1.5 h of reflux, a molar equivalent of acetophenone was added. This procedure resulted in a 62% reduction of acetophenone with an 8.3% enantiomeric excess of (+)-methylphenylcarbinol. This result is likewise consistent with the Wiegers–Smith model for reducing solutions derived from lithium aluminum hydride and *tert*-butyl alcohol.

Another aspect of reduction by alkoxyaluminohydride species involves the steric bulk imposed by the alkoxy unit. Numerous workers[2] have attested to the fact that such bulk imparts a slower rate of reduction for alkoxyaluminohydride species vs. their nonalkoxy counterpart. When Wiegers and Smith combined this feature with hindered ketone substrates, they found[4] that the kinetics describing such reductions pointed to a greater percentage of the reduction coming from lithium aluminum hydride rather than the alkoxyaluminohydride species. The most dramatic example was provided from the reduction of 2,4,6-trimethylbenzophenone by reducing solutions derived from lithium aluminum hydride and *tert*-butyl alcohol. The kinetics from this experiment suggest that the reduction was accomplished by lithium aluminum hydride.[4]

The production of chiral hydride reagents from lithium aluminum hydride and chiral alcohols is, of course, not immune to these disproportionation processes either. The low levels of enantiomeric excess[1] realized from the reducing solutions derived from lithium aluminum hydride and 1 implied that an appreciable amount of reduction was due to the achiral hydride species. We have previously reported[1] on experiments, involving excess hydride, which substantiated the disproportionation process. A further test of this contention would be the reduction of the hindered 2,4,6-trimethylbenzophenone by solutions composed of lithium aluminum hydride and 1. This reduction should give carbinol of low enantiomeric excess, and the overall yield, as well, should be predictably lower than when acetophenone was the substrate.

We found that the reduction of 2,4,6-trimethylbenzophenone by hydride solutions derived from lithium aluminum hydride and 1 was indeed quite different than that obtained when acetophenone was the substrate. The latter had given a 96% production of carbinol with a 7.7% enantiomer excess of the (+)-carbinol. The former gave only a 55% production of carbinol, and the resultant carbinol was optically inactive![8] The low level of reduction and the optical inactivity of the product are consistent with some disproportionation with reduction occurring via achiral lithium aluminum hydride.

Indeed, optical activity has proven to be a very useful probe for examining alkoxyaluminohydride disproportionations. The method is sensitive enough to distinguish between the different disproportionation modes obtained from lithium aluminum hydride and methanol solutions and those obtained from lithium aluminum hydride and *tert*-butyl alcohol. The probe is also sensitive enough to determine the major reducing species when hindered substrates such as 2,4,6-trimethylbenzophenone are used. The results are consistent with the stereochemical and kinetic results of previous workers.

Experimental Section

Acetophenone Reduction with Lithium Aluminum Hydride and Methanol Solutions. To a 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 1.00 g (0.025 mol) of lithium aluminum hydride and 100 mL of anhydrous ether. To this stirred solution was added 0.8 g (0.025 mol) of methanol in 20 mL of ether. The reaction was heated to reflux for 1 h. Then, 4.3 g (0.025 mol) of 1 in 40 mL of THF was added dropwise, and the reaction was heated for another 1.5 h. The reaction was then cooled to room temperature, and 3.0 g (0.025 mol) of acetophenone in 20 mL of ether was added, dropwise. After 2 h of additional reflux, the reaction was cooled to room temperature and quenched by the dropwise addition of 1 mL of water, followed by 1 mL of 15% aqueous sodium hydroxide, and finally by 3 mL of water. The precipitate was filtered and washed with 25 mL of ether. The filtrate was dried quickly over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant residue was purified and analyzed as previously described.[1]

Acetophenone Reduction with Lithium Aluminum Hydride and *tert*-Butyl Alcohol Solutions. The reaction was carried out as described above except that 0.025 mol of *tert*-butyl alcohol was used in place of methanol.

2,4,6-Trimethylbenzophenone Reduction with Lithium Aluminum Hydride and 1. To a 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 0.76 g (0.02 mol) of lithium aluminum hydride and 100 mL of anhydrous ether. To this stirred solution was added, dropwise, 3.4 g (0.02 mol) of 1 in 40 mL of THF. The reaction was heated to reflux for 1 h after the addition of 1 had been completed. The reaction was then cooled to room temperature, and 8.9 g (0.04 mol) of 2,4,6-trimethylbenzophenone in 40 mL of ether was added, dropwise. After 2 h of additional reflux, the reaction was cooled and worked up as described above.

