Selective Bromination of α-Chloro and α-Bromo Carboxylic Acid Derivatives

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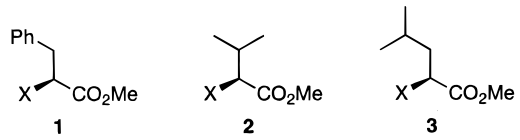
Introduction

Structural modification of chiral pool compounds is often a convenient synthetic route to scalemic molecules. In this respect, free radical bromination has been applied with conspicuous success to the elaboration of α-amino acid derivatives.[1−6] The directing influence of proximate substituents in these reactions, exploiting radical stability, polar effects, and pro- and counteractive groups, has provided considerable control of regiochemistry. However, proximate substituent directing effects in radical reactions of other α-substituted carboxylic acid systems remain relatively unexplored. In this report we describe the regiochemical and stereochemical influence of the α-chloro and α-bromo substituents in the preparation of bromo-substituted optically pure α-chloro and α-bromo carboxylic acid derivatives. Apart from substitution of the α-amino group of suitable proteinogenic α-amino acids[7] there is a lack of methods for the synthesis of optically pure α-chloro and α-bromo acids. Introduction of a versatile bromide functionality to readily available scalemic α-chloro and α-bromo acids would facilitate the preparation of a wider range through structural elaboration.

Results and Discussion

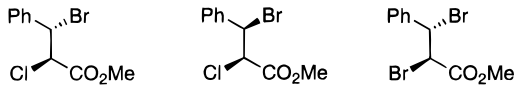
Scalemic α-chloro and α-bromo acids are readily prepared from their corresponding α-amino acids, with retention of configuration.[7] Thus, the α-chloro compounds **1a**−**3a**, and the α-bromo compounds **1b**−**3b**, were synthesized from L-phenylalanine, L-valine, and L-leucine, respectively.



1 **2** **3**

a: X = Cl
b: X = Br
c: X = PhthN

Bromination of the α-halo acid derivatives was carried out with *N*-bromosuccinimide in refluxing CCl_4, with irradiation from a 160 W mercury gas discharge lamp. The reaction of **1a** gave a 19:1 mixture of the diastereomeric *β*-bromides **4** and **5**, in 89% yield. The major diastereomer **4** was readily isolated by fractional crystallization from hexane. The structure was confirmed by x-ray crystallography[8] to be 2*R*,3*S*. The minor diastereomer was assigned the complementary structure **5**.



4 **5** **6**
(2R*,3S*)

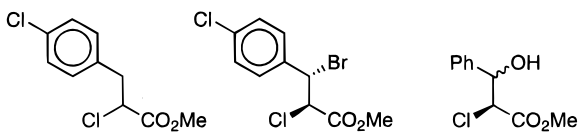
In contrast, the reaction of **1b** gave the racemic (2*R**,3*S**) dibromide **6**. Presumably, *trans*-methyl cinnamate was formed through *β*-scission of the α-bromo substituent and electrophilic addition of molecular bromine to *trans*-methyl cinnamate gave racemic dibromide **6**.[9] The bromo compound **1b** would be more susceptible to *β*-scission than the chloro compound **1a** as a consequence of the greater lability of the α-bromo substituent.

7 **8**
a: X = Cl
b: X = Br

The reaction of **2a** with *N*-bromosuccinimide gave the corresponding *β*-bromo compound **7** in 78% yield. Lability of the 2-bromo substituent to *β*-scission was again evident in the reaction of **2b**, which gave an intractable mixture of products. This is not unexpected as the product from *β*-scission, methyl 3,3-dimethylacrylate, would be susceptible to electrophilic addition and allylic bromination reactions. The products from these reactions could react further to produce a complex mixture of compounds.

Bromination of the compounds **3a** and **3b** gave the corresponding *γ*-bromides **8a** and **8b** in high yields. The α-bromo substituent of **3b** was stable under the reaction conditions presumably because hydrogen abstraction at the *γ*-position could not lead to scission of the α-C−Br bond.

The regioselectivities of bromination of **1a**, **2a**, **3a**, and **3b** parallel those observed with the corresponding *N*-phthaloyl α-amino acids, **1c**, **2c**, and **3c**. This can be attributed to the counteractive effect[3] of the α-halo substituent in combination with the carboxyl substituent to disfavor reaction at the α-position. Consequently, hydrogen abstraction occurs at benzylic and tertiary positions with complete regioselectivity whilst the stereochemistry at the α-position is preserved.



