Stereospecific Construction of Chiral Quaternary Carbon Compounds from Chiral Secondary Alcohol Derivatives

Yukio Masaki,* Hideki Arasaki, and Masashi Iwata
Gifu Pharmaceutical University, 5-6-1 Mitahora-Higashi, Gifu 502-8585

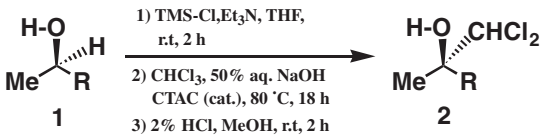
(Received September 13, 2002; CL-020785)

Chiral tertiary dichloromethylcarbinol derivatives, prepared by stereospecific α C–H insertion reaction of dichlorocarbene with protected chiral secondary alcohols, were converted into intermediary α-chloroepoxides which gave stereospecifically chiral quaternary carbon compounds, α-aminoacids via α-azide-aldehydes and α-cyanoacetic acids through cyanation, respectively. The fashion generating the quaternary centers from dichloromethylcarbinols via α-chloroepoxides was proved to be quite different depending on the substrates: inversion of configuration of non-benzylic substrates and apparent retention with benzylic one.

Optically active compounds which contain quaternary carbon stereocenters including tertiary alcohol derivatives, α,α-disubstituted amino acids and their derivatives, and compounds with a quaternary carbon bearing four different carbon substituents are widely distributed in biologically active compounds including medicine.[1] Although much effort has been devoted to synthesize chiral carbon compounds, it still has been a great challenge in organic synthesis to create chiral quaternary carbon stereocenters[2] highly enantioselectively by facile manipulations. Contrary to the scarcity of widely applicable enantioselective synthetic methods for chiral tertiary alcohol derivatives,[3] several excellent practical methods have been developed to obtain chiral secondary alcohol derivatives with nearly perfect enantioselectivity.[4] In the context, we have recently found protected secondary alcohols to undergo stereospecific α C–H insertion reaction with dichlorocarbene generated from chloroform and 50% aqueous NaOH in the presence of a phase transfer catalyst,[5] providing chiral tertiary dichloromethylcarbinol functional group which is believed to be a promising chiral building block. Tertiary dichloromethylcarbinol group has hitherto been made by addition reaction of ketones with dichloromethyl lithium prepared from dichloromethane and LDA,[6] and the group was known to be transformed to α-chloro- and α-hydroxy-aldehyde moieties via α-chloroepoxide functionality albeit with stereochemical ambiguity.[7] Recently Sato, et al.,[8a] Deloisy, et al.,[8b] Nakamura, et al.,[8c] and Yoshikawa, et al.[8d] have reported diastereoselective addition reactions of dichloromethyl lithium with cyclic ketones derived from a sugar and with a carbonyl group on the side chain of a sugar derivative to give dichloromethylcarbinol intermediates which were led to α-chloro-, α-hydroxy-, and α-azide-aldehydes via unstable α-chloroepoxides. More recently, Satoh has developed another route to α-chloroepoxides by oxidation of 2,2-disubstituted 1-chloroolefins with m-chloroperbenzoic acid.[9] They have claimed that the transformations of α-chloroepoxides to the functional groups mentioned above proceeded in S_N2 fashion. It, however, still has been unclear whether the reaction of α-chloroepoxide under weakly basic conditions providing with α-chloro-, α-hydroxy-, and α-azide-aldehydes proceeded in net S_N2 mechanism or took place highly diastereoselectively, because the substitution reactions proceeded in the highly diastereotopic environment of the sugar derivatives used as the substrate. Thus, intrinsic stereochemical behavior of the substituted α-chloroepoxide functionality in ring opening substitution reactions remains to be cleared.

