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Enantioselective Synthesis of β-Hydroxy-α-amino Acid Esters by Aldol Coupling Using a Chiral Quaternary Ammonium Salt As Catalyst

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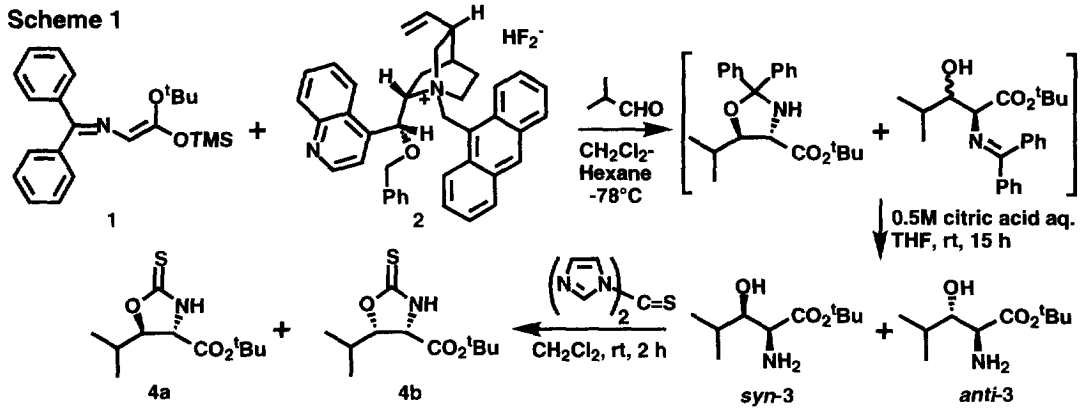
Abstract: *A variety of chiral β-hydroxy-α-amino acids and derivatives thereof can be synthesized enantioselectively using the aldol reaction of an aldehyde, the glycinate* ***1*** *and the cinchonidine-derived catalyst* ***2****, as indicated in Schemes 1 and 2 and Table 1.*

Recent studies in this laboratory have resulted in the development of an excellent catalyst for highly enantioselective alkylation[1,2] and Michael addition reactions[3] under phase transfer conditions. In addition, a rational and predictive mechanistic model had been provided along with supportive experimental evidence.[1,2] Among the outstanding applications of this methodology is the asymmetric synthesis of α-amino acids with up to 400 : 1 enantioselection.[1,4] Reported herein is the extension of this system to the synthesis of chiral β-hydroxy-α-amino acids by aldol coupling of aldehydes with the trimethylsilyl enol ether derivative of *tert*-butylglycinate-benzophenone Schiff base (**1**) using the cinchonidine-derived bifluoride salt **2** as catalyst (Scheme 1).[5,6]

A solution of **1** in CH_2Cl_2–hexane at -78 °C was treated with 5 equiv of isobutyraldehyde and a solution of 10 mole % of **2** in CH_2Cl_2 (final solvent ratio 3 : 1 hexane–CH_2Cl_2). After 7 h at -78 °C, the reaction product was isolated by quenching with saturated aqueous NH_4Cl solution and extraction. The resulting isomeric mixture of oxazolidine and β-hydroxy-α-amino acid ester Schiff base with benzophenone was transformed by exposure to 0.5% aqueous citric acid for 15 h at 23 °C into the principal product, the *syn* α-amino-β-hydroxy ester *syn*-**3**, and the minor product *anti*-**3** (ratio of 6 : 1). Column chromatography of the mixture on silica gel using 4% MeOH in CH_2Cl_2 for elution provided pure *syn*-**3** in 61% yield and *anti*-**3** in 9% yield. The