9 **10** **11**
(2R*,3S*)

(1) Easton, C. J.; Tan, E. W.; Hay, M. P. *J. Chem. Soc., Chem. Commun.* **1989**, 385.
(2) Easton, C. J.; Scharfbillig, I. M.; Tan, E. W. *Tetrahedron Lett.* **1988**, *29*, 1565.
(3) Easton, C. J.; Hutton, C. A.; Rositano, G.; Tan, E. W. *J. Org. Chem.* **1991**, *56*, 5614.
(4) Sinclair, P. J.; Zhai, D.; Reibenspeis, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.
(5) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021.
(6) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501.
(7) For example, see (a) Fischer, E., Schoeller, W. *Liebigs Ann.* **1907**, *357*, 1. (b) Renard, M. *Bull. Soc. Chim. Biol.* **1946**, *28*, 497. (c) Karrer, P., Reschofsky, H., Kaase, W. *Helv. Chim. Acta* **1947**, *30*, 271. (d) Gaffield, W., Galetto, W. G. *Tetrahedron* **1971**, *27*, 915.
(8) Shaw, J. P.; Tan, E. W.; Blackman, A. G. *Acta Crystallogr.* **1995**, *C51*, 134.
(9) This reaction was checked by addition of Br_2 to *trans*-methyl cinnamate in CCl_4, which gave exclusively the (2*R**,3*S**) diastereomer.

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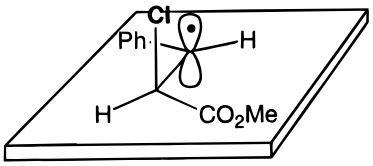

Figure 1. The preferred bridged configuration of the radical intermediate in the bromination of **1a**. Approach of bromine from the less hindered lower face would give the diastereomer **4**.

The high stereoselectivity observed in bromination of **1a**, however, is in contrast to the nonstereoselective bromination of **1c**.[1] In order to investigate the generality of stereoselective bromination with α-chloro hydrocinnamates, the 4-chlorophenyl derivative **9** was prepared from 4-chlorophenylalanine and brominated under similar conditions. The reaction took longer to reach completion but afforded an 18:1 mixture of diastereomers. The major diastereomer **10** was isolated by recrystallization from hexane, and assigned the (2*R**,3*S**) configuration based on the similarity in chemical shift and vicinal coupling constant of the α- and *β*-protons to those of the highly analogous compound **4**.

The stereochemical outcome of the reactions of **1a** and **9** can be envisaged to arise from either 1,2-asymmetric induction[10] or bridging by the neighbouring Cl.[11] To explore the possibility of the former, and also the selective reaction of the 3-bromo over the 2-chloro substituent, the chloro-bromo compound **4** was hydroxylated under conditions which favor the formation of a benzylic cation. It has been shown that in these resonance-stabilized systems reaction generally involves an open ion with no participation from chlorine.[12] Compound **4** in water/acetone with $AgNO_3$ gave a 1:1 mixture of the diastereomeric *β*-hydroxy compounds **11**.[13] This result is again in contrast to the comparable *N*-phthaloyl phenylalanine system where hydroxylation of the corresponding *β*-bromo derivative afforded almost exclusively the 2*S*,3*R* diastereomer.[14] The contrasting stereoselectivities of the radical bromination of **1a** and the hydroxylation of **4** would suggest that the reaction intermediates of the two reactions are not of similar configuration. The asymmetric environment about the α-carbon does not, by itself, induce stereoselectivity of reaction at the benzylic postion. Presumably, the radical intermediate adopts a bridged configuration, where C−Cl bond deformation occurs to bring the chlorine closer to, and eclipsing, the unpaired electron orbital.[15] Bonds to the other substituents at the 2-position are appropriately rehybridized leading to a conformation which is locked by an increase in the barrier of rotation about the C−C bond. Formation of the more stable *trans* bridged intermediate (Figure 1) and subsequent approach by bromine, from the less hindered face, would lead to the predominant (2*R*,3*S*) diastereomer.

Conclusion

A number of scalemic α-chloro and α-bromo carboxylic acids can be brominated with absolute regioselectivity, with reaction occurring at benzylic or tertiary positions. The stereochemistry at the α-carbon is not compromised. For 2-chloro-3-phenylpropanoic acid derivatives **1a** and **9**, bromination occurs with high diastereoselectivity to give predominantly the 2*R*,3*S* diastereomers, **4** and **10**, respectively. However, selective hydroxylation of **4** was not stereoselective, which suggests bridging of the chloro substituent in the radical intermediate during bromination.

