Zirconium-Mediated, Highly Diastereoselective Ring Contraction of Carbohydrate Derivatives: Synthesis of Highly Functionalized, Enantiomerically Pure Carbocycles

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Ring contraction of carbohydrate derivatives is one of the significant methods for constructing functional, enantiomerically pure carbocycles,[1,2] which have considerable utility in the synthesis of biologically active compounds.[3] In recent contributions, intramolecular radical cyclization[1b,c,4] or metal-mediated intramolecular coupling reactions[5] of carbohydrate derivatives are noteworthy.

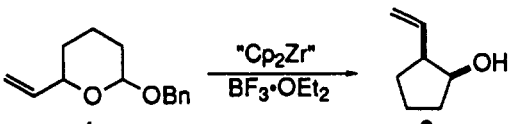
Recently, generation and reactions of zirconacycles, which could be easily prepared by treating a zirconocene equivalent ("Cp_2Zr") with unsaturated compounds, have been extensively developed.[6] During the course of our studies of the "Cp_2Zr" chemistries,[7] we have reported a method for preparing allylic zirconiums by treating allyl ethers with "Cp_2Zr" (Scheme I). To extend the possibility of our allylic zirconium chemistry, we examined the intramolecular cyclizations of allylic zirconium reagents. We report herein the novel "Cp_2Zr"-mediated, highly stereoselective ring contraction of vinyl carbohydrate derivatives and a reaction mechanism based on an NMR study of the reactive allylic zirconium intermediate.

In the initial work with the 6-vinyl cyclic acetal derivatives **1**, the ring contraction proceeded smoothly to give *cis*-2-vinylcyclopentanol (**2**) as a single isomer (87% yield)[8] under the conditions of "Cp_2Zr" and BF_3·OEt_2 in THF (Scheme II).[9] This procedure was applicable to vinyl carbohydrate derivatives (**3**, **5**, **7**, **10**, **11**, **13**, and **16**),[10] and the results are shown in Table I.[11] 5-Vinylpyranoside **3**, which is easily prepared from methyl α-D-glucopyranoside, was converted to carbocycle **4** in toluene by sequential treatment with "Cp_2Zr" and BF_3·OEt_2 in 65% yield as a single isomer (entry 1). In the absence of BF_3·OEt_2, uncyclized aldehyde **18** was obtained (80%) after acidic hydrolysis, along with a trace amount of **4**. This fact suggests the presence of a stable intermediate which is converted to **4** or **18** upon addition of BF_3·OEt_2 or 1 N HCl (*vide infra*). Similar treatment of **5** with "Cp_2Zr" in THF followed by addition of BF_3·OEt_2 gave carbocycle **6** in excellent diastereoselectivity in 75% yield (entry 2). The stereochemistry of the product was unaffected by the absence or presence of BF_3·OEt_2. Our strategy was also applicable to the synthesis of highly functionalized cyclobutane derivatives. In the reaction of methyl D-glucofuranoside derivatives **10** and **11**, both anomeric isomers gave cyclobutane derivative **12** in low yields without any difference in reactivity (entries 4 and 5).[12] Replacement of the 3-alkoxyl group of **10** by a hydrogen atom, 3-deoxyfuranoside (**13**), or a benzyloxymethyl substituent, 3-deoxy-3-(benzyloxymethyl)furanoside (**16**), improved the yield of products (**14**, **15**, and **17**) significantly (60% and 77%, entries 6 and 7) under the influence of BF_3·OEt_2.

In all cases examined, complete *cis*-selectivity between the hydroxyl and vinyl groups is noteworthy. The stereochemical relationships between the new chiral centers and inherent carbohydrate substituents in the products were heavily dependent on the stereochemistry of the 4- or 3-substituent of the starting pyranoside or furanoside, respectively, rather than the stereo-

Scheme I

Scheme II



1 **2**

87% *cis* only

(1) Recent reports on ring contraction of cyclic ethers to carbocycles: (a) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375–377. (b) Vite, G. D.; Alonso, R. A.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268–2271. (c) Alonso, R. A.; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573–584.

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(3) For reviews, see: (a) Ogawa, S. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 26–39. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623. (c) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768. See also: (d) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745–8747. (e) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444–458, and references cited therein.

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(5) (a) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841–5843. (b) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463–6465. (c) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128–7135.

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(7) (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295–1298. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769–3772. (c) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469–4472. (d) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873–7876. (e) Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774–775.

(8) The *cis*-stereochemistry of **2** was confirmed by comparing the NMR spectrum with that of the reported *trans*-isomer, see: (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451. (b) Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 779–789.