Scheme 1



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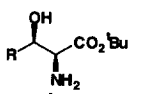
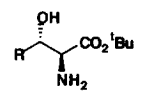
enantiomeric purity of these amino esters was established by transformation using thiocarbonyl bisimidazole (CH_2Cl_2 at 23 °C) into the oxazolidine-2-thione derivatives **4a** and **4b** and HPLC analysis using a Chiral Pak AD column using 10% isopropyl alcohol in hexanes for elution; found for **4a**, 95% ee and for **4b**, 83% ee. The absolute configuration of *syn*-**3** was established as (2*S*,3*R*) by comparison of its optical rotation, $[\alpha]_D^{23}$ + 11.9 (c=1.0, $CHCl_3$) with an authentic sample of the enantiomer;[7] that of **4b** was similarly determined.[7,8] Experimental procedures and data for the syntheses of *syn*-**3**, *anti*-**3**, **4a** and **4b** follow below.[9] The conversion of **4a** and **4b** to the free acids corresponding to *syn*-**3** and *anti*-**3** can be carried out as previously described.[10]

The aldol coupling of **1** in the presence of catalyst **2** with a number of other aldehydes was studied; the results are summarized in Table 1. Variability in the ratio of *syn* to *anti* aldol products, *syn*-**5** to *anti*-**5**, was observed with lower ratios being associated with unbranched aldehydes of the type RCH_2CH_2CHO. On the other hand the highest *syn/anti* ratio, 13 : 1 was found for cyclohexanecarboxaldehyde. In this case the high preference for formation of *syn*-**5**, R = C_6H_{11}, seems quite consistent with the mechanistic model proposed previously,[1,2] the high preference for the 2*S* configuration in the products **5** being predicted. The special feature of cyclohexanecarboxaldehyde which is responsible for the high *syn/anti* selectivity is suggested by the model to be substantial van der Waals (dispersion) attraction between the cyclohexyl group of the aldehyde and the *tert*-butyl and *E*-phenyl groups of the enolate substrate in the contact quaternary ammonium ion-enolate ion pair.[1,2] The same model leads to the expectation of lower *syn/anti* ratios for the unbranched aldehydes.

The aldol products **5**, R = $Cl(CH_2)_3$, illustrate a broader utility of the new methodology as outlined in Scheme 2. The mixture **7a** + **7b** was separated chromatographically and transformed into the diastereomeric 3-hydroxy-(*S*)-pipecolic acids **8a** and **8b**.[11] Similarly, after chromatographic separation, **9a** and **9b** were converted to the diastereomeric amino acids **10a** and **10b**, as shown.[12]

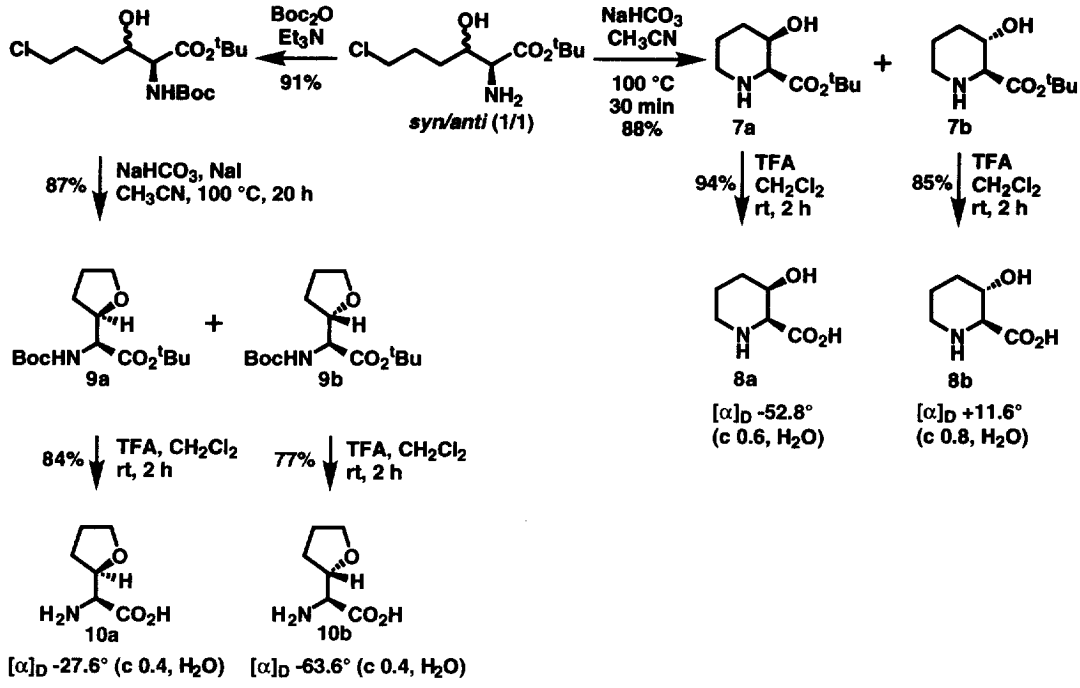
The syntheses of β-hydroxy-α-amino acids and derivatives described herein provide ready access to these useful substances.[13]

