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Improved synthetic method for preparing spiro α-chloroepoxides

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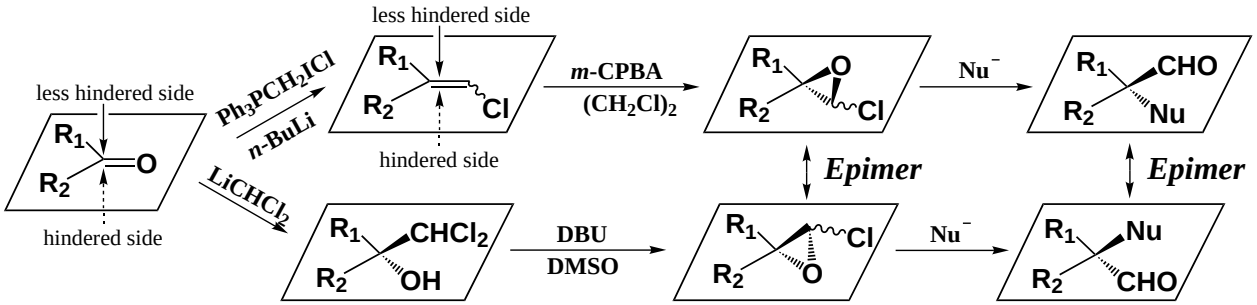
Abstract—A new synthetic method via α-chloroolefine derivatives for preparing epimers of spiro α-chloroepoxides (2-chlorooxyrane derivatives), which are useful key intermediates for the synthesis of branched-chain functionalized compounds, is developed as an alternative to previous methods requiring dichloromethyllithium.

In previous papers,[1] one author reported a facile, effective and simple reagent, dichloromethyllithium, for synthesizing various functionalized branched-chain sugars to be used as 'chirons'[2] via 2,2-dichloroethanol and spiro α-chloroepoxy derivatives. However, this method is not totally efficient for the synthesis of functionalized branched-chain sugars having the required configuration at the branching carbon atom other than α-hydroxyaldehyde derivatives,[1a,1c] because the configurations of the products depend on the stereoselectivity of the reaction between the carbonyl compounds and dichloromethyllithium, which attacks from the less hindered side.[3] In order to develop a procedure for constructing functionalized branched-chains, we have conducted experiments to obtain the epimers of spiro α-chloroepoxides which are not synthesized by previous methods.

One author has reported methods for synthesizing both epimers of unsubstituted spiro epoxides from the same carbohydrate carbonyl compounds and the stereoselectivities attained in the reaction of carbonyl compounds with various nucleophiles.[3] The results show that the configurations of the oxygen of the products of the reactions between carbohydrate carbonyl compounds with general nucleophiles and the corresponding products derived from carbohydrate *exo* olefine compounds with peracid are complementary. Considering the above results, we adopted a synthetic route via chloroolefine to obtain the epimers of spiro α-chloroepoxides instead of those synthesized in the reaction of a carbonyl compound with dichloromethyllithium.

In 1978, Miyano et al. reported[4] a reagent, chloromethyltriphenylphosphonium iodide,[5] which can



Scheme 1.

Keywords: carbonyl compounds; carbohydrates; Wittig reactions; epoxidation.

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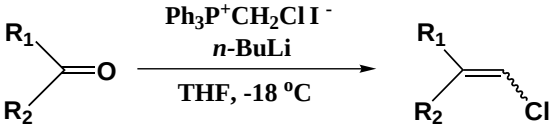
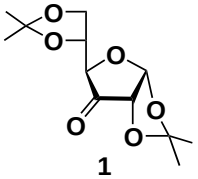
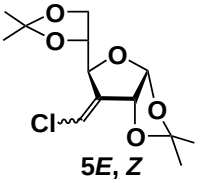
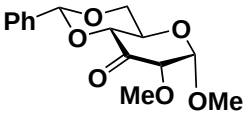
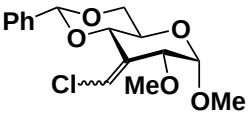
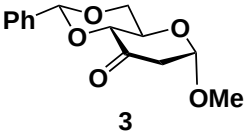
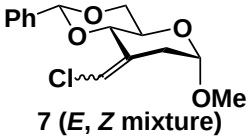
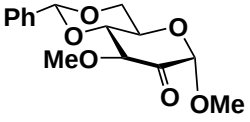
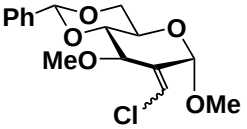
be utilized for the conversion of aldehydes and ketones into chloroolefins. We designed chloroolefins which could be easily converted into chloroepoxides using organic peracid via the same stereochemical course as reported[6] (Scheme 1). In this work, we selected carbohydrate carbonyl compounds as the substrates in order to easily confirm the stereochemistry.