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Registry No. 1, 68510-42-9; acetophenone, 98-86-2; 2,4,6-trimethylbenzophenone, 954-16-5; lithium aluminum hydride, 16853-85-3; methanol, 67-56-1; *tert*-butyl alcohol, 75-65-0.

(8) An α value of 0.001 would have been detectable.

Stereospecific Synthesis of α-Amino-β-hydroxy Acids

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α-Amino-β-hydroxy acids have been prepared by various different methods, including epoxidation of unsaturated carboxylic acids and subsequent amination,[2] condensation of isonitriles with aldehydes or ketones,[3] and base-catalyzed reactions of glycine (or its derivatives) with carbonyl compounds.[4] Most of these procedures suffer however from one or another limitation, requiring either scarce starting materials or drastic reaction conditions, or providing mixtures of stereoisomers. We wish to describe a promising new method for the synthesis of α-amino-β-hydroxy acids which affords exclusively either the erythro or threo isomers in an efficient one-pot procedure. The procedures involve base-catalyzed condensation of glycine derivatives with carbonyl compounds: *N,N*-bis(trimethylsilyl)glycine trimethylsilyl ester (1) serving as

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Table I. Preparation of *erythro*-α-Amino-β-hydroxy Acids

amino acid	yield,[a] %	chemical shift (δ)[b] CHN	CHO	CH_3	C_6H_5	$CH(CH_3)_2$
dl-allo-threonine (3a)[c]	70	3.84 (d, J = 4 Hz)	4.36 (dq, J = 4 Hz, J = 6.5 Hz)	1.21 (d, J = 6.5 Hz)		
dl-erythro-β-hydroxyleucine (3b)[c]	90	3.92 (d, J = 3.2 Hz)	3.55 (dd, J = 3.2 Hz, J = 8.7 Hz)	1.01 (d, J = 6.5 Hz)		1.98 (m)
dl-erythro-β-phenylserine (3c)[c]	80	4.09 (d, J = 4 Hz)	5.36 (d, J = 4 Hz)		7.42 (s)	
dl-β-hydroxyvaline (3d)[d]	50	3.61 (s)		1.25, (s), 1.46 (s)		

[a] The yields of amino acids 3b and 3c are based on isolated material and those of amino acids 3a and 3d on NMR analysis of the crude mixture of amino acids, consisting of starting material and hydroxy amino acid. [b] The NMR spectra were recorded on a 90 MHz Bruker HFx90 spectrometer, using FT techniques. D_2O was employed as solvent and TSP as internal standard. The limit of detectibility of the possible stereoisomer was estimated to be 5% or less. [c] J. Marchand, M. Pais, and F. X. Jarreau, *Bull. Soc. Chim. Fr.*, 3742 (1971). [d] C. Berie and P. Bessette, *Can. J. Chem.*, **49**, 2610 (1971).

Table II. Preparation of Oxazolidone-4-carboxylic Acid Derivatives (5)

oxazolidone	yield,[a] %	chemical shift (δ)[b] CHN	CHO	CH_3	C_6H_5	CH
trans-5-methyl-2-oxazolidone-4-carboxylic acid (5a)[c]	80	4.08 (d, J = 5 Hz)	4.73 (quint)	1.47 (d, J = 6.5 Hz)		
trans-5-isopropyl-2-oxazolidone-4-carboxylic acid (5b)[c]	85	4.16 (d, J = 5 Hz)	4.42 (t, J = 5 Hz)	0.98 (d, J = 6.5 Hz)		1.87 (m)
trans-5-phenyl-2-oxazolidone-4-carboxylic acid (5c)[c]	90	4.31 (d, J = 5 Hz)	5.66 (d, J = 5 Hz)		7.40 (s)	
5,5-dimethyl-2-oxazolidone-4-carboxylic acid (5d)	90	4.16 (s)		1.36 (s), 1.55 (s)		

[a] The yields are based on NMR analysis of crude product mixtures consisting of starting material and oxazolidone derivative. [b] The NMR spectra were recorded on a 80 MHz Varian A80 spectrometer, using FT techniques. CD_3OD was employed as solvent and Me_4Si as internal standard. The limit of detectibility for the possible isomer was estimated to be less than 5%. [c] S. Futagawa, T. Inui, and T. Shiba, *Bull. Chem. Soc. Jpn.*, **46**, 3308 (1973).

