trans*-cyclohexanol **8**[5] was successfully constructed in a completely stereocontrolled manner through the same reductive cyclizations of (*E*)-8-(phenylthio)-6-octenal (**6**).[3] Furthermore, similar reductive cyclization reactions of (*E*)-7-(phenylsulfonyl)-5-heptenal (**2**),[3] (*Z*)-7-(phenylsulfonyl)-5-heptenal (**5**),[3] and (*E*)-8-(phenylsulfonyl)-6-octenal (**7**)[3] sufficiently proceeded even at −78 °C with high diastereoselectivity, and the same *trans*-alcohols **3** and **8** were

† This paper is dedicated to the memory of the late Dr. Mitsutoshi Yanagiya.

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(3) The allyl sulfides **1**, **4** and sulfones **2**, **5** were prepared from 1,5-pentanediol in seven and eight steps, respectively. Similarly, the allyl sulfide **6** and sulfone **7** were derived from 1,6-hexanediol.

(4) The *trans* stereochemistry of (1*S**,2*R**)-2-vinyl-1-cyclopentanol (**3**) was unambiguously determined by converting **3** into (1*R**,2*S**)-2-[(*tert*-butyldimethylsilyl)oxy]-1-cyclopentaneethanol, which showed physical and spectral data identical to those of the authentic sample synthesized from methyl (1*R**,2*S**)-2-hydroxy-1-cyclopentaneacetate bearing definite relative stereochemistry. The *trans*-hydroxy ester was obtained along with the corresponding *cis*-product isolated as an annulated γ-lactone, *via* the samarium(II) iodide promoted cyclization of methyl (*E*)-7-oxo-2-hepenoate.[2f,g]

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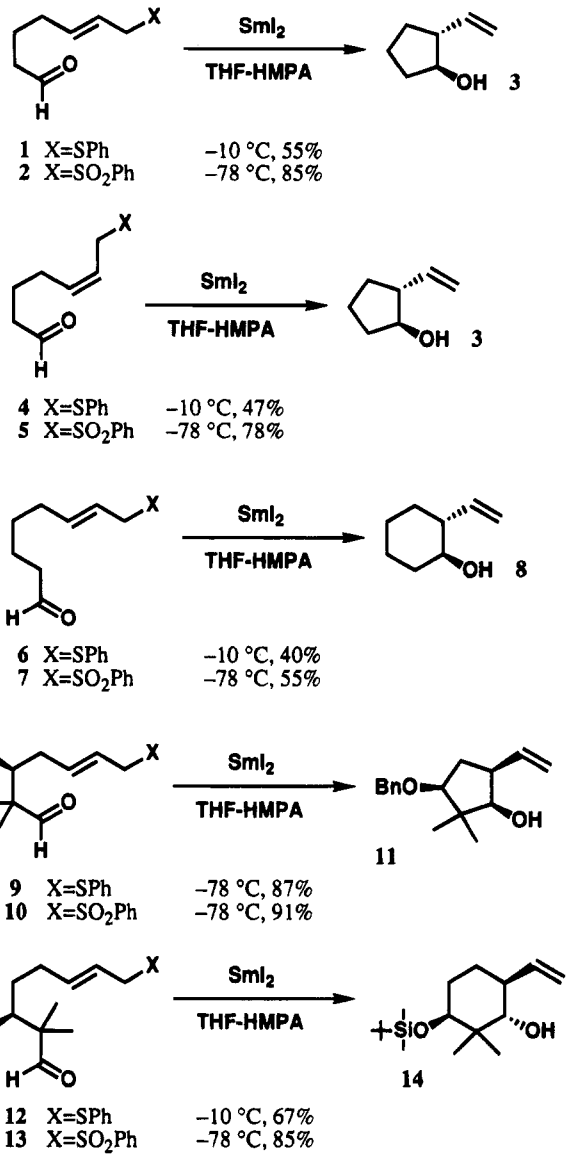
Scheme 1



