Stereospecific Construction of Chiral Quaternary α-Oxygenated Aldehydes from Chiral Secondary Alcohol Derivatives

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Received 18 November 2003

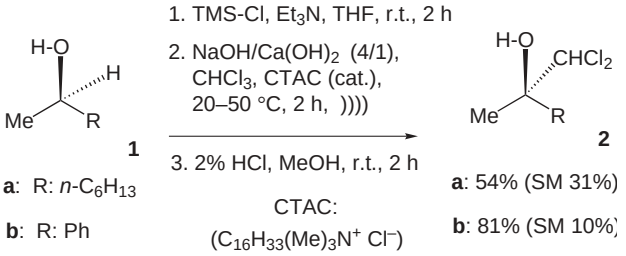
Abstract: Chiral tertiary dichloromethylcarbinol derivatives **2**, prepared from protected chiral secondary alcohols **1**, were converted stereospecifically into chiral quaternary α-oxygenated aldehyde derivatives **4** and **11** via intermediary α-chloroepoxides **3** under weakly basic conditions (K_2CO_3/MeOH/r.t.). The fashion generating the quaternary centers was proved to be quite different depending on the substrates: inversion of configuration of non-benzylic substrate **2a** and apparent retention with benzylic one **2b**.

Key words: α,α-disubstituted α-oxyaldehyde, chiral synthesis, α-chloroepoxide, ring opening, methoxide anion

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[1] highly enantioselectively by facile manipulations. Contrary to the scarcity of widely applicable enantioselective synthetic methods for chiral tertiary alcohol derivatives,[2] several excellent practical methods have been developed to obtain chiral secondary alcohol derivatives with nearly perfect enantioselectivity.[3] In the context, we have 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,[4] providing chiral tertiary dichloromethylcarbinol functional group which is believed to be a promising chiral building block. In the extension of the work facile stereospecific transformation of chiral tertiary dichloromethylcarbinols to α-azide-aldehydes and α-cyano-aldehydes has been reported recently.[5]

In this paper we report on stereospecific ring opening reactions of chiral α-chloroepoxides **3**, which were prepared from stereochemically defined dichloromethylcarbinols **2** derived via dichlorocarbene C-H insertion reaction of TMS-protected chiral secondary alcohols **1**, with methoxide anion under weakly basic conditions. The product obtained from the non-benzylic substrates **3a** was found to be configurationally inverted quaternary carbon compounds, α-methoxyaldehyde **4** resulted from epoxide-ring opening in complete S_N2 fashion. On the other hand, a benzylic substrate **3b** was found to provide a configurationally retained α-hydroxyaldehyde derivative **11** through an absolute double inversion of the quaternary stereogenic center.

Chiral quaternary dichloromethylcarbinols **2a** and **2b**[5] were obtained in 54% and 81% yield with 31% and 10% recovery of the starting alcohols, respectively, by dichlorocarbene insertion reaction of TMS-ethers of (*R*)-(–)-2-octanol (**1a**) and (*R*)-(+)-1-phenylethanol (**1b**) under ultrasonic conditions with $CHCl_3$ and powdered NaOH/$Ca(OH)_2$ (4:1) in the presence of a catalytic amount of cetyltrimethylammonium chloride (CTAC) at 20–50 °C, followed by acidic hydrolysis (aq HCl and MeOH/r.t./2 h) of the crude products (Scheme 1).[6]