Table 1. Data for  **(*syn*-5) and**  **(*anti*-5) and the corresponding thiocarbamates (6a and 6b, respectively).**

R	solvent Hex-CH_2Cl_2	temp (°C)	time (h)	yield of 5 (%)	*syn/anti*	ee (%)[a] 6a	ee (%)[a] 6b	R_f (30% EtOAc-Hex) 6a	R_f (30% EtOAc-Hex) 6b
i-Pr	3 : 1	-78	7	70	6 / 1	95	83	0.51	0.45
c-Hex	5 : 1	-50	1	81	13 / 1	88	46	0.54	0.45
n-Hex	3 : 1	-78	2	79	3 / 1	89	91	0.55	0.45
$Cl(CH_2)_3$-	5 : 1	-78	2	48	1 / 1	82	86	0.40	0.31
$Ph(CH_2)_2$-	3 : 1	-78	6	64	1 / 1	72	86	0.48	0.43
i-Bu	5 : 1	-45	2	61	3 / 1	76	70	0.56	0.48

[a]ee values were determined after chromatographic separation of *syn*-5 and *anti*-5 by conversion to 6a and 6b and analysis by HPLC using a Chiral Pak AD column with 10% *i*-PrOH-Hexanes for elution at 23 °C.

Scheme 2



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5. The cinchonidine-derived bifluoride salt **2** was prepared from the corresponding bromide[1-3] by passage of a methanolic solution through a column of ion exchange resin Amberlyst A-26 (OH^-) to afford the corresponding quaternary ammonium hydroxide, neutralizing with 2 equiv of 1*N* HF solution, removal of solvent under reduced pressure, and drying of the resulting solid *in vacuo* over P_2O_5.
6. The silyl ketene acetal **1** was prepared from *tert*-butylglycinate-benzophenone imine by deprotonation with lithium diisopropylamide in THF at -78 °C for 1 h and subsequent reaction with trimethylchlorosilane. The product was isolated by removal of THF under reduced pressure, addition of hexane, removal of LiCl, removal of solvent under reduced pressure, dissolved in dry CH_2Cl_2 and stored at -20 °C under dry N_2. An E/Z ratio of 7 : 1 was determined by ^1H NMR analysis; see Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron* **1988**, *44*, 3671. Silyl ketene acetal **1** is quite unstable in CH_2Cl_2 solution at room temperature and should be kept cold.