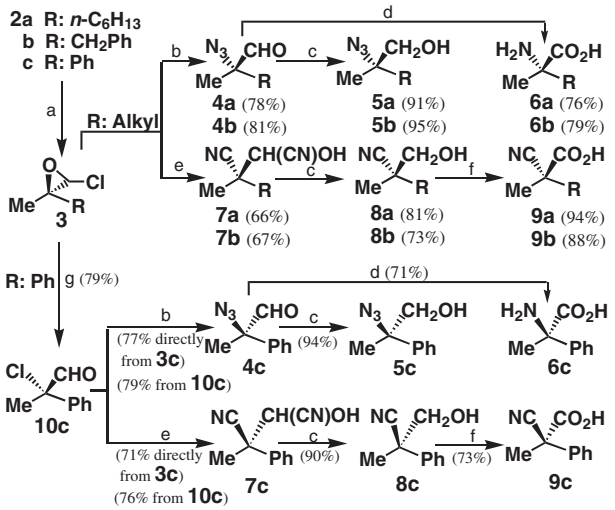
In this paper we report on stereospecific ring opening reactions of chiral α-chloroepoxides **3**, prepared from stereochemically defined dichloromethylcarbinols **2** derived via dichlorocarbene C–H insertion reaction of TMS-protected chiral secondary alcohols **1**. The products obtained from the non-benzylic substrates **3a** and **3b** were found to be configurationally inverted quaternary carbon compounds, α-azide- **4a**,**b** and α-cyano-aldehyde derivatives **7a**,**b** resulted from epoxide-ring opening in complete S_N2 fashion. On the other hand, a benzylic one **3c** was found to provide configurationally retained **4c** and **7c** through an absolute double inversion of the quaternary stereogenic center.

Treatment of (*R*)-(−)-2-octanol **1a** with chloro-trimethylsilane (TMS-Cl) and Et_3N in THF at room temperature for 2 h gave the corresponding crude TMS-ether which underwent dichlorocarbene C–H insertion reaction by stirring with $CHCl_3$ and 50% aqueous NaOH in the presence of a catalytic amount of cetyltrimethylammonium chloride (CTAC) for 18 h at 80 °C.[5] The crude product obtained was treated with aq. conc. HCl and MeOH at room temperature for 2 h to give a dichloromethylcarbinol **2a** in 39% overall yield with a 52% recovery of the starting alcohol **1a**. Other substrates **1b** and **1c** were transformed to the corresponding dichloromethylated products **2b** and **2c** in 31 and 60% overall yield with 61 and 23% recovery of the starting alcohols, respectively, as shown in Scheme 1. Stereochemistry of the C–H insertion reaction proceeding with complete retention of configuration of the starting alcohols has been established with non-benzylic as well as benzylic alcohol derivatives.[5] Stereospecificity of the reaction performed on TMS-ethers was also verified by homogeneity of **2c** observed in chiral HPLC analysis.[10]



a R: *n*-C_6H_{13} 39% (SM 52%)
b R: CH_2Ph 31% (SM 61%)
c R: Ph 60% (SM 23%)

Scheme 1.



Scheme 2. Reagents and conditions: a: K_2CO_3 (5 eq.), MeOH., r.t., 10 min, b: NaN_3 (3 eq.), 15-crown-5 (1 eq.), THF, r.t., 12 h, c: $NaBH_4$ (5 eq.), MeOH, r.t., 10 min, d: 1) Jones' reagent, acetone, 0 °C, 15 min, 2) H_2, Pd/C, EtOH, r.t., 16 h, e: KCN (3 eq.), 18-crown-6 (1 eq.), THF, r.t., 12 h, f: Jones' reagent, acetone, 0 °C, 10 min, g: THF, r.t., 12 h.