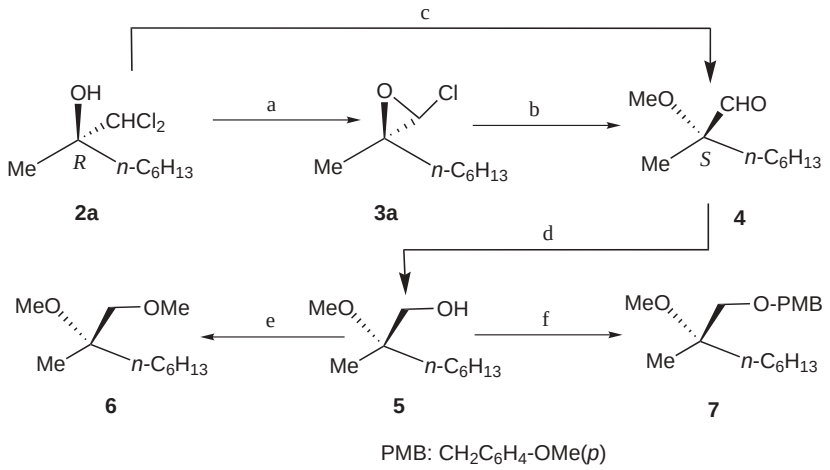
Scheme 1

The dichloromethylcarbinol **2a** was treated with 3 equivalents of K_2CO_3 in MeOH at room temperature for 10 minutes, providing a crude α-chloroepoxide **3a**, which was converted into an α-methoxy-aldehyde **4** in 75% overall yield on treatment with 3 equivalents of K_2CO_3 in MeOH at room temperature for 10 hours. The aldehyde was also obtained directly in a higher yield (79%) by treatment of **2a** with 5 equivalents of K_2CO_3 in MeOH at room temperature for 10 hours (Scheme 2).[6]

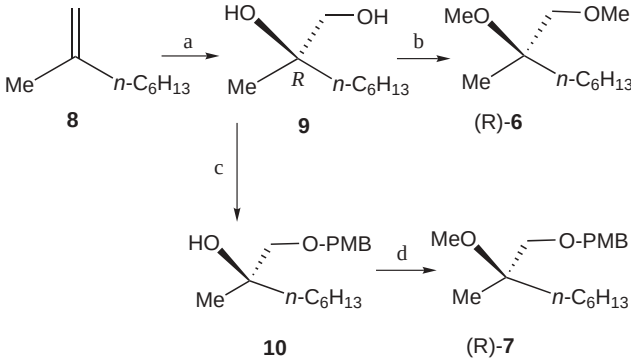
Stereochemistry of *S*-configuration and stereochemical homogeneity of the product **4** were verified by derivation to (*S*)-1,2-dimethoxy-2-methyloctane (**6**) and (*S*)-1-(*p*-methoxybenzyloxy)-2-methoxy-2-methyloctane (**7**) via a methoxy-aldehyde **5**, followed by comparison of $[\alpha]_D$ and chiral HPLC[7] with those of the corresponding authentic samples prepared through Sharpless dihydroxylation of 2-methyloctene (**8**) with AD-mix-β,[8] which was known to produce selectively (*R*)-glycol **9** according to Scheme 3.

The treatment of the benzylic one **2b** under the same conditions gave (*R*)-2-hydroxy-2-phenylpropanal dimethyl acetal (**11**) in an excellent yield (92%). Stereochemical homogeneity of **11** was characterized by chiral HPLC[7] in comparison with the corresponding racemic one. The

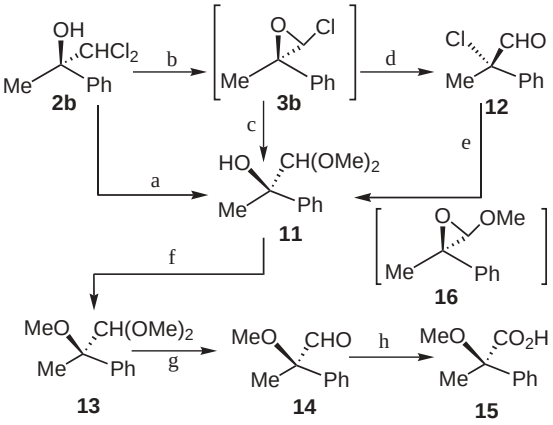
SYNLETT 2004, No. 3, pp 0546–0548
Advanced online publication: 12.01.2004
DOI: 10.1055/s-2004-815406; Art ID: U24503ST



Scheme 2 a) K_2CO_3 (3 equiv), MeOH, r.t., 10 min; b) K_2CO_3 (3 equiv), MeOH, r.t., 10 h (two steps 75%); c) K_2CO_3 (5 equiv), MeOH, r.t., 10 h (79%); d) $NaBH_4$, MeOH, r.t., 1 h (92%); e) NaH, MeI, DMF, r.t., 10 h (88%); f) NaH, PMBCl, DMF, r.t., 10 h (78%).



