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Acetoxyl Group Directed Cyclization Promoted by SmI_2: Directing Group Determined Stereocomplementarity

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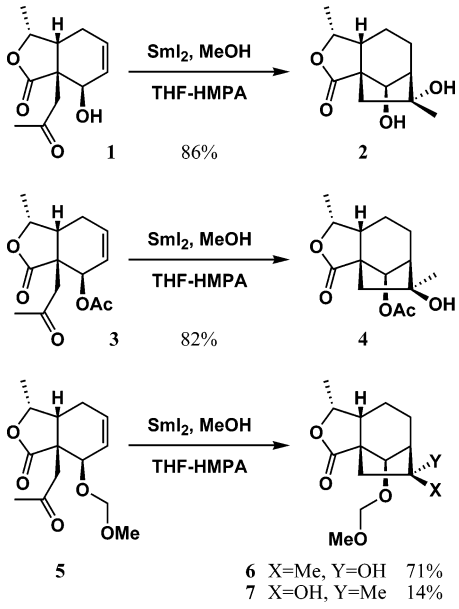
Abstract: Complete reversal of diastereoselectivity was observed in the SmI_2-promoted ketyl−olefin coupling cyclizations of the hydroxy ketone or aldehyde and its acetate. For example, the stereodivergent synthesis of the epimeric five-membered-ring alcohols **2** and **4** has been accomplished through the SmI_2-induced ketyl−olefin coupling cyclizations of the δ-hydroxy ketone **1** and δ-acetoxy ketone **3**.

Samarium(II) iodide (SmI_2) has become an exceedingly reliable reagent for promoting the reductive coupling reactions difficult to accomplish by any other existing methodologies.[1] For example, the Barbier reactions, Reformatsky reactions, ketone-olefin reductive couplings, and pinacol couplings have been reported. Previous research from this laboratory established the powerful influence of a pendant hydroxyl group in directing the stereochemical course of the reductive cyclizations promoted by SmI_2.[2,3] All of these hydoxyl-directed carbon−carbon bond formation reactions proceed with good yields and provide entry into highly functionalized molecules with excellent stereocontrol, and the sense of the diastereoselectivity was in full accord with a chelation-control model. As a result of further investigations, we have now discovered another type of substrate-directable annulation reaction promoted by SmI_2. During the stereocontrolled cyclization, when the directing hydroxyl group was protected as its acetate ester, the SmI_2-induced reductive coupling of the acetate was controlled by the acetoxyl group with a complete reversal of diastereoselectivity.[4,5] In this paper, we describe this new and highly stereoselective cyclization mediated by SmI_2.

SCHEME 1. Cyclization of Five-Membered Rings



The features of this new process are exemplified in the cyclization reactions of the γ-hydroxy ketone **1** and γ-acetoxy ketone **3** (Scheme 1). As previously reported, the hydroxyl-directed cyclization of **1** resulted in the exclusive generation of the diol **2**.[2c] Remarkably, the SmI_2-induced cyclization of the corresponding γ-acetoxy ketone **3** proceeded with opposite diastereoselectivity, providing the alcohol **4** as the sole product.[6] In these coupling products **2** and **4**, the stereochemistry about the new tertiary hydroxyl group is opposite. In contrast to these stereocomplementary cyclizations, the SmI_2-mediated coupling of the γ-methoxymethyoxy ketone **5** gave the epimeric mixture of the alcohols **6** and **7** (5:1).

As shown in Scheme 2, similar stereocomplementarity was also observed during the transformation of the carbohydrate templates, the δ-hydroxy aldehyde **8**, and

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(1) Reviews: (a) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (b) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (c) Molander, G. A. *Chem. Rev.* **1992**, *92,* 29. (d) Molander, G. A.; Harris, R. H. *Chem. Rev.* **1996**, *96*, 307.

(2) (a) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391. (b) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532. (d) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (e) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (f) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 987. (g) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (h) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479. (i) Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252. (j) Kan, T.; Nara, S.; Ozawa, T.; Shirahama, H.; Matsuda, F. *Angew. Chem.* **2000**, *112*, 363; *Angew. Chem., Int. Ed.* **2000**, *39*, 355.

(3) Recently, the SmI_2-mediated 5- and 6-*exo-trig* cyclizations stereocontrolled by hydroxyl groups have been reported by Molander and Losada. During these hydroxyl-directed transformations, the observed diastereoselectivity can be rationalized by the chelation-control model proposed by us: Molander, G. A.; Losada, C. P. *J. Org. Chem.* **1997**, *62*, 2935.