(9) Typical experimental procedure: to a solution of $Cp_2Zr(nBu)_2$, prepared *in situ* by the reaction of zirconocene dichloride (246 mg, 0.84 mmol) in THF or toluene (4 mL) with 2 equiv of *n*-butyllithium in hexane at −78 °C for 1 h, was added a solution of starting vinyl carbohydrate (0.7 mmol) in THF or toluene (3 mL) at −78 °C, and the temperature was raised to ambient temperature. After being stirred for 3 h, a solution of BF_3·OEt_2 (1.4 mmol) in THF or toluene (2 mL) was added at 0 °C, and stirring was continued for 2 h at ambient temperature. Next, 1 N HCl was added and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

(10) Preparative procedures of starting carbohydrate derivatives (**3**, **5**, **7**, **10**, **11**, **13**, and **16**). **3** and **7** were prepared from methyl α-D-glucopyranoside and methyl α-D-mannopyranoside, respectively, according to an analogous method reported for **5**. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *J. Antibiot.* **1991**, *44*, 456–458. **10** and **11** were prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Sherk, A. E.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 932–935. **13** was prepared according to the above-mentioned procedure from 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranoside. Iacono, S.; Rasmussen, J. R. *Org. Synth. Collect. Vol. VII* **1990**, 139–141. **16** was prepared as in the case of **10** and **11** from 3-*C*-(benzyloxymethyl)-3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-5-hexeno-furanose. Nakata, M.; Enari, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3283–3296.

(11) All products are new compounds, and the structures were determined by ^1H and ^{13}C NMR, phase-sensitive NOESY, HRMS, and combustion analysis. Full details are described in supplementary material.

(12) The reaction was carried out without using BF_3·OEt_2. The addition of BF_3·OEt_2, as in the case of pyranoside derivatives, gave a complex reaction mixture, and the yield of the desired product was much lower.

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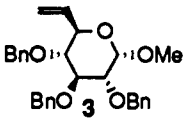
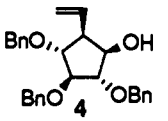
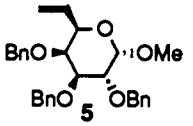
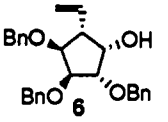
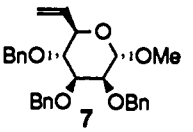
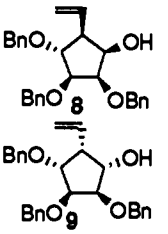
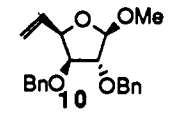
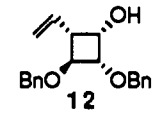
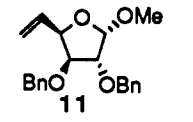
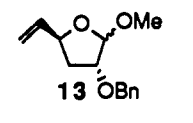
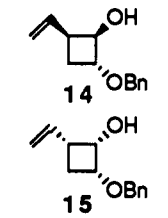
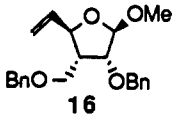
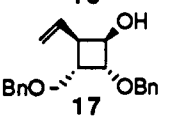
Table I. "Cp_2Zr"-Mediated Ring Contraction Reaction

entry	substrate[10]	product[11]	yield (%)[a]
1			65[b]
2			75 (47)[b]
3			49 8:9=13:1
4			(25)[b]
5			(36)[b]
6			60 14:15=3:1
7			77[b]

[a] Numbers in parentheses are yields in the absence of Lewis acid. [b] >98% de. Minor isomer could not be detected with 300-MHz ^{1}H NMR.

chemistry of the 2-substituent of the starting compound (entries 3 and 6). The stereochemistry of the vinyl group in all of the products was *trans* to the adjacent benzyloxy or benzyloxymethyl group. It deserves comment that the diastereoselectivity between the new chiral centers and the benzyloxy group in the reaction of **13** is conspicuously low compared to other reactions (entry 6).