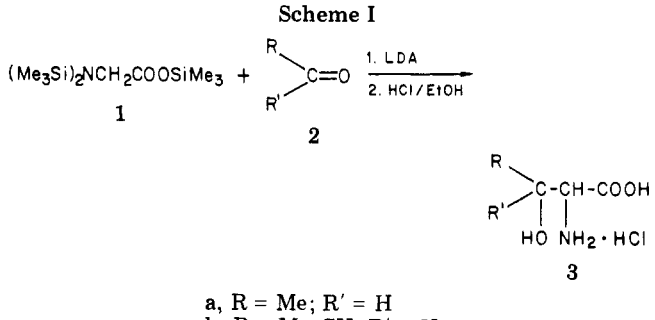
precursor for the preparation of the erythro isomers and *N*-carbobenzoxyglycine ethyl ester (4) as precursor of the threo isomers.

The preparation of the erythro isomers was achieved by condensation of the trisilylated glycine 1 with various carbonyl compounds, using lithium diisopropylamide as catalyst. Ethanolysis of the crude reaction mixture with ethanolic hydrogen chloride afforded the corresponding amino acid derivatives 3 as their salts in good yields (Scheme I).

Following this procedure, a series of α-amino-β-hydroxy acids 3 was prepared in a smooth reaction sequence, as summarized in Table I. The stereochemical purity of the products was analyzed by NMR spectroscopy of the crude reaction mixtures, as the chemical shifts and coupling constants of the two isomers are known to be distinctly different.[6] Inspection of the measured NMR spectra and comparison with the corresponding literature data established the configuration of the isolated products as erythro isomers (Table I).

The above employed *N*,*N*-bis(trimethylsilyl)glycine trimethylsilyl ester (1) proved thereby to be far superior to the earlier used disilylated glycine derivative[7] for the preparation of α-amino-β-hydroxy acids in respect to both reactivity and stereospecificity. While the trisilylated glycine 1 reacted smoothly with aldehydes and ketones to afford stereochemically pure products, the disilylated

Scheme I



a, R = Me; R′ = H
b, R = Me_2CH; R′ = H
c, R = Ph; R′ = H
d, R = Me; R′ = Me

glycine ester failed to react with ketones and enolizable aldehydes.[7]

The stereospecificity of the former reaction may be attributed to the bulkyness of the disilylated amino group which directs the condensation reactions to form the sterically less hindered and thermodynamically favored erythro isomer.

The preparation of the corresponding *threo*-α-amino-β-hydroxy acids 6, on the other hand, was based on the use of *N*-carbobenzoxyglycine ethyl ester (4) as the amino acid precursor. The latter compound was chosen as starting material for the synthesis of the threo isomers since *N*-carbobenzoxy-α-amino-β-hydroxy acids are known to readily form 2-oxazolidones,[8] whose esters undergo rapid

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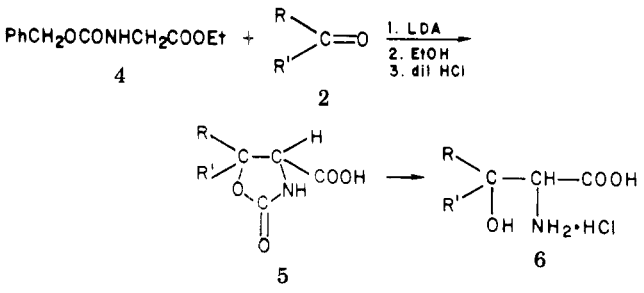
Scheme II



isomerization to the trans configuration upon treatment with base.[9] The latter ring systems may however easily be cleaved to the corresponding threo-α-amino-β-hydroxy acids[8] (Scheme II). Following this line of thought, *N*-carbobenzoxyglycine ethyl ester (**4**) was condensed under basic reaction conditions with a series of carbonyl compounds **2** to the corresponding oxazolidone derivatives **5**. NMR analysis of the crude reaction products revealed for all cases studied the exclusive formation of the transoid oxazolidones **5** (Table II). Subsequent hydrolytic cleavage with concentrated hydrochloric acid afforded the corresponding *threo*-α-amino-β-hydroxy acids **6** in quantitative yields.

The major advantages of the two procedures for the preparation of α-amino-β-hydroxy acids are their stereospecificity, ease of performance, and broad range of applicability, requiring only commonly available starting materials. The use of the synthesized amino acids for the preparation of stereochemically pure fluorinated derivatives is under current investigation.