As substrates, 1,2:5,6-di-*O*-isopropyden-α-D-*ribo*-hexofuranose-3-ulose (**1**),[7,8] methyl 4,6-*O*-benzyliden-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (**2**),[9] methyl 4,6-*O*-benzyliden-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**3**),[10,11] methyl 4,6-*O*-benzyliden-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**4**)[12] were prepared by Swern oxidation[8,13] of the corresponding hydroxy derivatives in almost quantitative yields. The reaction of **1**–**4** with chloromethyltriphenylphosphonium iodide (3.0 equiv.) and *n*-BuLi (1.5 mol/L in hexane, 2.8 equiv.) in THF at −18°C gave the corresponding α-chloroolefin derivatives **5**–**8** (*E*, *Z* mixture) in good yields. The results are shown in Table 1. All the products consist of *E* and *Z* diastereomer mixtures, of which only **5** was isolated and identified. The compounds **5** (*E* and *Z*) were purified with preparative TLC (hexane–ethyl acetate = 3:1, v/v) to separate each isomer. Both the *E* and *Z* diastereomers were oxidized with *m*-chloroperbenzoic acid (*m*CPBA) (5.0 equiv.) in 1,2-dichloroethane at 70°C. Both compound **5** (*E*: more polar) and **5** (*Z*: less polar) gave the corresponding unstable spiro α-chloroepoxide **9** (*S*) and **9** (*R*) in 65 and 75% yields, respectively, in almost the same reaction time. The configuration of each product **5** (*E*), **5** (*Z*), **9** (*S*), **9** (*R*) at 3 and 3′-*C* was confirmed by NMR (NOESY). Additionally, the configuration of com-

Table 1. Synthesis of α-chloroolefin derivatives from uloses



Ulose	α-Chloroolefin	Yield (*Diastereomer Ratio**) less polar : more polar
 1	 5*E*, *Z*	79% (1 : 1)
 2	 6 (*E*, *Z* mixture)	83% (1 : 1)
 3	 7 (*E*, *Z* mixture)	83% (1 : 1)
 4	 8 (*E*, *Z* mixture)	80% (2 : 1)

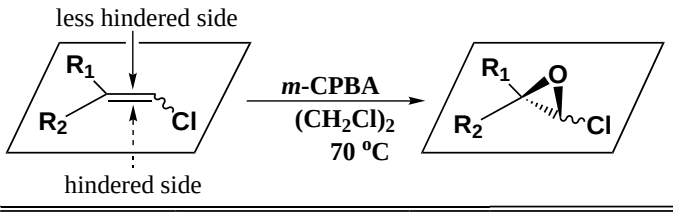
*Determined by NMR spectrum and TLC (Silica gel 60 F_{254}, Merck; Hexane / EtOAc 1 : 1 - 3 : 1).

pounds **9** (*S*) and **9** (*R*) at 3-*C* was supported by converting them into the known unsubstituted spiro epoxides by reduction of chlorine with *n*-Bu_3SnH, AIBN in toluene at 100°C.[14] Under these oxidation conditions, there was no difference in reactivity between the (*E*) and (*Z*) isomers; therefore, the (*E*) and (*Z*) mixtures were used without isolation. The structures of **10**–**12** were confirmed by converting them into the known unsubstituted spiro epoxides[15–17] in a similar manner to that mentioned above. Compounds **9**–**12** are more unstable than the corresponding 3-*C* epimer. The results are summarized in Table 2. These results show that oxygen attacks from the less hindered side to give the corresponding spiro α-chloroepoxide in moderate yields. Thus, we were able to establish a new synthetic procedure for synthesizing epimeric spiro α-chloroepoxides complementary to our previously described method.

Finally, we examined the reaction of **9** (*R*), **9** (*S*), and **10** (*R*,*S* mixture) with NaN_3 and 15-crown-5 in DMSO at 80°C as a model nucleophilic reaction to show the relative reactivities. The results are summarized in Table 3. The epimers of **13** and **14** are not detected in the polar degradation remains. The reaction time and yields were almost the same for both epimers at 3-*C* of **9** and **10**. The structures of α-azidoaldehyde compounds **13** and **14** were confirmed by comparison of their physical constants with compounds prepared from the 3-*C* epimers of the corresponding spiro α-chloroepoxides.[1] NMR data for **13**, **14** and their epimers are summarized in Ref. 18. It is noteworthy that **13** and **14** could not be synthesized by the previously described methods. According to our previous work, other nucleophiles such as H^- and AcO^- may react in a similar manner to that reported.[1]

In conclusion, we have elaborated the methods for synthesizing various functionalized branched-chain compounds having the desired configuration at the branching carbon.