(4) In contrast, acetylation of the directing hydroxyl groups resulted in complete depression of the ability of the substrates to undergo the coupling reactions in several of the SmI_2-mediated coupling cases already reported: ref 2b,d,i.

(5) Complete stereocomplementarity was also observed in the intermolecular, SmI_2-promoted ketone-olefin coupling chelation-controlled by the α-hydroxyl and α-(alkoxycarbonyl)amino groups: (a) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (b) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371.

(6) The relative stereochemistry of **4** was verified as follows. Removal of the acetyl group of **4** via basic hydrolysis gave the diol (the epimer of the diol **2** with regard to the tertiary hydroxyl group), of which the physical and spectral data were completely identical with those of the authentic sample having definite stereochemistry. For the synthesis of the authentic diol (the epimer of the diol **2**) see: Kan, T.; Oikawa, M.; Hosokawa, S.; Yanagiya, M.; Matsuda, F.; Shirahama, H. *Synlett* **1994**, 801, 805.

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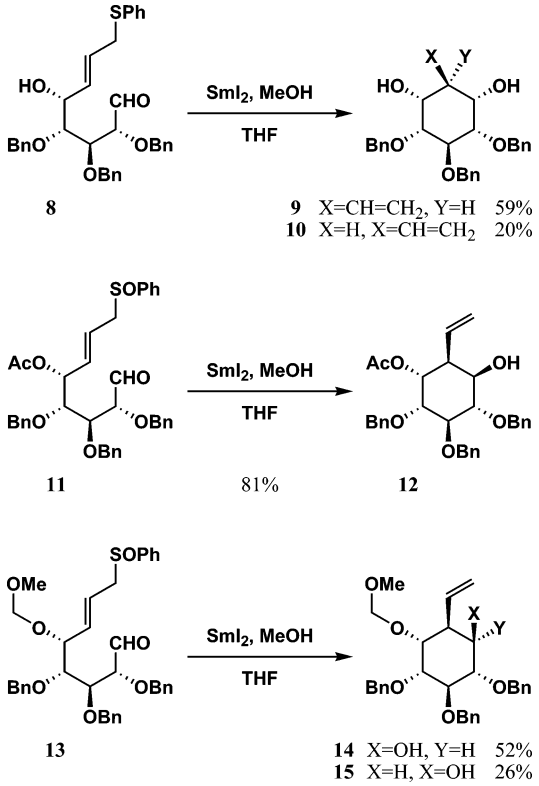
SCHEME 2. Cyclization of Six-Membered Rings



δ-acetoxy aldehyde **11** prepared from methyl β-D-glucopyranoside into the six-membered carbocycles.[7] As previously described, the *cis*-1,3-cyclohexanediols **9** and **10** (3:1) were exclusively obtained through the hydroxyl-directed coupling mediated by SmI_2 of the δ-hydroxy aldehyde **8**.[2j] On the other hand, the annulation reaction of the δ-acetoxy aldehyde **11** was controlled by the δ-acetoxyl group. When **11** was reacted with SmI_2, the self-terminating cyclization[8] proceeded with complete stereochemical control to furnish the cyclohexanol **12** as the sole product.[9] In the cyclization product **12**, the relative stereochemistry between the hydroxyl and acetoxyl groups is trans on the newly formed six-membered ring. In contrast, the SmI_2-induced coupling of the δ-methoxymethyoxy aldehyde **13** gave a mixture of the epimeric alcohols **14** and **15** (2:1).

The observed *cis*-1,3-diol stereochemistry of the diols **2**, **9**, and **10** may be explained by assuming a chelation-control model as illustrated in Figure 1.[2,3] Thus, chelation of the Sm(III) cation generated during the initial single-electron transfer from SmI_2 to the γ-hydroxy ketone **1** or

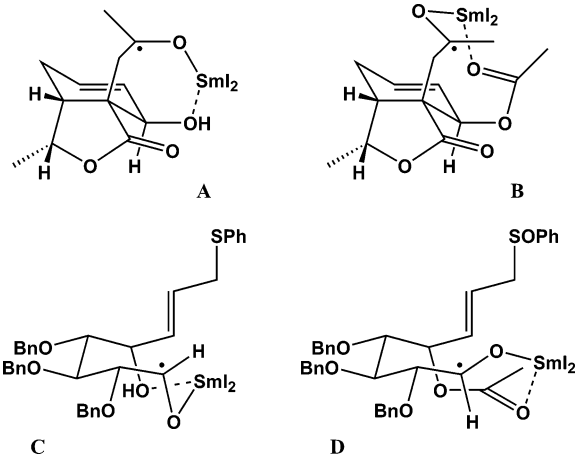


FIGURE 1. Chelation-control model.

