

# Facile Synthesis of Optically Active Tertiary Alcohol Building Blocks by Stereospecific C–H Insertion Reaction of Dichlorocarbene with Secondary Alcohol Derivatives

Yukio Masaki,\* Hideki Arasaki, and Motoo Shiro<sup>†</sup>

*Gifu Pharmaceutical University, 5-6-1 Mitahora-Higashi, Gifu 502-8585*

*<sup>†</sup>Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196-0003*

(Received August 8, 2000; CL-000761)

Stereospecific C–H insertion of dichlorocarbene generated from a system  $\text{CHCl}_3/50\%\text{NaOH}/\text{cetyltrimethylammonium chloride}$  (as a PTC) proceeded at the carbinol carbon in the reaction of chiral secondary alcohol derivatives to provide  $\alpha$ -dichloromethylated tertiary alcohol derivatives with complete retention of configuration.

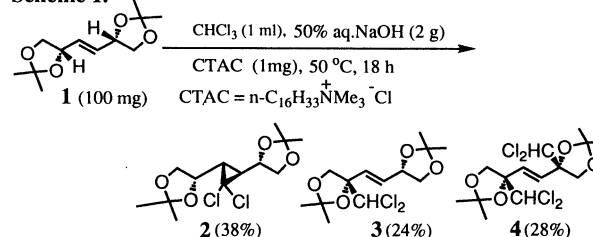
Optically active tertiary alcohols and the related compounds are widely distributed in biologically active compounds including pharmaceuticals.<sup>1</sup> Chiral tertiary alcohol derivatives as building blocks for the synthesis of such bioactive compounds have generally been prepared synthetically by biological and chemical methods including kinetic resolution of racemates,<sup>2</sup> enantioselective oxygenation of 1,1-disubstituted olefins or substituted aromatics,<sup>3</sup> desymmetrization of prochiral tertiary alcohols,<sup>4</sup> enantioselective nucleophilic addition to ketones,<sup>5</sup> and asymmetric alkylation of chiral secondary carbinol carbon with memory of chirality.<sup>6</sup> High levels of chiral induction (>95% ee), however, have been hardly attained by these methods. On the other hand, several excellent practical methods have been developed to obtain optically active secondary alcohols in nearly perfect enantioselectivity.<sup>7–9</sup> Therefore, devices for introduction of carbon substituents into the  $\alpha$ -methine C–H bond of such optically active secondary alcohols with complete stereospecificity in the sense of retention or inversion of configuration would offer facile methods for production of optically active tertiary alcohol derivatives.

In 1968, Landgrebe reported insertion of dichlorocarbene ( $:\text{CCl}_2$ ), generated by pyrolysis of trichloroacetate, to the  $\text{C}_\beta$ –H bond of a dialkylmercury compound with retention of configuration.<sup>10</sup> Seyferth also found that carbene insertion proceeds at the benzylic C–H bond with retention of configuration in the reaction of chiral 2-phenylbutane with  $:\text{CCl}_2$  generated by pyrolysis of phenyl(bromodichloromethyl)mercury  $[\text{PhHgCCl}_2\text{Br}]$ .<sup>11</sup> With oxygen-containing substrates so far, in 1980 Steinbeck reported stereospecific versions of insertion reaction of diastereomeric dioxolanes or diastereomeric mixture of tetrahydrofurans with  $:\text{CCl}_2$ , generated from  $\text{CHCl}_3$  and 50%aq NaOH in the presence of  $\text{Et}_3(\text{Bn})\text{NCl}$  as a phase-transfer catalyst (PTC), at the  $\text{C}_\alpha$ –H bond to the oxygen atom.<sup>12</sup> Steinbeck, however, has not proved exactly except by NMR analysis the stereochemical fashion, retention or inversion, in spite that the substrates used contain oxygen functional group(s), acetal and ether, of high coordination property to carbene at the position near the reaction site. Oku has reported enhanced reactivity of the  $\text{C}_\alpha$ –H bond of alkoxide anions with  $:\text{CCl}_2$ , chlorophenylcarbene, phenylthiocarbene, dimethylvinylidene carbene, and alkylidenemethylene carbenoids.<sup>13</sup> Stereochemical outcomes of the C–H insertion reaction, however, appear ambiguous because limited examples indicated are insufficient to claim the generality of the stereospecificity

in the reactions, and because direct concerted insertion mechanism and/or hydride abstraction–recombination mechanism are thought to be involved in the reaction depending on the type of carbenes (carbenoids) and substrates. In the context, here we report C–H insertion reaction of dichlorocarbene ( $:\text{CCl}_2$ ) and protected chiral secondary alcohols to provide chiral tertiary alcohol derivatives with complete stereospecificity and retention of configuration.

