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A facile method for the synthesis of enantiopure α-unsubstituted β-hydroxy esters

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Abstract

One-pot deacylation–debromination reactions involving the transesterification of the initial chiral α-bromo-β-hydroxy thioimide aldol adducts and subsequent Al–Hg mediated reductive cleavage of the C–Br bond allow for a facile synthesis of enantiopure β-hydroxy esters. © 2000 Published by Elsevier Science Ltd.

1. Introduction

As a consequence of the importance of enantiomerically pure aldol adducts, considerable effort has been directed toward the development of asymmetric syntheses of homochiral α-unsubstituted β-hydroxy carboxylate compounds[1,2] and the use of homochiral β-hydroxy esters as key building blocks in the synthesis of drugs and natural products.[3] Asymmetric aldol additions are one-step routes to chiral α-unsubstituted β-hydroxy carboxylates. However, the stereocontrol observed in metal-assisted aldolizations of chiral unsubstituted enolates of the 'acetate' type are not as good as those obtained from α-substituted metal enolates.[1,4] Quite recently, Yamamoto has developed a chiral acetate ester which adds to a variety of aldehydes in good to excellent yield (57–90%) with excellent diastereoselectivity (94–99% de).[5] The other main general solution to this problem is based on the incorporation of an auxiliary substituent in the α-position.[4] The ease of access to chiral α-sulfenylated and bromohydrin aldol adducts of 85–99% ee makes the conversion of α-substituted aldol adducts into α-unsubstituted β-hydroxy carboxylates a useful transformation. The recently developed catalytic hydrogenolysis[4,6] and tri-*n*-butyltin hydride mediated radical cleavage of the carbon–bromine bond afforded β-hydroxy esters in good to excellent yields.[7] Our recent discovery of a one-pot process for the asymmetric bromination–aldolization of acetate thioimide enolate provided an incentive to find uses for the chiral bromohydrin aldol adducts.[8] We report here on a facile process for the conversion of chiral bromohydrin aldols to enantiopure β-hydroxy esters.

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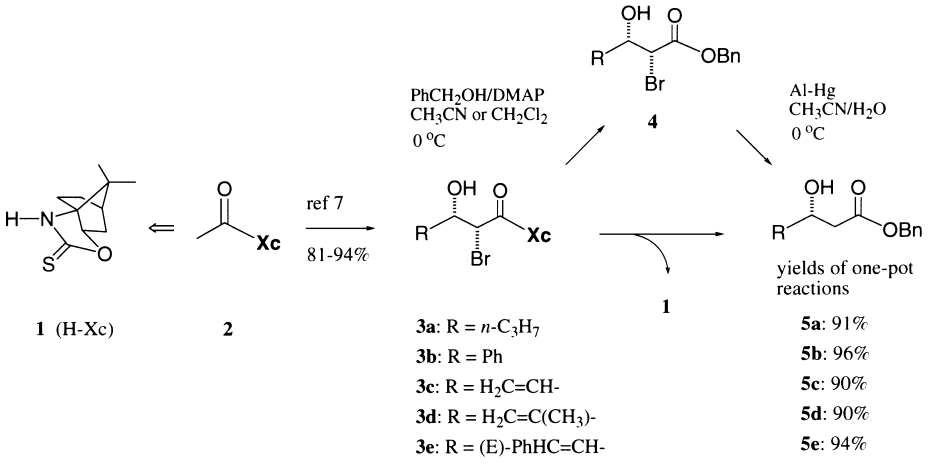
2. Results and discussion