δ-hydroxy aldehyde **8** with the hydroxyl group produces the cyclic ketyl radicals **A** or **C**. The ketyl radial center adds to the olefinic part to form the carbon−carbon bond with complete stereoselectivity. On the other hand, the hypothesis that the ketyl-radical addition reaction proceeds involving the coordination of the carbonyl oxygen atom of the acetoxyl group to the Sm(III) cation attached to the ketyl radical, as shown in **B** or **D** during the cyclization of the γ-acetoxy ketone **3** or δ-acetoxy aldehyde **11**, may account for the observed dramatic reversal of diastereoselectivity.

As described in this paper, we are able to reveal the ability of the acetoxyl group to change the stereochemical course of the SmI_2-induced ketone-olefin cyclization as compared to the case where the hydroxyl group is free. From a synthetic point of view, the observed stereocomplementarity is highly advantageous because it enhances the possibilities of application to divergent synthesis of products with complementary stereochemistry about the newly formed hydroxyl group.[5]

Experimental Section[10]

Cyclization of 1. To a solution of **1** (70.0 mg, 0.263 mmol), MeOH (0.32 mL, 7.90 mmol), and HMPA (0.92 mL, 5.29 mmol) in THF (1.0 mL) cooled at −78 °C was added a 0.10 M THF solution of SmI_2 (13.2 mL, 1.32 mmol). The mixture was stirred at −78 °C for 2 h, quenched with saturated aqueous NH_4Cl, and extracted with AcOEt. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel column chromatography (AcOEt/hexane, 40:60) to give **2** (57.7 mg, 82%) as white crystals: mp 139−140 °C; $[\alpha]^{25}_D$ +38.4 (*c* 0.900, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1750, 1730, 1450, 1350, 1250, 1020, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, d, *J* = 7.0 Hz), 1.57 (3H, s), 1.73 (1H, d, *J* = 13.5 Hz), 2.08 (3H, s), 2.53 (1H, m), 2.64 (1H, d, *J* = 13.5 Hz), 4.70 (1H, dq, *J* = 8.2, 7.0 Hz), 5.35 (1H, s); MS (FAB-MS) *m/z* 269 [M^+ + H]. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.82; H, 7.47.

Cyclization of 11. To a solution of **11** (85.0 mg, 0.136 mmol) in a mixture of THF (1.6 mL) and MeOH (1.0 mL) cooled at −78 °C was added a 0.10 M THF solution of SmI_2 (3.40 mL, 0.340 mmol). After being stirred at −78 °C for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification

(7) In the past decade, organic chemists have paid much attention to the conversion of carbohydrates to carbocycles. Now, a wide range of highly functionalized cyclopentane and cyclohexane derivatives have been made from sugar, the particular advantage being gained by the passing of chirality from the starting material to the product; review: Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.

(8) Utilization of the allyl sulfoxide as a ketyl radical acceptor is essential for the SmI_2-induced annulation reactions of the aldehydes **11** and **13** in contrast to that of the allyl sulfide **8**. Treatment of the corresponding allyl sulfides with SmI_2 affected the reduction of the aldehyde moieties to afford the primary alcohols. We reported the stereoselective cyclization mediated by SmI_2 using allyl sulfides and sulfones as a ketyl radical acceptor: Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111.

(9) The stereostructure of **12** was confirmed by 2D-COSY and 2D-NOESY experiments on **12**.

(10) The reactions of compounds **5** and **13** were performed under the same conditions as for the transformations of **3** and **11**.

by silica gel column chromatography (AcOEt/hexane, 40:60) gave **12** (55.3 mg, 81%) as a colorless oil: $[\alpha]^{25}_{D}$ −32.5 (*c* 0.300, $CHCl_3$); IR (neat) 3410, 2920, 1745, 1655, 1460, 1375, 1255, 1090, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.12 (3H, s), 2.93 (1H, br s), 3.55 (1H, t, J = 9.1 Hz), 3.76 (1H, dd, J = 3.5, 9.1 Hz), 3.85 (1H, t, J = 9.1 Hz), 3.98 (1H, dd, J = 5.4, 9.1 Hz), 4.52, 4.68, 4.70, 4.76, 4.93, 4.99 (each 1H, d, J = 11.0 Hz), 5.26 (1H, d, J = 18.1 Hz), 5.28 (1H, d, J = 10.0 Hz), 5.46 (1H, t, J = 3.5 Hz), 5.79 (1H, ddd, J = 7.6, 10.0, 18.1 Hz), 7.27−7.40 (15H, m); MS (EI) *m/z* 502 [M^+]. Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 73.95; H, 6.98.

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