Upon vigorous stirring 100 mg of a chiral  $\text{C}_2$ -symmetric olefin (**1**) derived from D-mannitol<sup>14</sup> in  $\text{CHCl}_3$  (1.0 mL) and aqueous 50% NaOH (2.0 g) with 1.0 mg of cetyltrimethylammonium chloride (CTAC) as a PTC for 18 h at 50 °C, besides a cyclopropane derivative (**2**) (38% yield), dichloromethylated compound (**3**) and bis-dichloromethylated product (**4**) were obtained as a sole diastereoisomer in 24 and 28% yields, respectively (Scheme 1).

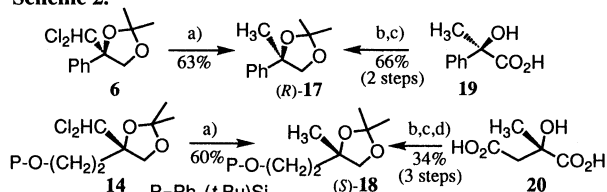
Scheme 1.



The absolute stereochemistry of the bis-adduct (**4**) was determined by X-ray crystallography<sup>15</sup> to be (*S,S*), which stood for the reaction taking place with retention of configuration of the stereogenic center of the substrate (**1**). The structure of the mono-adduct (**3**) was characterized by the fact that the bis-adduct (**4**) was derived from the mono-adduct (**3**) under the same reaction conditions. Because an inevitable competition between C–H insertion and cyclopropanation occurred with the allylic alcohol derivative (**1**), we turned our focus on the reaction of protected benzylic and non-olefinic secondary alcohols. Reactions of protected chiral benzylic alcohols such as styrenediol acetonide (**5**) and protected  $\alpha$ -phenethylalcohols **7**, and protected non-allylic alcohols such as acetonides **9**, **11**, and **13** of 3-phenyl-1,2-propanediol, hexane-1,2-diol, and 4-*tert*-butyldiphenylsilyloxy-butane-1,2-diol, respectively, and 2-methoxyoctane (**15**) are summarized in Table 1. With (*R*)-styrenediol acetonide (**5**), an excellent regioselectivity of insertion of  $:\text{CCl}_2$  favoring at the  $\alpha$ -methine C–H was observed to afford a dichloromethylated compound (**6**) as a single enantiomer<sup>16</sup> in an excellent chemical yield. The stereochemistry of the compounds (**6**) and (**14**), which was provided from (*S*)-**13** as a single enantiomer,<sup>16</sup> was assigned to be (*R*) and (*S*), respectively, by derivation through reduction with *n*- $\text{Bu}_3\text{SnH}$  to (*R*)-(-)-2-phenylpropanediol acetonide (**17**) and (*S*)-(-)-4-*tert*-

**Table 1.** Dichlorocarbene insertion reaction of secondary alcohol derivatives

Alcohol Deriv. (100 mg)		Time/h		Product	Yield/% (SM/%)
		50% aq. NaOH (6 g), CHCl <sub>3</sub> (3 ml), CTAC (0.1 mg), 80 °C			
		12		<b>6</b>	86 (8)
<b>7a</b> P= Me		12		<b>8a</b>	52 (42)
<b>7b</b> P= TBDMS		12		<b>8b</b>	87 (11)
<b>7c</b> P= MOM		12		<b>8c</b>	7 (81)
<b>7d</b> P= Ac		12		<b>8d</b>	0 (72) <sup>a</sup>
<b>9</b> R= Ph		18		<b>10</b>	22 (76)
<b>11</b> R= n-Pr		18		<b>12</b>	53 (22)
<b>13</b> R= CH <sub>2</sub> O-TBDPS		18		<b>14</b>	36 (43)
<b>15</b>		18		<b>16</b>	58 (22)