Experimental Section

General. A Philips MLU 160-W (220−240 V) mercury lamp was used for NBS brominations. α-Halo acid methyl esters **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, and **9** were prepared by diazotization[7a−c] of the corresponding amino acids in either HCl or H_2SO_4/KBr, and esterification of the α-halo acids overnight in methanol (excess), which had been pretreated with thionyl chloride (1 mol equiv).

General Procedure for Bromination. A mixture of the appropriate α-halo acid methyl ester and NBS in CCl_4 (250 mL) was heated at reflux under nitrogen. The reaction was initiated by irradiation with a 160 W mercury lamp. After the reaction period the mixture was allowed to cool to rt, filtered, washed with water, and evaporated under reduced pressure to give the crude product.

Methyl (2*R*,3*S*)-3-Bromo-2-chloro-3-phenylpropanoate (4). Bromination of **1a** (560 mg, 2.8 mmol) with NBS (640 mg, 3.6 mmol), as described above, for 2 h gave crude **4** and **5** (18:1 ratio determined NMR analysis) in 89% yield. Recrystallization from hexane gave **4** in 53% overall yield: mp 97 °C; ^{1}H NMR *δ* 3.90 (3H, s), 4.81 (1H, d, *J* = 11.3 Hz), 5.24 (1H, d, *J* = 11.3 Hz) 7.40 (5H, m); LRMS (EI) *m*/*z* 276/278/280 ([M]$^+$, BrCl). Anal. Calcd for $C_{10}H_{10}BrClO_2$: C, 43.25; H, 3.63; Br, 28.80; Cl, 12.78. Found: C, 43.31; H, 3.40; Br, 29.04; Cl, 13.09. $[\alpha]_D$ (*c* 0.2 in CH_3Cl) 90.4°.

Methyl (2*R,3*S**)-2,3-Dibromo-3-phenylpropanoate (6).** Bromination of **1b** (500 mg, 2.1 mmol) with NBS (440 mg, 2.4 mmol), as described above, for 2 h gave crude **6**. Recrystallization of the mixture from hexane gave **6** in 55% yield: mp 112 °C; ^{1}H NMR *δ* 3.90 (3H, s), 4.98 (1H, d, *J* = 11.8 Hz), 5.34 (1H, d, *J* = 11.8 Hz), 7.39 (5H, m); LRMS (EI) *m*/*z* 320/322/324 ([M]$^+$, Br_2). Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.28; H, 3.13; Br, 49.66. Found: C, 37.56; H, 2.82; Br, 49.56.

Methyl (*R*)-3-Bromo-2-chloro-3-methylbutanoate (7). Bromination of **2a** (360 mg, 2.0 mmol) with NBS (540 mg, 3.0 mmol), as described above, for 18 h and vacuum distilation gave **7** as an oil in 45% yield: ^{1}H NMR *δ* 1.79 (3H, s), 1.88 (3H, s), 3.80 (3H, s), 4.50 (1H, s); LRMS (EI) *m*/*z* 193/195 ([M − 35]$^+$, Br). Anal. Calcd for $C_6H_{10}BrClO_2$: C, 31.40; H, 4.39; Br, 34.82, Cl 15.45. Found: C, 31.10; H, 4.27; Br, 35.23, Cl, 15.81. $[\alpha]_D$ (*c* 0.2 in CH_3Cl) 3.5°.

Methyl (*S*)-4-Bromo-2-chloro-4-methylpentanoate (8a). Bromination of **3a** (1.0 g, 6.1 mmol) with NBS (1.6 g, 9.1 mmol), as described above, for 11 h and chromatography on silica gel (EtAc/hexane) gave **8a** as an oil in 43% yield: ^{1}H NMR *δ* 1.75 (3H, s), 1.85 (3H, s), 2.35 (1H, dd, *J* = 15.4 Hz, *J* = 5.2 Hz), 2.81 (1H, dd, *J* = 15.4 Hz, *J* = 7.0 Hz), 3.81 (3H, s), 4.60 (1H, dd, *J* = 7.0 Hz, *J* = 5.2 Hz); LRMS (CI, C_4H_{10}) *m*/*z* 321/323/325 ([M]$^+$, BrCl). Anal. Calcd for $C_7H_{12}BrClO_2$: C, 34.52, 4.97; Br, 32.81,

(10) (a) Porter, N. A., Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Hart, D. J., Krishnamuthy, R. *J. Org. Chem.* **1992**, *57*, 4457. (c) Smadja, W. *Synlett* **1994**, 1.