The origin of the complete stereoselectivity in the present ring contractions was investigated by obtaining clean NMR spectral data of the intermediate **19** derived from **3** and "Cp_2Zr" in toluene without adding BF_3·OEt_2 (*vide ante*) as shown in Scheme III.[13] Significant features of the NMR spectrum of **19** were the olefin

(13) ^{1}H NMR (400 MHz, benzene-d_6): δ 7.71–7.07 (m, 15 H, aromatic), 6.51 (dt, J = 8.0, 10.3 Hz, 1 H, 4-H), 5.94 (s, 5 H, Cp), 5.62 (s, 5 H, Cp), 5.11 (s, 1 H, 9-H), 5.10 (d, J = 11.5 Hz, 1 H, benzylic), 5.04 (d, J = 11.5 Hz, 1 H, benzylic), 5.03 (t, J = 10.3 Hz, 1 H, 5-H), 4.85 (d, J = 11.5 Hz, 1 H, benzylic), 4.82 (d, J = 11.5 Hz, 1 H, benzylic), 4.71 (d, J = 11.5 Hz, 1 H, benzylic), 4.66 (d, J = 11.5 Hz, 1 H, benzylic), 4.50 (m, 1 H, 6-H), 3.84–3.79 (m, 2 H, 7- and 8-H), 2.98 (s, 3 H, OMe), 2.74 (t, J = 10.3 Hz, 1 H, 3-H'), 0.98 (dd, J = 8.0, 10.3 Hz, 1 H, 3-H). ^{13}C NMR (100.6 MHz, benzene-d_6): δ 141.2, 140.6, 139.8, 139.6, 129.2–127.1 (aromatic), 115.2, 110.8, 110.5, 103.2, 82.7, 81.1, 75.3, 75.1, 74.2, 68.0, 54.6, 42.4.

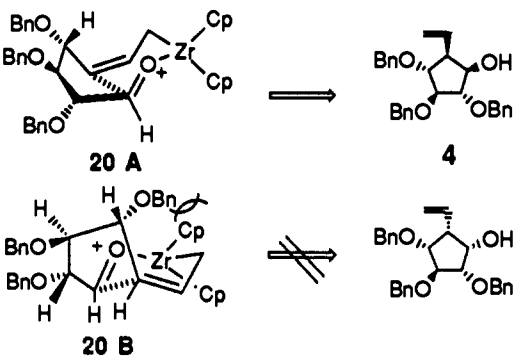
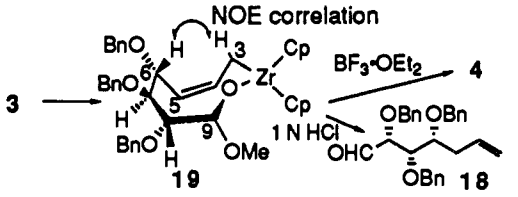


Figure 1. Diastereofacial differentiation of the allylic zirconium double bond in the oxocarbenium transition state.

Scheme III



protons at 6.51 and 5.03 ppm with a *cis* coupling constant (10.3 Hz)[14] and the absence of an aldehyde proton. The *cis* relationship of olefinic portion was further confirmed by the significant NOE correlations between the olefinic protons and also between the allylic protons (Scheme III). The proof of **19** as an intermediate in the reaction of **3** (entry 1) was confirmed by the conversion of **19** to **4** upon addition of BF_3·OEt_2. It is probable that BF_3·OEt_2 accelerates the elimination of the methoxyl group through coordination to the methoxy oxygen of **19** to form oxocarbenium ion **20A** or **20B**. The stereoselectivity of the present reaction can be explained by comparing the pseudochair transition-state models of **20A** and **20B** (Figure 1). It is obvious that the sterically favored transition state is **20A**. Therefore, it is reasonable that the low diastereoselectivity of the deoxy derivative **13** is a result of the inability of the substituent at the 3-position of the furanoside to control the stereochemistry of the product. The easy access to a variety of vinyl carbohydrate derivatives should make this approach a viable method for the preparation of enantiomerically pure and highly functionalized carbocycles.

In conclusion, we opened a new avenue for an efficient and stereoselective construction of highly functionalized carbocycles by applying "Cp_2Zr" chemistry to carbohydrate derivatives. The present procedure provides an alternative method to the reported procedure[1-5] for the preparation of highly functionalized optically pure carbocycles.

Acknowledgment. We thank Professor H. Shindo and Mrs. C. Sakuma at Tokyo College of Pharmacy for helpful discussion on the NMR experiments.

Supplementary Material Available: ^{1}H, ^{13}C NMR spectra and listing of specific rotation, IR, HRMS, elemental analysis, and NOE data of products **4**, **6**, **8**, **9**, **12**, **14**, **15**, and **17** (20 pages). Ordering information is given on any current masthead page.

(14) The olefinic coupling constants 14–16 and 12 Hz for the (*E*)- and (*Z*)-allylic zirconium derivatives, respectively, have been reported. See: Mashima, K.; Asami, K.; Yasuda, H.; Nakamura, A. *Chem. Lett.* **1983**, 219–222.