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A NEW PROCESS FOR THE ENANTIOSELECTIVE SYNTHESIS OF CHIRAL α-ARYLOXY- AND α-HYDROXY ACIDS

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Summary: *Chiral trichloromethyl carbinols **3**, readily available by catalytic enantioselective reduction of trichloromethyl ketones, are converted with inversion of configuration into chiral α-aryloxy and α-hydroxy carboxylic acid derivatives.*

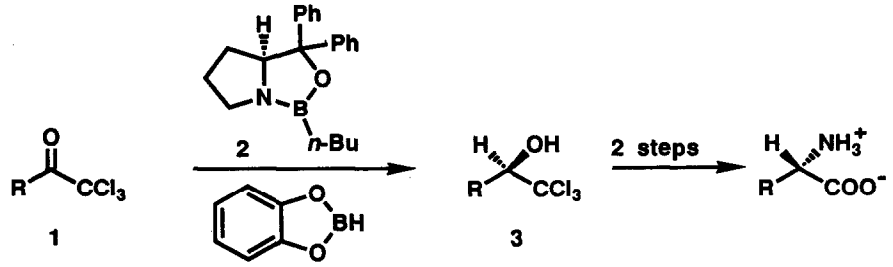
The reduction of a series of trichloromethyl ketones **1** by catecholborane in the presence of oxazaborolidine **2** as catalyst[1] produces the corresponding chiral secondary trichloromethyl carbinols **3** with high enantioselectivity.[2] This is an exceedingly useful process since the carbinols **3** can be converted in two simple steps (reaction with aqueous NaN_3–NaOH and subsequent reduction with H_2–Pd/C) to α-amino acids which are obtained in enantiomerically pure form by simple recrystallization (**Scheme I**).[2] We describe herein another valuable application of chiral trichloromethyl carbinols, specifically to the enantioselective synthesis of chiral α-hydroxy acids via the corresponding *p*-methoxyphenyl ether derivatives, themselves useful building blocks for synthesis.[3]

Table I summarizes the results obtained for the reduction of a representative set of four trichloromethyl ketones using 1.5 equiv of catecholborane and 0.1 equiv of catalyst **2** in toluene or methylene chloride solution to give the chiral alcohols **3**.[2] The new process for the transformation of **3** into chiral α-aryloxy acids and α-hydroxy acids is outlined in **Scheme II**.

The reaction of chiral trichloromethyl carbinols (**3**) with *p*-methoxyphenol in basic aqueous

yields of **4** in the case of primary alkyl substitution, R = *n*-C_5H_{11} (77%), and R = $C_6H_5CH_2CH_2$ (84%), were higher than for secondary alkyl substitution, R = cyclohexyl (62%).[5b] As expected the transformation of **3** to **4** for R = tertiary butyl was quite inefficient (10% yield) because of the extreme degree of steric retardation of displacement for a neopentyl system.

Scheme I



Recrystallization of the acids **4**, R = *n*-C_5H_{11}, $C_6H_5CH_2CH_2$, or cyclohexyl, from ether–hexane or hexane afforded each α-*p*-anisyloxy acid in 100% enantiomeric purity as determined by HPLC analysis using a chiral column.[4] The various acids were converted in 98-99% yield to the corresponding methyl esters **5** using dimethyl sulfate at pH 7-8 in a phase transfer system. Finally, these esters were treated with ceric ammonium nitrate in dimethylformamide-water at -20 °C (30 min) and 0 °C (30 min) to give the corresponding enantiomerically pure α-hydroxy acid methyl esters in 86-90% yield.[6] It is important to carry out this deprotection at lower temperatures to avoid competing nitration of the *p*-anisyloxy group in **5**. In addition, the oxidative deprotection of the methyl esters **5** is advantageous since it avoids the problem of oxidative decarboxylation which is observed in the reaction of the free carboxylic acids **4** with ceric ammonium nitrate.