Previous reports from our laboratory have documented the utility of acetate thioimide **2** for the construction of homochiral bromohydrin aldols **3**.[8] The bromination–aldolization of acetate thioimide enolate to a variety of aldehydes was carried out by a standard procedure.[8] With chiral bromohydrins **3** in hand, the stage was set for establishing the feasibility of Al–Hg as a mild reducing reagent to effect chemoselective cleavage of the C–Br bond in **3**. However, attempts to reductively cleave the C–Br bond in **3** resulted in a complex mixture as a consequence of the instability of the α-bromo thioimide aldol adducts. The above problems were circumvented by the bromo thioimide aldol adducts **3** being first converted to the stable benzyl α-bromo esters **4**,[8] and reductive debromination then performed at this stage. Simply adding Al–Hg (mercury content ~2.5%) to the bromo ester **4a** led to clean debromination within 30 min to give β-hydroxy ester **5a** in 91% isolated yield (Scheme 1). Aldol adduct **4b** derived from benzaldehyde gave a similar result. Thus, the same conditions effected deacylation–debromination of **4b** to afford 96% overall yield of β-hydroxy ester **5b**. Extension of these observations to other unsaturated α-bromo esters confirms their generality. Our attention next turned to exploring the chemoselective cleavage of the C–Br bond of bromo esters **4c–e**, which by virtue of the sensitivity of the unsaturation within a molecular framework demand mild reduction conditions (Scheme 1). Fortunately, we found that the Al–Hg promoted debromination not only resulted in the suppression of olefin saturation, which is a major problem with H_2/Pd/C, but also afforded complete control for the desired mode of reductive cleavage. Potential dehydroxybromination in the intermediate carbanion does not appear to compete kinetically with carbon–hydrogen formation. Most gratifyingly, the transesterification–debromination approach to the conversion of the initial homochiral bromohydrin aldols to β-hydroxy esters could be accomplished in a one-pot procedure in good to excellent yields. The simplicity of this one-pot procedure is exemplified by the details given for the case of **3b** in the Experimental. The enantiomeric excesses of these β-hydroxy esters were measured by direct comparison to the racemic esters and analyzed by chiral HPLC. The analyses by HPLC on a Chiralcel OD column (Daicel Chemical Industries) indicated that β-hydroxy esters **5a–e** were essentially enantiomerically pure (>99% ee).



Scheme 1.

3. Conclusions

Unlike the reported debromination conditions employed, such as catalytic hydrogenolysis (H_2/Pd–C) and tri-*n*-butyltin hydride mediated reduction, the Al–Hg mediated chemoselective cleavage of the C–Br bond allows for a mild transformation of bromohydrin aldols into β-hydroxy esters in the presence of sensitive functionality. Synthetically, the present studies offer an efficient and high-yielding asymmetric synthesis of enantiopure α-unsubstituted β-hydroxy esters.

4. Experimental

4.1. General

Diisopropylethylamine and dichloromethane were dried by distillation under N_2 from calcium hydride. $TiCl_4$ (1 M in CH_2Cl_2) was used as received. All aldehydes were freshly distilled prior to use. Unless otherwise noted, all non-aqueous reactions were carried out under a dry nitrogen atmosphere with oven-dried glassware. Flash chromatography was done on E. Merck silica gel 60 (230–400 mesh). Concentrations for rotation data are given as g/100 mL of solvent. Diastereomeric excesses (de) were determined by HPLC on a Chiralcel OD column (Daicel Chemical Industries).

4.2. General procedure for the deacylation–debromination reactions of **3**

Aluminum amalgam was prepared from granular aluminum (~40 mesh, 0.1 g), which was immersed, all at once, into an aqueous solution of $HgCl_2$ (1%, 2.5 mL). After shaking for 10 s, the grey amalgamated metal was washed with distilled water (10 mL) and used at once. To a solution of **3b** (390 mg, 1 mmol) and $PhCH_2OH$ (1.2 mmol) in CH_3CN or CH_2Cl_2 (4 mL) at 0°C was added a solution of DMAP (0.2 mmol) in 0.5 mL of CH_2Cl_2. The mixture was stirred at that temperature for 4 h, and aluminum amalgam was added followed by water (0.2 mL). After stirring for 30 min at 0°C, the mixture was filtered and the residue was washed with two 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with 5% HCl and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give β-hydroxy ester **5b** and recovered **1**. New compounds have been satisfactorily characterized spectroscopically, and elemental composition has been established by high-resolution mass spectroscopy or combustion analysis.