respectively obtained as the sole product in excellent yields. Obviously, the allyl sulfones have proven to be superior as a radical acceptor to the corresponding allyl sulfides. Optimum reaction conditions for these self-terminating 5- and 6-*exo-trig* radical–alkene cyclizations[6] of the allyl sulfides and sulfones involved the slow addition of a solution of the starting materials in tetrahydrofuran (THF) to a 0.1 M solution of samarium(II) iodide containing 8 equiv of HMPA in THF at −10 and −78 °C, respectively. Reactions run in the presence of methanol provided only low yields of the cyclization products with simple reduction of the aldehyde as a major side reaction. In contrast to these highly stereocontrolled ring annulation reactions, the intramolecular reductive coupling of the corresponding α,β-unsaturated esters, namely methyl (*E*)-7-oxo-2-heptenoate, (*Z*)-7-oxo-2-heptenoate, and (*E*)-8-oxo-2-octenoate, produced mixtures of the corresponding *trans*- and *cis*-diastereomers in ratios of 5:1, 2:1, and 4:1 and in modest yields (66%, 61%, 34%), carrying out the reactions in the presence of methanol in a similar way (−10 °C) to that of the allyl sulfides **1**, **4**, and **6**.[2f,g] Moreover, the presence of methanol was essential for these ketone–olefin couplings promoted by samarium(II) iodide.[2,7] Similar intramolecular couplings mediated by samarium(II) iodide of the allyl sulfide **9**[8] and sulfone **10**[8] led to exclusive generation of the functionalized *cis*-cyclopentanol **11**[9] upon performing the reactions under the same conditions (−78 °C) as those for the allyl sulfones **2**, **5**, and **7**. It is noteworthy that a single stereochemical result was obtained from four possible products. Indeed, when the corresponding α,β-unsaturated methyl ester was treated with samarium(II) iodide in the presence of methanol in a manner (−78 °C) similar to that of **9** and **10**, the mixture of the four diastereomers was obtained in a 3:3:1:1 ratio and 76% yield. Strikingly, in spite of carrying out the reaction of the allyl sulfide **9** at −78 °C, the cyclization product **11** was generated very cleanly as well as with the corresponding allyl sulfone **10**. On the other hand, the homologous allyl sulfide **12**[8] and sulfone **13**[8] were cyclized with complete diastereoselectivity utilizing the optimized reaction conditions for the allyl sulfides **1**, **4**, **6** (−10 °C) and sulfones **2**, **5**, **7** (−78 °C), respectively. Thus, the *trans*-cyclohexanol **14**[10] was derived from **12** and **13** in moderate and excellent yields, respectively.[11] Undoubtedly, the cyclizations of **9**, **10**, **12**, and **13** were facilitated by the presence of a *gem*-dimethyl group in the cyclizing chain. Especially, the 5-*exo-trig* cyclizations successfully occurred with the aid of the *geminal* substitution in the trimethylene chain. Interestingly, the *trans* stereochemistry about the hydroxyl and adjacent vinyl groups was observed except for the case of the allyl sulfide **9** and sulfone **10**. Many of the ketone–olefin cyclizations induced by samarium(II) iodide have demonstrated preferred *trans* arrangement of the appendages.[2a–d,f,g,n] The preferred *cis* cyclizations of the allyl sulfide **9** and sulfone **10** may be ascribed to the extremely high rate of the reductive coupling cyclizations.

(5) Stereochemical assignment for (1*S**,2*R**)-2-vinyl-1-cyclohexanol (**8**) followed directly from its ^{1}H-NMR spectrum. The $J_{1,2}$ of 9.8 Hz is agreement with the axial–axial relationship between the C_1- and C_2-protons, that is, the *trans-vicinal* stereochemistry.

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(8) The allyl sulfides **9**, **12**, **15**–**20** and sulfones **10**, **13** were synthesized from (*S*)-5-[(4-methoxyphenyl)methoxy]-4,4-dimethyl-1,3-pentanediol prepared from 2-(2-hydroxy-1,1-dimethyl)-1,3-dioxolane in six steps through Sharpless asymmetric epoxidation. For the preparation of the starting material, see: Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469.