<sup>a</sup> α-Phenethylalcohol was obtained.**Scheme 2.**

Reagents and conditions: a) *n*-Bu<sub>3</sub>SnH (10 eq.), AIBN (cat.), toluene, reflux, 11 h, b) LAH (2 eq.), THF, reflux, 2 h, c) H<sub>2</sub>SO<sub>4</sub>, CuSO<sub>4</sub>, acetone, r.t., 2 h, d) TBDPS-Cl (2 eq.), Imid., THF, r.t., 12 h

butyldiphenylsiloxy-2-methylbutane-1,2-diol acetonide (**18**), which were identified with those derived from known (*R*)-(-)-atrolactic acid (**19**) and (*S*)-(+)-citramalic acid (**20**), respectively<sup>17</sup> (Scheme 2). These facts showed that also in secondary benzylic and non-allylic alcohol systems, the carbene insertion reaction proceeded with complete retention of configuration of the chiral center of the starting alcohols. In addition to acetonide, such protecting groups of alcohol as methyl (**7a**) and *tert*-butyldimethylsilyl (TBDMS) ethers (**7b**) are compatible with the reaction conditions, although the corresponding methoxymethyl (MOM) ether (**7c**) and acetate (**7d**) appeared to be poor substrates to yield little or no desired products with recovery of large amounts of the starting material **7c** and the hydrolyzed product, α-phenethylalcohol, respectively. The α-methine C–H bond of protected non-allylic alcohols (**9–15**) was transformed highly regioselectively to the corresponding dichloromethyl group albeit in moderate yields.

A high level of kinetic isotope effect (*k<sub>H</sub>*/*k<sub>D</sub>* = 3.4) observed in this carbene insertion reaction of mono-deuterated benzylmethyl ether PhCH(D)OCH<sub>3</sub>, and the perfect retention of configuration of the starting secondary alcohols observed strongly suggest the reaction mechanism associated with three membered transition state involving a free carbene of singlet state and the C<sub>α</sub>–H bond.<sup>11</sup>

In conclusion, a simple operation of protected optically active secondary alcohols in CHCl<sub>3</sub>/50% NaOH in the presence of PTC offers a facile and practical method for synthesis of optically active tertiary alcohol building blocks. Synthetic manipulations of the α-dichloromethylated tertiary alcohol derivatives directed to optically active natural products are in progress in this laboratory.