Scheme 3 a) AD-mix-β, H_2O–*t*-BuOH, 0 °C, 18 h (89%); b) NaH, MeI, DMF, r.t., 18 h (82%); c) NaH, PMBCl, DMF, r.t, 18 h (67%); d) NaH, MeI, DMF, r.t., 18 h (63%).



Scheme 4 a) K_2CO_3 (5 equiv), MeOH, r.t., 10 h (92%); b) K_2CO_3 (3 equiv), MeOH, r.t., 10 min; c) K_2CO_3 (3 equiv), MeOH, r.t., 10 h (two steps 86%); d) THF, r.t., 10 h (76%); e) K_2CO_3 (5 equiv), MeOH, r.t., 10 h (95%); f) NaH, MeI, DMF, r.t., 10 h (95%); g) 5% aq H_2SO_4, THF, reflux, 5 h (75%); h) Jones reagent, acetone, r.t., 10 min (85%).

acetal **11** was obtained via α-chloroaldehyde **12**, which was produced from dichloromethylcarbinol **2b** through an unstable α-chloroepoxide **3b**, as illustrated in Scheme 4. Although several chemists have reported formations and reactions of 3-substituted 2-chlorooxiranes including 3-methyl-3-phenyl-2-chlorooxirane (racemic **3b**) with NaOMe in MeOH affording α-hydroxyaldehyde dimethyl acetals, no stereochemistry in the reaction has been addressed.[9] The configuration of the stereogenic center of the acetal **11** was determined to be *R* by conversion into α-methoxyaldehyde **14** through the methyl ether **13** followed by acidic hydrolysis, and comparison of $[\alpha]_D$ with the corresponding data $\{[\alpha]_D\}$ for the known (*S*)-2-methoxy-2-phenylpropanal (**14**).[10] Furthermore, Jones oxidation of the aldehyde **14** led to (*R*)-2-methoxy-2-phenylpropionic acid (**15**).[10] Stereospecific double inversion of configuration of the α-chloroepoxide **3b** was postulated to explain the results. Thus, the crude α-chloroepoxide **3b** was rearranged with inversion of configuration to an α-chloroaldehyde **12** which was converted into **11** by successive nucleophilic attack of methoxide anion on the aldehyde **12** and on the generated α-methoxyepoxide **16**[9] as shown in Scheme 4.

In conclusion, a dramatic change of behavior of 3,3-disubstituted 2-chlorooxirane **3** was observed depending on pattern of the substituents, non-benzylic and benzylic one, to give opposite stereochemical outcome. A new method for preparation of stereochemically defined quaternary α-oxygenated non-benzylic and benzylic aldehydes such as **4** and **14** from chiral secondary alcohols has been developed.

Acknowledgment

This study was financially supported in part by a Grant-in-Aid for Scientific Research (No.14657566) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

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

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

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

(4) Masaki, Y.; Arasaki, H.; Shiro, M. *Chem. Lett.* **2000**, 1180.

(5) Masaki, Y.; Arasaki, H.; Iwata, M. *Chem. Lett.* **2003**, *32*, 4.