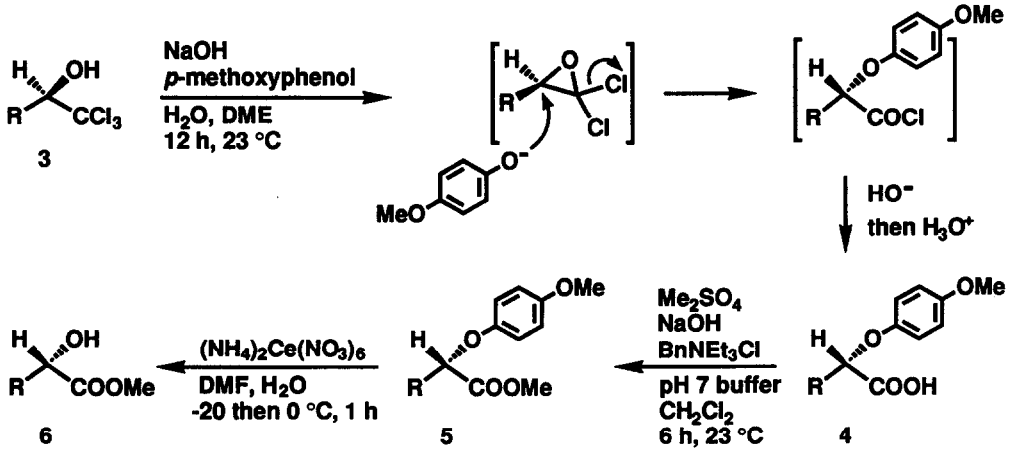
In conclusion, a highly effective process for the synthesis of optically pure α-hydroxy acids has been developed which has the advantage of employing a catalytic step for the introduction of chirality and a chiral reagent which can be recovered efficiently. The new process should allow access to a large series of useful chiral α-hydroxy acids and esters.[7]

The following procedures are representative.

(*R*)-4-Phenyl-1,1,1-trichloro-2-butanol. Addition of 4-phenyl-1,1,1-trichloro-2-butanone (1.59 g, 7.4 mmol) to a solution of preformed oxazaborolidine catalyst **2**[2] (3.7 mL, 0.74 mmol, 0.2 *M* in toluene, 0.1 equiv), cooling to -78 °C and dropwise addition of freshly distilled catecholborane (5.5 mL, 11 mmol, 2 *M* in toluene) over 10 min with vigorous stirring afforded a white precipitate. At 4 h the colorless solution was homogeneous and after 12 h at -78 °C the reaction was quenched with methanolic HCl (1.8 mL, 0.5 *M*) and allowed to warm to 23 °C. Partial concentration *in vacuo* afforded a fine white precipitate ((*S*)-α,α-diphenylprolinol•HCl) which was recovered by filtration. The filtrate was diluted with 40 mL of ether, washed with pH 13 buffer until colorless (6 x 20 mL), then brine (3 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 1.54 g (96%) of (*R*)-4-phenyl-1,1,1-trichloro-2-butanol as a colorless solid after chromatography through a short plug of silica gel (sg) (10 : 1 hexane–ethyl acetate); mp 53-5 °C; $[\alpha]_D^{24}$ +49.4° (c = 2.39, $CHCl_3$); 95% ee ^1H NMR (270 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 4.0 (ddd, 1H, *J* = 9.3, 5.4, 1.6 Hz), 3.0 (m, 1H), 2.8 (d, 1H, *J* = 5.4 Hz, -OH), 2.75 (m, 1H), 2.4 (m, 1H), 2.0 (m, 1H); FTIR (neat) 3400, 1455 cm^{-1}; CIMS 289 $[M+Cl]^-$; HRMS: calcd. for $[C_{10}H_{11}Cl_3O+Cl]^-$: 288.9535; found: 288.9517.

(*S*)-2-*p*-Anisyloxy-4-phenylbutanoic acid. To a mixture of (*R*)-4-phenyl-1,1,1-trichloro-2-butanol (1.06 g, 4.18 mmol), and *p*-methoxyphenol (1.04 g, 8.36 mmol), in dimethoxyethane (DME) (24 mL) was added water (15.9 mL) and then (dropwise) aqueous NaOH (2.33 mL, 24.9 mmol, 10.75 *M*) over 10 min with vigorous stirring at 23 °C (the solution remained homogeneous). After 12 h the DME was removed at 20 torr and the mixture was diluted with sat. $NaHCO_3$ (50 mL) and washed with CH_2Cl_2 (3 x 20 mL) to remove excess *p*-methoxyphenol. The CH_2Cl_2 was extracted with sat. $NaHCO_3$ (2 x 10 mL). The combined aqueous extracts were acidified to *ca.* pH 4 with solid KH_2PO_4, extracted with ether (40 mL), then acidified to pH 1 (12 *M* HCl) and extracted with ether (2 x 20 mL); the ether was dried ($MgSO_4$) and concentrated *in vacuo* to afford (*S*)-2-*p*-anisyloxy-4-phenylbutanoic acid (1.01 g, 84%) as a colorless solid after filtration through a 3 cm sg plug with 9 : 1 toluene–ethyl acetate - 3% acetic acid as eluent. Recrystallization from ether–hexane afforded a 92% recovery of optically pure acid; mp 81.5 - 82.5 °C; $[\alpha]_D^{24}$ -31.9° (c = 1.6, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.3-7.2 (m, 5H), 6.8 (s, 4H), 4.6 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.8 (s, 3H), 2.9