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9. **Synthesis of *tert*-butyl (2*S*,3*R*)-3-hydroxyleucinate (*syn*-3):** To solution of silyl ketene acetal **1** (248 mg, 0.676 mmol) in methylene chloride (4.0 mL) and hexanes (14.4 mL) under nitrogen at -78 °C were added isobutyraldehyde (0.31 mL, 3.38 mmol) and phase transfer catalyst **2** (40 mg, 16.9 μmol) in methylene chloride (0.8 mL). The solution was stirred for 7 h at -78°C and then treated with saturated aqueous ammonium chloride and ether. The ethereal solution was extracted with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To a solution of the crude reaction product in THF (8.0 mL) was added 0.5 M citric acid aqueous solution (5.0 mL, 2.5 mmol) at 23 °C and the solution was stirred at 23 °C for 15 h. After removal of THF *in vacuo* at 20 °C or below, the aqueous solution was extracted with ether two times and then neutralized with $NaHCO_3$ and saturated with NaCl and Rochelle salt. The mixture was extracted with methylene chloride three times. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel using 4% MeOH in CH_2Cl_2 for elution afforded 79 mg (61%) of *syn*-**3** and 12 mg (9%) of *anti*-**3**. Data for *syn*-**3** (95% ee): R_f, 0.52 (10% MeOH-CH_2Cl_2); $[\alpha]_D^{23}$ +11.9 (*c* 1.0, $CHCl_3$) (lit (enantiomer of *syn*-**3**)[7] $[\alpha]_D^{20}$ -11.6 (*c* 0.7, $CHCl_3$) (92% ee)); FTIR (film) 3380, 3316, 2975, 2934, 2875, 1730, 1592, 1472, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.39 (m, 2H), 2.12 (br s, 3H), 1.71 (m, 1H), 1.46 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 81.6, 77.1, 56.4, 30.3, 28.0 (3C), 19.5, 17.6 ppm; CIMS 204 $[M+H]^+$; HRMS calcd for $[C_{10}H_{22}NO_3]^+$, 204.1600; found, 204.1605.

To a solution of *syn*-**3** (10.9 mg, 57.0 μmol) in methylene chloride (2.0 mL) was added thiocarbonyl bisimidazole (10.2 mg, 57.0 μmol). After stirring at 23 °C for 2 h, the solvent was removed and the residue was purified by column chromatography (40% EtOAc-Hex) to afford cyclic thiocarbamate **4a** (11.8 mg, 48.1 μmol, 84%): (95% ee by HPLC analysis using a Chiral Pak AD column with 10% isopropyl alcohol in hexanes); R_f, 0.51 (30% EtOAc-Hex); $[\alpha]_D^{23}$ +66.1 (*c* 1.07, $CHCl_3$); FTIR (film) 3318, 3204, 2971, 2934, 2879, 1739, 1501, 1471, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 4.71 (app.t, *J* = 6.0 Hz, 1H), 4.16 (d, *J* = 6.0 Hz, 1H), 2.06 (d-sept, *J* = 6.0, 7.0 Hz, 1H), 1.48 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 167.6, 90.1, 84.3, 60.2, 32.4, 27.9 (3C), 17.1, 16.8 ppm; CIMS 246 $[M+H]^+$; HRMS calcd for $[C_{11}H_{20}NO_3S]^+$, 246.1164; found, 246.1163.

Found for *anti*-**3** (83% ee): R_f, 0.40 (10% MeOH-CH_2Cl_2); $[\alpha]_D^{23}$ +12.3 (*c* 0.35, $CHCl_3$); FTIR (film) 3359, 3300, 2976, 2934, 2874, 1729, 1596, 1474, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.47 (d, *J* = 4.8 Hz, 1H), 3.37 (dd, *J* = 4.8, 6.9 Hz, 1H), 2.23 (br s, 3H), 1.77 (d-sept, *J* = 6.9, 6.7 Hz, 1H), 1.46 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 81.8, 78.6, 57.1, 30.8, 28.1 (3C), 19.5, 18.1 ppm; CIMS 204 $[M+H]^+$; HRMS calcd for $[C_{10}H_{22}NO_3]^+$, 204.1600; found, 204.1602. **Thiocarbamate (4b)** (83% ee): R_f, 0.45 (30% EtOAc-Hex); $[\alpha]_D^{23}$ -6.7 (*c* 0.42, $CHCl_3$); FTIR (film) 3318, 2975, 2933, 2879, 1784, 1495, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (br s, 1H), 4.67 (app.t, *J* = 8.5 Hz, 1H), 4.45 (d, *J* = 8.5 Hz, 1H), 2.06 (d-sept, *J* = 8.5, 6.7 Hz, 1H), 1.50 (s, 9H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 166.8, 90.0, 84.2, 61.0, 29.0, 27.8 (3C), 19.2, 17.9 ppm; CIMS 246 $[M+H]^+$; HRMS calcd for $[C_{11}H_{20}NO_3S]^+$, 246.1164; found, 246.1154.
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