(11) For an overview, see: Skell, P. S.; Shea, K. J. Bridged Free Radicals. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons, Inc.: New York, 1973; Vol. II, pp 809−852.

(12) (a) Cabaleiro, M. C., Johnson, M. D. *J. Chem. Soc. B* **1967**, 565. (b) Fahey, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 4681. (c) Fahey, R. C., Schubert, R. C. *J. Am. Chem. Soc.* **1965**, *87*, 5172. (d) de la Mare, P. B. D., Koenigsberger, R. *J. Chem. Soc.* **1964**, 5327. (e) Cristol, S. J., Stermitz, F. R., Ramsey, P. S. *J. Am. Chem. Soc.* **1956**, *78*, 4939.

(13) Compound **4** and $AgNO_3$ (1.2 mol equiv) were stirred in a 1:1 mixture of acetone/water overnight. The mixture was filtered, and the solvents were evaporated under reduced pressure. The residue was dissolved in deuteriochloroform and analyzed by ^{1}H NMR. The diastereomeric mixture of the hydroxy derivative **11** was identified by comparison of the ^{1}H NMR spectrum with published spectral data: de la Mare, P. B. D.; Wilson, M. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 653.

(14) Easton, C. J., Hutton, C. A., Tan, E. W., Tiekink, E. R. *Tetrahedron Lett.* **1990**, *31*, 7059.

(15) (a) Lyons, A. R.; Symons, M. C. R. *J. Am. Chem. Soc.* **1971**, *93*, 7330. (b) Bowles, A. J.; Hudson, A., Jackson, R. A. *Chem. Phys. Lett.* **1970**, *5*, 552. (c) Edge, D. J., Kochi, J. K. *Tetrahedron Lett.* **1972**, 1341. (d) Edge, D. J., Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 6485.

Cl, 14.56. Found: C, 34.71; H, 5.03; Br, 32.91, Cl, 14.79. $[\alpha]_D$ (*c* 0.2 in CH_3Cl) −11.7°.

Methyl (*S*)-2,4-Dibromo-4-methylpentanoate (8b). Bromination of **3b** (1.4 g, 6.9 mmol) with NBS (1.8 g, 10.4 mmol), as described above, for 9 h and chromatography on silica gel (EtAc/hexane) followed by vacuum distillation gave **8b** as an oil in 39% yield: ^{1}H NMR δ 1.69 (3H, s), 1.84 (3H, s), 2.48 (1H, dd, J = 15.3 Hz, J = 3.6 Hz), 2.91 (1H, dd, J = 15.3 Hz, J = 9.0 Hz), 3.80 (3H, s), 4.57 (1H, dd, J = 9.0 Hz, J = 3.6 Hz); LRMS (CI, C_4H_{10}) m/z 287/289/291 ($[M + 1]^+$, Br_2). Anal. Calcd for $C_7H_{12}Br_2O_2$: C, 29.19; H, 4.20; Br, 55.49. Found: C, 29.52; H, 4.13; Br, 53.72. $[\alpha]_D$ (*c* 0.2 in CH_3Cl) −7.0°.

Methyl (2*R,3*S**)-3-Bromo-2-chloro-3-(4-chlorophenyl)-propanoate (10).** Bromination of **9** (1 g, 4.3 mmol) with NBS (990 mg, 5.6 mmol) as described above for 18 h gave crude **10** (mixture of diastereomers, 9:1 ratio determined by NMR analysis). Recrystallization of the mixture from hexane gave **10** in 85% yield: mp 85 °C; ^{1}H NMR δ 3.90 (3H, s), 4.75 (1H, d, J = 11.1 Hz), 5.21 (1H, d, J = 11.1 Hz) 7.37 (4H, bs); LRMS (EI) m/z (relative intensity) 310/312/314 ($[M]^+$, $BrCl_2$). Anal. Calcd for $C_{10}H_9BrCl_2O_2$: C, 38.50; H, 2.91; Br, 25.61; Cl, 22.73. Found: C, 38.21; H, 2.81; Br, 25.76; Cl, 22.79.

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