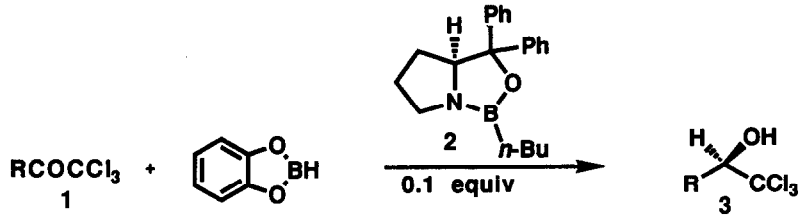
Scheme II



(m, 2H), 2.2 (m, 2H); FTIR (neat) 3400-2700, 1723, 1507 cm^{-1}; FAB MS: 286 $[M]^+$; HRMS: calcd. for $[C_{17}H_{18}O_4]^+$: 286.1205; found: 286.1208.

(*S*)-Methyl-2-*p*-anisyloxy-4-phenylbutanoate. To a vigorously stirred mixture of (*S*)-2-*p*-anisyloxy-4-phenylbutanoic acid (573 mg, 2.0 mmol), CH_2Cl_2 (1.5 mL), pH 7 aqueous buffer (1.8 mL), NaOH (186 μL, 2.0 mmol, 10.75 *M*), and benzyltriethylammonium chloride (62 mg, 0.2 mmol), was added dimethyl sulfate (285 μL, 3.0 mmol) at 23 °C. After 6 h NaOAc (272 mg, 2.0 mmol) was added to consume unreacted dimethyl sulfate and the mixture was stirred for 1 h. The mixture was diluted with 10 mL of pH 7

Table I. Enantioselective Reduction of α,α,α-Trichloromethyl Ketones



R in $RCOCCl_3$	solvent	temperature, °C (time, h)	3, % ee[b]
n-C_5H_{11}	toluene	-60[a] (12)	95[c]
$C_6H_5(CH_2)_2$	toluene	-78 (12)	95[c]
c-C_6H_{11}	CH_2Cl_2	-20[a] (48)	92[d]
t-C_4H_9	toluene	-20[a] (56)	98[e]

[a]These reactions were initiated at -78 °C and brought to the indicated temperature after 1 h. [b]Alcohol % ee determined by Chiracel (Diacel Co.) HPLC analysis with the following columns: [c]Chiracel AD. [d]Chiracel OJ. [e]Chiracel OD analysis on the benzoate ester.

buffer and extracted with ether (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*; chromatography on a short sg column (10:1 hexane–ethyl acetate) afforded optically pure (*S*)-methyl-2-*p*-anisyloxy-4-phenylbutanoate as a colorless oil (589 mg, 98%); $[\alpha]_D^{24}$ -39.5° (c = 1.33, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.3–7.2 (m, 5H), 6.8 (s, 4H), 4.5 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 2.9 (m, 2H), 2.2 (m, 2H); FTIR (neat) 1755, 1734, 1506 cm^{-1}; EIMS: 300 $[M]^+$; HRMS: calcd. for $[C_{18}H_{20}O_4]^+$: 300.1361; found: 300.1349.