Table 2. Oxidation of α-chloroolefin with *m*CPBA



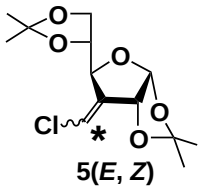
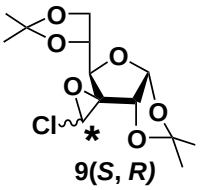
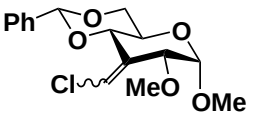
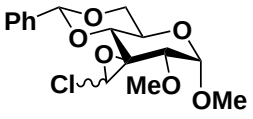
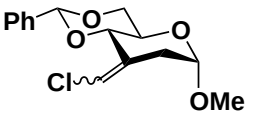
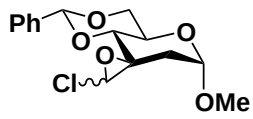
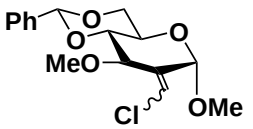
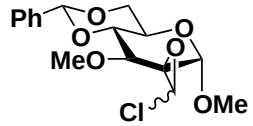
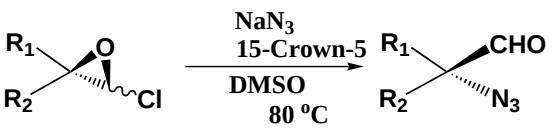
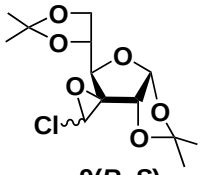
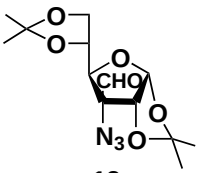
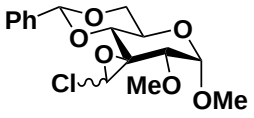
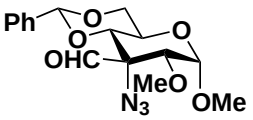
α-Chloroolefin	Spiro α-Chloroepoxide	Yield
 5(*E*, *Z*)	 9(*S*, *R*)	9*S*: 65% from 5*E* 9*R*: 76% from 5Z
 6 (*E*, *Z* mixture)	 10 (*R*, *S* mixture)	10 (*R*, *S* mixture): 69% from 6 (*E*, *Z* mixture)
 7 (*E*, *Z* mixture)	 11 (*R*, *S* mixture)	11 (*R*, *S* mixture): 79% from 7 (*E*, *Z* mixture)
 8 (*E*, *Z* mixture)	 12 (*R*, *S* mixture)	12 (*R*, *S* mixture): 75% from 8 (*E*, *Z* mixture)

Table 3. Nucleophilic reaction of spiro α-chloroepoxides with N_3^-



α-Chloroolefin	Spiro α-Chloroepoxide	Yield
 9(*R*, *S*)	 13	66% from 9(*R*) 65% from 9(*S*)
 10 (*R*, *S* mixture)	 14	52%