The dichloromethylcarbinol **2a** were treated with K_2CO_3 in MeOH at room temperature for 10 min, providing a crude α-chloroepoxide **3a**, which was converted into an α-azide-aldehyde **4a** in 78% overall yield on treatment with 3 equiv of NaN_3 in the presence of 15-crown-5 in THF at room temperature. Chiral HPLC analysis[10] of the benzoate of alcohol **5a** derived from **4a** indicated stereospecificity of the ring opening reaction of **3a**. The stereochemistry of (*S*)-configuration of the α-azide-aldehyde **4a** was demonstrated by transformation to (*S*)-(+)-α-hexylalanine **6a**[11] in 76% overall yield by a sequence of reactions, Jones oxidation and catalytic hydrogenation. In turn attention was focused on the construction of all carbon-substituted quaternary centers. Thus, the crude α-chloroepoxides **3a** was treated with 3 equiv of KCN in the presence of 18-crown-6 in THF at room temperature provided in 66% yield a diastereomeric mixture of cyanohydrine **7a**, which was successfully led to a β-cyanohydrine **8a** in 81% yield by reduction with $NaBH_4$ in MeOH. Stereochemical homogeneity of **8a** was demonstrated by chiral HPLC analysis[10] of the derived *t*-butyldiphenylsilyl (TBDPS)-ether. Jones oxidation of **8a** gave (*R*)-2-cyano-2-methyloctanoic acid **9a** in a high yield (94%). The other one **2b** was also transformed to (*S*)-(−)-α-methylphenylalanine **6b**[12] in 64% overall yield through α-azide-aldehyde **4b**, and (*R*)-(−)-2-cyano-2-methyl-3-phenylpropionic acid **9b**[13] in 43% overall yield by way of aldehyde cyanohydrine **7b** and β-cyanohydrine **8b** by the same treatments as for **2a**, respectively. Chiral HPLC analysis[10] of the derived alcohol **5b** and **8b** indicated stereospecificity of the nucleophilic substitution reactions of **3b**.

A dramatic change was observed in the outcome of benzylic substrate **2c**. The crude unstable α-chloroepoxide **3c** analogously obtained from **2c** was treated with NaN_3 or KCN to afford an α-azide-aldehyde **4c** in 77% yield or a diastereomeric mixture of cyanohydrine **7c**, which was successfully led to a β-cyanohydrine **8c** in 64% overall yield, respectively by the same treatments as for the transformation of **2a**. Stereochemical purity of **5c** derived from **4c**, and **8c** was proved by chiral HPLC analysis.[10] Unexpectedly, the derived amino acid **6c** and cyanoacetic acid **9c** were identified with (*R*)-(−)-α-methylphenylglycine[14] and (*S*)-(+)-2-cyano-2-methylphenylacetic acid,[15] respectively. Stereospecific double inversion of configuration of the α-chloroepoxide **3c** was postulated to explain the results. Thus, the crude α-chloroepoxide **3c** was stirred for 12 h in THF at room temperature to give a good yield (79%) of an α-chloroaldehyde **10c**, which was converted into **4c** by treatment with NaN_3 and **7c** with KCN, respectively.

In conclusion, a new method for construction of chiral quaternary stereogenic centers, substituted with amino group and with four different carbon ligands was developed by way of tertiary dichloromethylcarbinols derived stereospecifically from chiral secondary alcohols.

References and Notes

1 a) D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, **121**, 686 (1999) and references cited therein. b) T. Ooi, M. Takeuchi, M. Kameda, and K. Maruoka, *J. Am. Chem. Soc.*, **122**, 5228 (2000). c) C. Najera, *Synlett*, **2002**, 1388, and references cited therein. d) T. Wirth, *Angew. Chem., Int. Ed. Engl.*, **36**, 225 (1997). e) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, **40**, 1456 (2001). f) S. Takano, Y. Shimazaki, and K. Ogasawara, *Tetrahedron Lett.*, **31**, 3325 (1990). g) M. E. Jung and D. C. D'Amico, *J. Am. Chem. Soc.*, **117**, 7379 (1995). h) A. I. Meyers and G. P. Brengel, *Chem. Commun.*, **1997**, 1. i) S. Hosokawa, K. Sekiguchi, M. Enemoto, and S. Kobayashi, *Tetrahedron Lett.*, **41**, 6429 (2000). j) P. I. Dalko, V. Brun, and Y. Langlois, *Tetrahedron Lett.*, **39**, 8979 (1998).

2 K. Fuji, *Chem. Rev.*, **93**, 2037 (1993); E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, **37**, 388 (1998); J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, **40**, 4591 (2001).