(*S*)-Methyl-2-hydroxy-4-phenylbutanoate. A solution of (*S*)-methyl-2-*p*-anisyloxy-4-phenylbutanoate (569 mg, 1.90 mmol, in 1.7 mL of 4:1 DMF - H_2O) was added dropwise by cannula over 15 min to a cold (-23 °C) well-stirred solution of ceric ammonium nitrate (5.2 g, 9.5 mmol) in 4:1 DMF–H_2O (13 mL). After reaction for 30 min at -23 °C the solution was maintained at 0 °C for 30 min and then diluted with 10 mL each of 1:1 ether–hexane and water with stirring at 0 °C. Water (30 mL) was added and the mixture was extracted with 1:1 ether–hexane (3 x 20 mL). The organic extracts were washed (10 mL of 0.5 *M* Na_2CO_3), dried ($MgSO_4$), and concentrated *in vacuo* and the resultant orange oil was chromatographed on sg with 5:1 hexane–ethyl acetate to afford optically pure[4] (*S*)-methyl-2-hydroxy-4-phenylbutanoate (330 mg, 90%) as a colorless oil; $[\alpha]_D^{24}$ +32.4° (c = 2.1, $CHCl_3$), lit.[6b] $[\alpha]_D^{25}$ -32.5° ($CHCl_3$) (*R*) enantiomer; ^1H NMR (270 MHz, $CDCl_3$) δ 7.3–7.2 (m, 5H), 4.2 (dd, 1H, *J* = 7.9, 4.0), 3.75 (s, 3H), 2.8 (m, 2H), 2.1 (m, 1H), 1.9 (m, 1H); IR (neat) 3450, 1734 cm^{-1}; EIMS: 194 $[M]^+$; HRMS: calcd. for $[C_{11}H_{14}O_3]^+$: 194.0943; found: 194.0939.

References and Notes

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861-2863. (d) Corey, E. J. in *Proceedings 31st National Organic Chemistry Symposium of the American Chemical Society*; 1989; p 1. (e) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275-6278. (f) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614. (g) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209-1216.
2. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.
3. For other pathways for the enantioselective synthesis of α-hydroxy acids by oxazaborolidine catalyzed enantioselective reduction see ref. 1f.
4. Analysis for enantiomeric purity was performed using a Chiracel OD analytical column (0.46 mm, 25 cm) with isopropyl alcohol in hexane for elution (10% *i*-PrOH for R = *n*-C_5H_{11} and R = $C_6H_5(CH_2)_2$; 1.5% *i*-PrOH for R = cyclohexyl). In each case the major enantiomer (*S*) eluted more rapidly than the minor (*R*) enantiomer. The retention times observed at a flow rate of 1 mL per min were as follows (major, minor in min): **5**, R = *n*-C_5H_{11} (5.0, 6.5); **5**, R = *c*-C_6H_{11} (7.3, 8.3); **6**, R = $C_6H_5(CH_2)_2$ (7.9, 10.5).
5. (a) Yields with *p*-anisoxide as the nucleophile are significantly higher than those employing direct hydrolysis to the α-hydroxy acid with hydroxide ($BnEt_3NCl$, NaOH, H_2O, CH_2Cl_2, **3** R = $C_6H_5(CH_2)_2$; 40%). Further, the *p*-anisyloxy group provides selective hydroxyl protection and also imparts UV activity for convenient TLC and HPLC detection. See Corey, E. J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782-4786 for the synthesis of α-aryloxy carboxylic acids from trichloromethyl carbinols and phenoxides. (b) For R = *c*-C_6H_{11} 4 equiv of *p*-methoxyphenol and 8 equiv of NaOH were used.
6. (a) **6**, R = *n*-C_5H_{11} $[\alpha]_D^{24}$ +12.8° (c = 2.35, $CHCl_3$), lit. $[\alpha]_D^{23}$ +10.7° (c = 4.57, $CHCl_3$): Grieco, P. A.; Takigawa, T.; Vedananda, T. R. *J. Org. Chem.* **1985**, *50*, 3111-3115. (b) **6**, R = $C_6H_5(CH_2)_2$ $[\alpha]_D^{24}$ +32.4° (c = 2.1, $CHCl_3$), lit. $[\alpha]_D^{25}$ -32.5° ($CHCl_3$) (*R*) enantiomer: Satoh, T.; Onda, K.-i.; Yamakawa, K. *Tetrahedron Lett.* **1990**, *31*, 3567-3570. (c) **6**, R = *c*-C_6H_{11} $[\alpha]_D^{24}$ +34.9° (c = 1.49, $CHCl_3$), lit. $[\alpha]_D^{20}$ -31.3° (c = 2.36, $CHCl_3$) (*R*) enantiomer: Ko, K. Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron.* **1984**, *40*, 1333-1343.

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