References

1. (a) Sato, K.; Suzuki, K.; Ueda, M.; Kajihara, Y.; Hori, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 225–230; (b) Sato, K.; Yamamoto, Y.; Hori, H. *Tetrahedron Lett.* **1996**, *37*, 2799–2800; (c) Sato, K.; Suzuki, K.; Hashimoto, Y. *Chem. Lett.* **1995**, 83–84; (d) Sato, K.; Suzuki, K.; Ueda, M.; Katayama, M.; Kajihara, Y. *Chem. Lett.* **1991**, 1469–1471.
2. Hanessian, S. *Total Synthesis of Natural Products*: *The 'Chiron' Approach*; Pergamon Press: Oxford, 1983.
3. Yoshimura, J.; Sato, K. *J. Synth. Org. Chem. Jpn. (Yuki Gousei Kagaku Kyoukaishi)* **1982**, *40*, 415–426.
4. Miyano, S.; Izumi, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 446–447.
5. Appel, R.; Morbach, W. *Synthesis* **1977**, 699–700.
6. Funabashi, M.; Sato, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 788–790.
7. Yoshimura, J.; Sato, K.; Hashimoto, H. *Chem. Lett.* **1977**, 1327–1330.
8. Baker, D. C.; Horton, D.; Tindall, C. G., Jr. *Carbohydr. Res.* **1972**, *24*, 192–197.
9. Sato, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2116–2121.
10. Rosenthal, A.; Catsoulacos, P. *Can. J. Chem.* **1968**, *46*, 2868–2872.
11. Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612–2614.
12. Miljkovic, M.; Gligorijevic, M.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 2118–2121.
13. Huang, H. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3331.
14. Funabashi, M.; Sato, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 788–790.
15. Funabashi, M.; Hong, N.; Kodama, H.; Yoshimura, J. *Carbohydr. Res.* **1978**, *67*, 139–145.
16. Sato, K.; Yoshimura, J. *Carbohydr. Res.* **1979**, *73*, 75–84.
17. Sato, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2116–2121.
18. The physical data of α-azidoaldehyde compounds **13**, **14** and epimers of **13**, **14**.
13: $[\alpha]_D^{25}$ +92.0 (*c* 1.0, $CHCl_3$); IR ν_{CHO}: 1734 cm^{-1}; ν_{N3}: 2120 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.60 (1H, s, CHO), 5.90 (1H, d, $J_{1,2}=3.6$ Hz, H-1), 4.64 (1H, d, H-2), 4.25 (1H, d, $J_{4,5}=8.3$ Hz, H-4), 4.16 (1H, dd, $J_{6,6'}=10.4$ Hz, H-6), 4.07 (1H, ddd, $J_{5,6'}=5.0$ Hz, H-5), 3.97 (1H, dd, H-6′), 1.61, 1.51, 1.38, 1.35 (12H, each s, $CH_3\times4$), NOE (CHO–H-5: 5.2%; CHO–H-2: 2.8%); elem. anal. ($C_{13}H_{19}O_6N_3$): calcd for C, 49.84; H, 6.11; N, 13.41. Found: C, 49.94; H, 5.92; N, 13.12%. **14**: IR ν_{CHO}: 1728 cm^{-1}; ν_{N3}: 2124 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.90 (1H, s, CHO), 7.65–7.34 (5H, m, Ph), 5.46 (1H, s, Ph–C*H*), 4.96 (1H, dd, $J_{1,2}=4.0$ Hz, H-1), 4.37 (1H, dd, $J_{6a,6e}=10.6$ Hz, H-6e), 4.23 (1H, dd, $J_{4,5}=9.6$. Hz, $J_{5,6e}=5.0$ Hz, $J_{5,6a}=10.6$ Hz, H-5), 3.86 (1H, d, H-4), 3.79 (1H, d, H-2), 3.73 (1H, dd, H-6a), 3.53, 3.39 (6H, each s, $OCH_3\times2$), NOE (no observation); epimer of **13**: $[\alpha]_D^{24}$ +76.9 (*c* 1.8, $CHCl_3$); IR ν_{CHO}: 1736 cm^{-1}; ν_{N3}: 2120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.67 (1H, s, CHO), 5.94 (1H, d, $J_{1,2}=3.4$ Hz, H-1), 4.63 (1H, d, H-2), 4.55 (1H, d, $J_{4,5}=8.5$ Hz, H-4), 4.23 (1H, ddd, $J_{5,6}=3.7$ Hz, $J_{5,6'}=5.9$ Hz, H-5), 4.15 (1H, dd, $J_{6,6'}=8.6$ Hz, H-6′), 4.04 (1H, dd, H-6), 1.61, 1.38, 1.33, 1.31 (12H, each s, $CH_3\times4$), NOE (CHO–H-4: 10.0%); elem. anal. ($C_{13}H_{19}O_6N_3$): calcd for C, 49.84; H, 6.11; N, 13.41. Found: C, 50.04; H, 6.31; N, 13.30; epimer of **14**: $[\alpha]_D^{27}$ +44.5 (*c* 2.0, $CHCl_3$); IR ν_{CHO}: 1732 cm^{-1}; ν_{N3}: 2120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.03 (1H, s, CHO), 7.43–7.26 (5H, m, Ph), 5.54 (1H, s, Ph–C*H*), 4.98 (1H, dd, $J_{1,2}=3.7$ Hz, H-1), 4.40 (1H, dd, $J_{6a,6e}=10.0$ Hz, H-6e), 4.22 (1H, ddd, $J_{4,5}=10.0$ Hz, $J_{5,6e}=4.5$ Hz, $J_{5,6a}=10.0$ Hz, H-5), 3.80 (1H, d, H-4), 3.75 (1H, dd, H-6a), 3.54, 3.52 (6H, each s, $OCH_3\times2$), 3.51 (1H, d, H-2), NOE (CHO–H-5: 37%); elem. anal. ($C_{16}H_{19}O_6N_3$): calcd for C, 55.01; H, 5.48; N, 12.03. Found: C, 55.35; H, 5.71; N, 12.33%.