(6) **Typical Experimental Procedures**: Dichlorocarbene insertion reaction of TMS-ether of **1** under ultrasonic conditions: A mixture of NaOH (4.0 g) and $Ca(OH)_2$ (1.0 g) was heated at 400 °C for 1.5 h, and the melted mixture was cooled to r.t. and ground to give a powdered alkali. Crude TMS-ether (155 mg) was obtained by stirring a mixture of **1a** (100 mg, 0.77 mmol), TMSCl (125 mg, 1.15 mmol), and Et_3N (150 mg, 1.5 mmol) in THF (2.0 mL) at r.t. for 3 h, followed by concentration. A mixture of the crude TMS-ether **1a**, the alkali powder (300 mg), and *n*-$C_{16}H_{33}N^+(Me)_3Cl^-$ (40 μL of 1 mg/mL $CHCl_3$ stock solution) in $CHCl_3$ (0.5 mL) was irradiated by ultrasound at 20–50 °C for 1 h. The mixture was filtered and the filtrate was washed with brine followed by concentration in vacuo to give a crude oil, which was submitted to the above conditions for the dichlorocarbene insertion reaction one more time. The crude product obtained was dissolved in MeOH (1.0 mL) and stirred with 3% HCl (0.1 mL) at r.t. for 2 h. The whole was concentrated, taken up with Et_2O, washed with brine, dried over Na_2SO_4, and evaporated to give an oil. Purification of the crude product by chromatography on silica gel to give **2a** (88 mg, 54%) as an oil with a recovery of **1a** (31 mg, 31%). The same treatment of **1b** (100 mg, 0.82 mmol) gave **2b** (135 mg, 81%) with a recovery of **1b** (10 mg, 10%). Compound **2a:** $[\alpha]_D^{20}$ +1.5 (*c* 1.05, $CHCl_3$). IR (neat): 3460, 2941, 2922, 2914, 2861, 1457 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.99 (s, 3 H), 1.40–1.87 (m, 13 H), 2.15 (br, 1 H), 5.78 (s, 1 H). Compound **2b:** $[\alpha]_D^{20}$ –21.2 (*c* 1.0, $CHCl_3$). IR (neat): 3558, 3479, 2990, 2918, 1495, 1448 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.92 (s, 3 H), 2.99 (br, 1 H), 6.05 (s, 1 H), 7.42–7.66 (m, 5 H).
Reaction of dichloromethylcarbinol **2** with K_2CO_3 in MeOH: A mixture of **2a** (100 mg, 0.47 mmol) and K_2CO_3 (345 mg, 2.5 mmol) in MeOH (2.0 mL) was stirred for 10 h at r.t., and filtered through a short column of silica gel to give a crude product as an oil. The oil was purified by chromatography on silica gel to give **4** (64 mg, 79%) as an oil. The same treatment of **2b** (100 mg, 0.49 mmole) gave **11** (88 mg, 92%) as an oil. Compound **4:** $[\alpha]_D^{20}$ –43.3 (*c* 1.15, $CHCl_3$). IR(neat): 2934, 2861, 2847, 1737, 1461 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (br t, *J* = 6.8 Hz, 3 H), 1.22 (s, 3 H), 1.20–1.45 (br, 8 H), 1.45–1.68 (br, 2 H), 9.57 (s, 1 H). Compound **11:** $[\alpha]_D^{20}$ –28.6 (*c* 1.10, $CHCl_3$). IR (neat): 3479, 2923, 2913, 2847, 1448 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 2.78 (bs, 1 H), 3.34 (s, 3 H), 3.44 (s, 3 H), 4.21 (s, 1 H), 7.26–7.55 (m, 5 H).

(7) Chiral HPLC was performed on CHIRALCEL OJ for **7** and **11** using a solvent system of hexane/*i*-PrOH (500/1 or 200/1). These compounds analyzed were determined to be >98% ee, which stands for no detection of the other enantiomer.

(8) (a) The reagent AD-Mix-β was purchased from Aldrich Com. The glycol **9** proved to be obtained in 72% ee from chiral HPLC of the derived **7** using CHIRALCEL OJ (hexane/*i*-PrOH = 500/1). (b) Krief, A.; Castillo-Colaux, C. *Synlett* **2001**, 501. (c) Kolb, H. C.; van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(9) (a) Kaczmarczyk, G.; Jonczyk, A. *Synlett* **1997**, 921. (b) Griesbaum, K.; Lie, G. O.; Keul, H. *J. Org. Chem.* **1984**, *49*, 679. (c) Kirrmann, A.; Duhamel, P.; Nouri-Bimorghi, R. *Liebigs Ann. Chem.* **1966**, *691*, 33. (d) Stevens, C. L.; Farkas, E.; Gillis, B. *J. Am. Chem. Soc.* **1954**, *76*, 2695.

(10) (a) Aoyama, Y.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 6731. (b) Paulmier, C.; Duturquin, F.; Plaquevent, J.-C. *Tetrahedron Lett.* **1988**, *29*, 5889. (c) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614.