Experimental Section

Preparation of *dl-allo*-Threonine (3a). Dry diisopropylamine (0.75 mL, 5.31 mmol) was added at 0 °C to a solution of 2 N *n*-butyllithium in hexane (1.92 mL, 3.84 mmol) in freshly distilled THF (25 mL). The colorless solution was then stirred for 30 min, at 0 °C, cooled to −78 °C, and treated dropwise with **1** (1.083 g, 3.75 mmol). The resulting light-brown reaction mixture was stirred for 1 h at the same temperature and subsequently treated with acetaldehyde (0.42 mL, 7.5 mmol). Stirring was continued for 1 h at −78 °C and for 0.5 h at 0 °C. Subsequent acidification of the solution with ethanolic hydrogen chloride and removal of the volatile components in vacuo provided the crude reaction products containing the salts of threonine, glycine, and diisopropylamine. Chromatography of the crude material on a column of AG 50W-X8, 200–400 mesh, H-form, and elution with aqueous ammonium hydroxide afforded *dl-allo*-threonine and glycine (in a 7:3 ratio by NMR) in 92% yield. Recrystallization from ethanol provided pure hydroxyamino acid **3a**. Amino acids **3b–d** were prepared by analogous reaction procedures, as summarized in Table I. The separation of the hydroxyamino acids from the glycine was achieved by fractionating crystallization from ethanol or by rechromatography on AG 50W-X8, 200–400 mesh, H-form, using 1 N HCl as eluent.

Preparation of *dl-trans*-5-Methyl-2-oxazolidone-4-carboxylic Acid (5a). To a cold solution of lithium diisopropylamide in THF, prepared from 5.5 mmol of *n*-butyllithium and 7.5 mmol of diisopropylamine as described above, was added 592 mg (2.5 mmol) of *N*-carbobenzoxyglycine ethyl ester (**4**). The resulting turbid solution was stirred for 1 h at −78 °C and subsequently treated with acetaldehyde (0.4 mL, 7.1 mmol). Stirring was continued for 1 h at the same temperature and for 1 h at 0 °C. Then 1 mL of ethanol was added and the reaction mixture allowed to warm up to room temperature. The reaction mixture was subsequently concentrated in vacuo and the residue was dissolved in water, washed with ether, and acidified at 0 °C with 4 N HCl. Extraction with ethyl acetate provided the crude reaction product (370 mg) containing oxazolidone **5a** and hydrolyzed starting material in a 5:1 ratio as established by NMR analysis. Recrystallization from ethyl acetate–*n*-hexane provided a pure sample of the oxazolidone **5a**.

Preparation of *dl*-Threonine (6a). A sample of *dl-trans*-5-methyl-2-oxazolidone-4-carboxylic acid (100 mg) was hydrolyzed with 2 mL of 6 N HCl in an evacuated sealed tube at 100 °C for 36 h. The reaction mixture was concentrated in vacuo and the residue chromatographed on a column of AG 50W-X8, 200–400 mesh, H-form. Elution with aqueous ammonium hydroxide gave pure *dl*-threonine, 80 mg.

Registry No. **1**, 5630-82-0; **3a**, 71264-40-9; **3b**, 71264-41-0; **3c**, 71264-42-1; **3d**, 71264-43-2; **4**, 1145-81-9; **5a**, 37791-36-9; **5b**, 50706-25-7; **5c**, 50706-23-5; **5d**, 71264-44-3; **6a**, 60143-52-4; acetaldehyde, 75-07-0; glycine, 56-40-6; isobutanal, 78-84-2; benzaldehyde, 100-52-7; acetone, 67-64-1.

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Selective Reduction of Aldehydes in the Presence of Ketones

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In synthetic organic chemistry, it is often necessary to reduce selectively an aldehyde in the presence of a ketone. The usual reagents such as $LiAlH_4$ or $LiBH_4$ show little selectivity so that if such a reduction is carried out in homogeneous solution, both aldehyde and ketone are reduced to a similar extent. Posner[1] has shown that isopropyl alcohol adsorbed on alumina can selectively reduce aldehydes in the presence of ketones, and a variety of other reducing agents derived from borohydrides or aluminum hydrides have been investigated by Brown.[2-4] We here report the selective reduction of aldehyde by $LiBH_4$ adsorbed on molecular sieve zeolites of types A and X.

The stereochemistry of aldehyde and ketone groups is different, and simple geometric calculations show that an aldehyde can penetrate the pore opening of the 5A zeolite, whereas, because of its greater critical diameter, a ketone (even acetone) will be excluded. We therefore decided to investigate the possibility of achieving a selective reduction of aldehyde by using as the reducing agent a 5A sieve containing preadsorbed $LiBH_4$. It proved possible to prepare such a reducing agent by contacting the dehydrated zeolite crystals with a dilute solution of $LiBH_4$ in tetrahydrofuran (THF); when contacted with representative aldehyde–ketone mixtures, this reagent showed the expected selectivity. The results of the competitive reduction experiments are summarized in Table I, and details of both the reagent preparation and the procedure in the reduction experiments are given below. In all experiments, the main product of reaction was the primary alcohol which was obtained in 70–80% yield with no trace of secondary alcohols. The remaining 20–30% of the

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