4.3. Phenylmethyl (S)-3-hydroxyhexanoate **5a**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H), 5.13 (s, 2H), 4.04–3.99 (m, 1H), 2.77 (bs, 1H), 2.53 (dd, $J=16$, 3.2 Hz, 1H), 2.44 (dd, $J=16$, 9.2 Hz, 1H), 1.52–1.32 (m, 4H), 0.90 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 131.55, 128.46, 128.22, 128.13, 127.52, 68.94, 66.53, 41.65, 34.26, 17.79, 13.52; $[\alpha]_D^{25}$ +19.7 (*c* 1.8, CH_2Cl_2); high-resolution MS (FAB+) *m*/*e* calcd for $C_{13}H_{19}O_3$ 223.1335, found 223.1342.

4.4. Phenylmethyl (R)-3-hydroxy-3-phenylpropanoate **5b**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.22 (m, 10H), 5.22 (s, 2H), 5.20 (dd, $J=8.8$, 4.0 Hz, 1H), 2.88 (dd, $J=16.0$, 8.8 Hz, 1H), 2.82 (dd, $J=16.4$, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.79, 142.21, 135.28, 128.40, 128.36, 128.16, 128.05, 127.63, 125.49, 70.26, 66.57, 43.39; HPLC

(Chiralcel OD; 95:5 hexane:isopropyl alcohol; flow rate 1 ml/min; UV 254 nm); $t_R = 21.2$ min (*S*), 29.7 min (*R*); $[\alpha]_D^{25}$ +28.6 (*c* 1.8, CH_2Cl_2); high-resolution MS (FAB+) *m*/*e* calcd for $C_{16}H_{16}O_3$ 257.1178, found 257.1177.

4.5. Phenylmethyl (R)-3-hydroxy-4-pentenoate **5c**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 5.86 (ddd, $J = 17.2$, 10.8, 5.6 Hz, 1H), 5.29 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.14 (s, 2H), 5.13 (dd, $J = 10.8$, 1.2 Hz, 1H), 4.57–4.53 (m, 1H), 2.63 (dd, $J = 16.8$, 4.0 Hz, 1H), 2.56 (dd, $J = 16.8$, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.69, 138.49, 135.33, 128.43, 128.20, 128.10, 115.35, 68.89, 66.56, 41.25; $[\alpha]_D^{25}$ +9.7 (*c* 1.8, CH_2Cl_2); high-resolution MS (EI) *m*/*e* calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0934.

4.6. Phenylmethyl (R)-3-hydroxy-4-methyl-4-pentenoate **5d**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 5.14 (s, 2H), 5.01 (s, 1H), 4.86 (s, 1H), 4.48 (dd, $J = 8.0$, 4.4 Hz, 1H), 2.69 (dd, $J = 15.6$, 4.4 Hz, 1H), 2.65 (dd, $J = 15.6$, 8.0 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.11, 145.17, 135.34, 128.46, 128.25, 128.19, 111.49, 71.51, 66.63, 40.14, 18.35; HPLC (Chiralcel OD; 95:5 hexane:isopropyl alcohol; flow rate 1 ml/min; UV 254 nm); $t_R = 14.1$ min (*S*), 19.2 min (*R*); $[\alpha]_D^{25}$ +6.2 (*c* 2.1, CH_2Cl_2); high-resolution MS (FAB+) *m*/*e* calcd for $C_{13}H_{17}O_3$ 221.1178, found 221.1181.

4.7. Phenylmethyl (R)-3-hydroxy-5-phenyl-(E)-4-pentenoate **5e**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 10H), 6.65 (d, $J = 16.0$ Hz, 1H), 6.22 (dd, $J = 16.0$, 6.0 Hz, 1H), 5.17 (s, 2H), 4.78–4.72 (m, 1H), 2.73 (dd, $J = 16.4$, 4.0 Hz, 1H), 2.67 (dd, $J = 16.4$, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.65, 136.16, 135.31, 130.72, 129.63, 128.45, 128.39, 128.22, 128.13, 127.66, 126.39, 68.88, 66.62, 41.62; $[\alpha]_D^{25}$ −1.9 (*c* 1.1, CH_2Cl_2); high-resolution MS (EI) *m*/*e* calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1260.

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