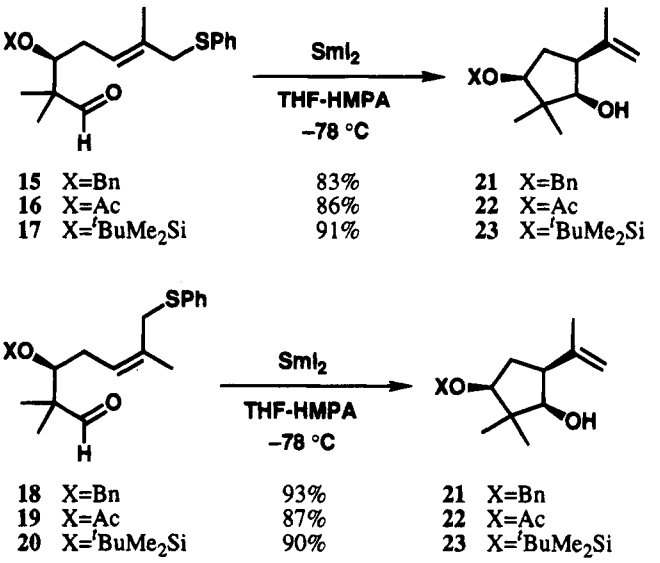
(9) In each case of the 2D-NOESY spectra of the acetates derived from the *cis*-cyclopentanols **11** and **21**, NOEs were observed between the three methine protons. The *cis*-cyclopentanols **21**, **22**, and **23** were independently deprotected to give the same *cis*-cyclopentanediol. Therefore, stereostructure of the *cis*-cyclopentanols **11**, **21**, **22**, and **23** was distinctly established.

(10) The relative stereochemistry of (1*S*,3*S*,6*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethyl-6-vinyl-1-cyclohexanol (**14**) was established by means of the *vicinal* coupling constants for the protons attached to the 6-membered ring. The coupling constants ($J_{1,6} = J_{5ax,6} = 10.3$ Hz, $J_{5ax,4ax} = 11.2$ Hz, and $J_{3,4ax} = 2.0$ Hz) indicated a chair conformation. In the conformation, the hydroxyl and vinyl groups occupy equatorial positions, while the (*tert*-butyldimethylsilyl)oxy group adopts the axial position.

(11) Interestingly, the samarium(II) iodide promoted cyclization of the corresponding α,β-unsaturated methyl ester exclusively afforded a 51% yield of the *trans*-hydroxy ester having the same relative stereochemistry between the three asymmetric centers to that of the *trans*-cyclohexanol **14**, upon performing the reaction in the presence of methanol under the same conditions (−10 °C) as those of the allyl sulfide **12**.

Apparently, this new annulation process possesses considerable synthetic utility not only because of the observed high diastereoselectivity but also because of the exceptional synthetic versatility of the cyclization products. Actually, the impact potential of this new methodology on organic synthesis is clearly evident during the total synthesis of (−)-grayanotoxin III.[12] In conjunction with the total synthesis, reductive cyclizations of the various trisubstituted allyl sulfides **15**−**20**[9] were examined (Scheme 2). As expected from the cyclizations of the allyl sulfide **9**, when the (*E*)-allyl sulfides **15**, **16**, and **17** were treated with samarium(II) iodide under the same conditions as those for **9**, the reductive couplings occurred in a completely stereocontrolled manner to exclusively give the *cis*-cyclopentanol **21**, **22**, and **23**,[10] respectively, in excellent yields. Obviously, relative stereochemistry between the three chiral centers of these cyclization products **21**, **22**, and **23** was consistent with that of the *cis*-cyclopentanol **11** derived from **9**. The same cyclizations of the corresponding (*Z*)-allyl sulfides **18**, **19**, and **20** with samarium(II) iodide afforded the same alcohols **21**, **22**, and **23**, respectively, as the sole product. Conveniently, stereochemical control at the three stereocenters was not affected by changing the geometry of the olefinic part and the alkoxyl groups of the substrates **15**−**20**. On the basis of the stereoselective cyclization mediated by samarium(II) iodide using allyl sulfides as a ketyl radical acceptor, one of the 5-membered rings of (−)-grayanotoxin III (A-ring) has been effectively cyclized with complete diastereoselectivity.[12]

Scheme 2



Supplementary Material Available: Typical experimental procedures for the samarium(II) iodide induced cyclizations, as well as physical and spectroscopic data for all cyclization products (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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