**References and Notes**

- Representative examples of biologically active tertiary alcohol derivatives: Cinatrin C, Integerrimine, Harringtonine, K-252a, Forstriein, Viridifungin, Erythromycin, and Zaragozic acid: References cited in the literature, D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, **121**, 686 (1999).
- Biological methods: K. E. Henegar, S. W. Ashford, T. A. Baughan, J. C. Sih, and R. -L. Gu, *J. Org. Chem.*, **62**, 6588 (1997); O. Jimenez, M. P. Bosch, and A. Guerrero, *J. Org. Chem.*, **62**, 3496 (1997).
- Biological methods: M. Takagi, N. Uemura, and K. Furuhashi, *Ann. N. Y. Acad. Sci.*, **613**, 697 (1990); V. J. Subramanian, *Ind. Microbiol.*, **1**, 119 (1986); W. Reineke, W. Otting, and H.-J. Knackmuss, *Tetrahedron*, **34**, 1707 (1978); J. T. Rossiter, S. R. Williams, A. E. G. Cass, and D. W. Ribbons, *Tetrahedron Lett.*, **28**, 5173 (1987).  
Chemical methods: B. D. Brandes and E. N. Jacobsen, *J. Org. Chem.*, **59**, 4378 (1994); T. Fukuda, R. Irie, and T. Katsuki, *Synlett*, **1995**, 197; D. Yang, M.-K. Wong, Y.-C. Yip, X.-C. Wang, M.-W. Tang, J.-H. Zheng, and K.-K. Cheung, *J. Am. Chem. Soc.*, **120**, 5943 (1998); Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masumune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987); Z.-M. Wang and K. B. Sharpless, *Synlett*, **1993**, 603; P. J. Walsh and K. B. Sharpless, *Synlett*, **1993**, 605; H. Becker and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, **35**, 448 (1996).
- Biological methods: H. Ohta and H. Tetsukawa, *Agric. Biol. Chem.*, **45**, 1895 (1981); T. Itoh, H. Ohara, Y. Takagi, N. Kanda, and K. Uneyama, *Tetrahedron Lett.*, **34**, 4215 (1993).  
Chemical methods: D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda, and R. R. Schrock, *J. Am. Chem. Soc.*, **120**, 9720 (1998).
- Chemical methods: P. I. Dosa and G. C. Fu, *J. Am. Chem. Soc.*, **120**, 445 (1998); M. Nakamura, A. Hirai, M. Sogi, and E. Nakamura, *J. Am. Chem. Soc.*, **120**, 5846 (1998); D. J. Ramon and M. Yus, *Tetrahedron Lett.*, **39**, 1239 (1998); D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997).
- Chemical methods: H. Paulsen, C. Graeve, and D. Hoppe, *Synthesis*, **1996**, 141; C. Derwing and D. Hoppe, *Synthesis*, **1996**, 149.
- A review for chemical and biological synthesis of chiral epoxides: P. Besse and H. Veschambre, *Tetrahedron*, **50**, 8885 (1994).
- Recent reviews on biological methods: E. Schoffers, A. Golebiowski, and C. R. Johnson, *Tetrahedron*, **52**, 3769 (1996); F. Theil, *Chem. Rev.*, **1995**, 2203; H. Stecher and K. Faber, *Synthesis*, **1997**, 1; T. Hudlicky, D. Gonzalez, and D. T. Gibson, *Aldrichimica Acta*, **32**, 35 (1999).
- Recent reviews on chemical methods: M. Wills and H. Tye, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1109; E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed. Engl.*, **37**, 388 (1998); H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994); R. Noyori and T. Ohkuma, *Pure Appl. Chem.*, **71**, 1493 (1999).
- J. A. Landgrebe and D. E. Turman, *J. Am. Chem. Soc.*, **90**, 6256 (1968).
- D. Seyferth and Y. M. Cheng, *J. Am. Chem. Soc.*, **95**, 6763 (1973).
- K. Steinbeck and J. Klein, *J. Chem. Res. (S)*, **1980**, 94; *J. Chem. Res. (M)*, **1980**, 1150; K. Steinbeck, *Tetrahedron Lett.*, **21**, 2149 (1980).
- A. Oku, T. Harada, K. Hattori, Y. Nozaki, and Y. Yamura, *J. Org. Chem.*, **53**, 3089 (1988); T. Harada, Y. Nozaki, and A. Oku, *Tetrahedron Lett.*, **24**, 5665 (1983); T. Harada, E. Akiba, and A. Oku, *J. Am. Chem. Soc.*, **105**, 2771 (1983); T. Harada and A. Oku, *J. Am. Chem. Soc.*, **103**, 5965 (1981).
- C. Morpain, B. Nasser, B. Laude, and N. Lutruffe, *J. Org. Prep. Proced. Intern.*, **22**, 540 (1990); F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, **11**, 5223 (1970).
- Crystal data for **4**: space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (#19), with *a*=13.886(2), *b*=16.231(2), *c*=7.970(1) Å, *V*=1796.3(4) Å<sup>3</sup>, *Z*=4, *D<sub>c</sub>*=1.457 g/cm<sup>3</sup>, *R*=0.047, *R<sub>w</sub>*=0.059 for 1495 reflections with *I* > 2σ (*I*) of 1881 unique ones (2θ<136.5°) measured on a Rigaku RAXIS-RAPID imaging plate using Cu Kα radiation. The absolute configuration of the molecule (**4**) was determined based on the Flack's parameter, 0.07(5) [Δ*F*<sup>2</sup> = 0.702 for Cl], and confirmed by the Bijvoet inequality relationship. Comparisons were made for the reflections of which calculated Bijvoet differences larger than σ values: 32 of 35 Bijvoet pairs showed the correct trend.
- Enantiomeric purity of all the dichloromethylated compounds obtained in this reaction of optically pure alcohol derivatives used was measured to be more than 98% ee in comparison with the corresponding racemates by HPLC using Daicel CHIRALCEL OD and OJ eluted with a mixed solvent of hexane/2-propanol (500/1).
- Optically pure (*R*)-(-)-atrolactic acid (**19**) and (*S*)-(+)-citramalic acid (**20**) were purchased from Lancaster Synth. Ltd. and Aldrich Chem. Co. Inc., respectively.