3 a) T. Katsuki and V. S. Martin, *Org. React.*, **48**, 1 (1996). b) R. A. Johnson and K. B. Sharpless, in "Catalytic Asymmetric Synthesis," ed. by I. Ojima, VCH, New York (1993), Chap. 4.4. c) B. D. Brandes and E. N. Jacobsen, *J. Org. Chem.*, **59**, 4378 (1994). d) T. Fukuda, R. Irie, and T. Katsuki, *Synlett*, **1995**, 17. e) M. Frohn and Y. Shi, *Synthesis*, **2000**, 1979, and references cited therein. f) H. C. Kolb, M. S. VanNiewenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994). g) D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, **121**, 686 (1999). h) B. M. Trost, *J. Am. Chem. Soc.*, **120**, 12702 (1998).

4 P. Besse and H. Veschambre, *Tetrahedron*, **50**, 8885 (1994); H. Stecher and K. Faber, *Synthesis*, **1997**, 1; M. Wills and H. Tye, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1109.

5 Y. Masaki, H. Arasaki, and M. Shiro, *Chem. Lett.*, **2000**, 1180.

6 G. Kobrich, *Angew. Chem.*, **84**, 557 (1972).

7 P. Blumbergs, M. P. LaMontagne, and J. I. Stevens, *J. Org. Chem.*, **37**, 1248 (1972); G. Kobrich and J. Grosser, *Tetrahedron Lett.*, **13**, 4117 (1972); H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **13**, 4661 (1972); H. Taguchi, S. Tanaka, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **14**, 2465 (1973).

8 a) K. Sato, K. Suzuki, M. Ueda, M. Katayama, and Y. Kajihara, *Chem. Lett.*, **1991**, 1469; K. Sato, Y. Kajihara, Y. Nakamura, and J. Yoshimura, *Chem. Lett.*, **1991**, 1559. b) S. Deloisy, T. T. Thang, A. Olesker, and G. Lukacs, *Tetrahedron Lett.*, **35**, 4783 (1994). c) T. Nakamura and M. Shiozaki, *Tetrahedron Lett.*, **42**, 2701 (2001). d) M. Yoshikawa, Y. Yokokawa, Y. Okuno, and N. Murakami, *Tetrahedron*, **51**, 6209 (1995); M. Yoshikawa, Y. Yokokawa, Y. Okuno, N. Yagi, and N. Murakami, *Chem. Pharm. Bull.*, **43**, 1647 (1995).

9 K. Sato, T. Sekiguchi, T. Hozumi, T. Yamazaki, and S. Akai, *Tetrahedron Lett.*, **43**, 3087 (2002).

10 Chiral HPLC was performed on CHIRALCEL OD-H for **2c**, the benzoate of **5a**, the TBDPS-ether of **8a**, **5b**, **8b**, **5c**, and **8c** using a solvent system of hexane/*i*-PrOH (500/1 or 30/1). All compounds analyzed were determined to be >98% ee, which stands for no detection of the other enantiomer.

11 (*R*)-(−)-α-hexylalanine: L. M. Harwood, K. J. Vines, and M. G. B. Drew, *Synlett*, **1996**, 1051.

12 (*R*)-(+)-α-methylphenylalanine HCl: S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **14**, 1138 (1966); (*S*)-(−)-α-methylphenylalanine: C. Najera, T. Abellan, and J. M. Sansano, *Eur. J. Org. Chem.*, **2000**, 2809.

13 (*S*)-(+)-2-cyano-2-methyl-3-phenylpropionic acid: S. Terashima, K. K. Lee, and S. Yamada, *Chem. Pharm. Bull.*, **17**, 2533 (1969).

14 (*S*)-(+)-α-methylphenylglycine: H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1749 (1967); F. A. Davis, S. Lee, H. Zhang, and D. L. Fanelli, *J. Org. Chem.*, **65**, 8704 (2000).

15 (*S*)-(+)-2-cyano-2-methylphenylacetic acid: J. Knabe and W. Koch, *Arch. Pharm.*, **305**, 849 (1972); (*R*)-(−)-2-cyano-2-methylphenylacetic acid: J. Knabe and C. Urbahn, *Liebigs Ann. Chem.*, **750**, 21 (1971); C. Cativiela, M. D. Diaz de Villegas, J. A. Galvesz, and Y. Lapena, *An. Quim.*, **90**, 432 (1994).