A Simple, Chiral-Pool-Independent Synthesis of Enantiomerically Pure Alanine-Derived α-Amino Aldehyde Acetals[1]

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Enantiomerically pure (*R*)- or (*S*)-1,1-dialkoxy-2-propanamines **5** are obtained in good chemical and optical yields, by asymmetric reduction of chiral imines prepared from 1,1-dialkoxy-2-propanones, using (*R*)- or (*S*)-1-phenylethylamine ((*R*)- or (*S*)-**2**) as an inexpensive, efficient chiral auxiliary.

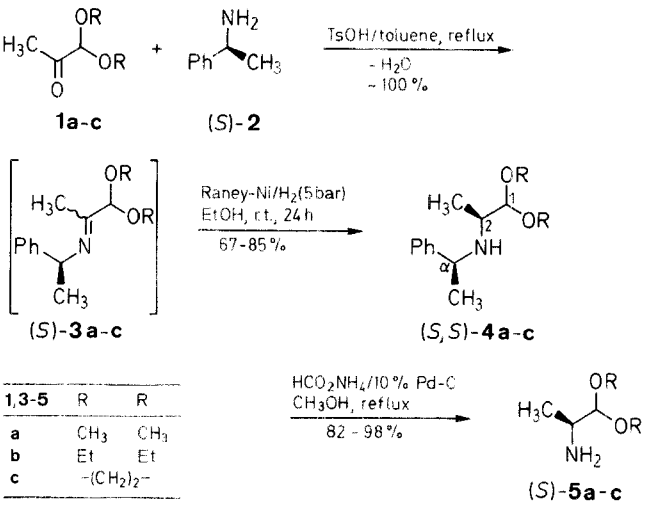
Optically active, *N-protected* α-amino aldehydes occur as *C*-terminal units of peptide aldehydes with enzyme inhibitor activity, for example, leupeptin.[2] In the chemical laboratory, they have gained importance for the asymmetric synthesis of amino sugars and of unusual amino acids.[3] In contrast, only very few applications of their *carbonyl-protected* analogues, e.g. the α-amino aldehyde acetals **5**, have been described,[4-6] although such small, bifunctional, chiral building blocks should be of broad general interest for the synthesis of enantiomerically pure nitrogen-containing natural products.[4,7]

Common syntheses of carbonyl- or *N*-protected α-amino aldehydes usually start from the corresponding amino acids.[3] After the obligatory protection of the amino function, the desired aldehyde is obtained, either by reduction of an acid derivative,[5-8] or by oxidation of the corresponding amino alcohol.[9] During these operations, problems often arise from a lack of chemoselectivity. Moreover, the amino aldehydes themselves show a pronounced tendency towards racemization, which makes purification procedures and a storage over longer periods impossible.[10] As a consequence, the optical purities achieved are sometimes disappointing. Only in some cases, by taking advantage of special *N*-protective groups[11] or through tedious, multistep synthetic detours,[12] *N*-protected α-amino aldehydes could be obtained in enantiomerically pure form.

For the preparation of the carbonyl-protected alanine-derived amino aldehydes **5**,[4-6] the additional acetalization of the configurationally labile aldehydes and subsequent *N*-deprotection is required. Apart from these synthetic difficulties and the number of required steps, a further disadvantage of such conventional α-amino aldehyde acetal syntheses results from the limitation that only amino acid precursors with L-configuration are easily accessible from the chiral pool.

In this paper, we wish to describe the synthesis of (*R*)- or (*S*)-α-amino aldehyde acetals **5** in essentially two steps: formation of imines of simple carbonyl precursors **1** with (*R*)- or (*S*)-1-phenylethylamine (**2**) and subsequent asymmetric catalytic reduction. As this procedure does not involve intermediates that are configurationally unstable, the enantiomeric excess of the amino aldehyde acetals **5** obtained are high, even if purification steps are required.

Our synthesis starts from the α-oxo aldehyde acetals **1**, which are either commercially available or synthetically accessible by standard procedures (e.g. from α-hydroxy aldehyde acetals[13]). Reaction of these ketones **1** with (*S*)-1-phenylethylamine ((*S*)-**2**) under standard conditions yields *E*/*Z* mixtures of the imines (*S*)-**3**, which are not isolated, but immediately hydrogenated with Raney nickel[14] as catalyst, thus avoiding hydrolytic decomposition.



The resulting *N*-(1-phenylethyl)-α-amino aldehyde acetals (*S*,*S*)-**4** are obtained in good yield and with high diastereoselectivity.[15] The diastereoisomeric excess (de) can be further improved by column chromatography ((*S*,*S*)-**4b–c**) or by recrystallization of the corresponding hydroperchlorates (for (*S*,*S*)-**4a**), to give stereochemically uniform material. Yields and properties of the amines **4** thus synthesized are summarized in Table 1.

Cleavage of the 1-phenylethyl group is attained either by high-pressure hydrogenation (180 bar H_2, Pd–C) or, more conveniently, by transfer hydrogenolysis[16] (HCO_2NH_4, Pd–C) in refluxing methanol, giving the desired α-amino aldehyde acetals[17] **5** in good yields (Table 2). The enantiomeric excess (ee), usually greater than 95%, was determined by derivatization according to Mosher's procedure,[18] and subsequent GC analysis. The absolute configurations of the α-amino aldehyde acetals **5** were assigned by comparison with literature data.[5,6]

The results show that corresponding with other reductive amination reactions using 1-phenylethylamine,[14,19,20] the *S*-configuration of **2** induces the *S*-configuration in the secondary amines **4**, and thus in the products **5**. Thus, optically pure α-amino aldehyde acetals bearing *R*-configuration (formally derived from D-alanine), such as (*R*)-**5a**, could likewise be prepared, using (*R*)-1-phenylethylamine as the chiral auxiliary (Tables 1 and 2).

In conclusion, the asymmetric reduction of chiral imines prepared from α-oxo aldehyde acetals **1** is a simple and useful method for the reliable preparation of configurationally stable α-amino aldehyde acetals **5**, with any desired configuration at the stereogenic center. Work to evaluate the synthetic utility of these alanine-related building blocks in the asymmetric synthesis of nitrogen-containing, biologically-active compounds is in progress.[21]

^{1}H-NMR spectra were recorded on Bruker WM 200 and AM 250 spectrometers, using TMS as internal standard. IR-spectra were obtained on a Perkin-Elmer 1420 IR-spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Varian MAT-CH 7. Gas chromatography was performed on a Dani 8520 gas chromatograph, equipped with a FI detector, using a J&W Scientific DB5-W30 silica fused capillary column, with N_2 as

carrier gas. TLC plates (60 F_{254}) and silica gel for column chromatography (0.063–0.2 mm) were purchased from Merck (Darmstadt). Microanalyses were carried out in the Microanalytical Laboratory of the University of Würzburg. Acetal **1a** was purchased from Janssen; **1b** was prepared from **1a** by transacetalization.[22] The ethylene acetal **1c** was prepared from **1a** by reduction ($NaBH_4$, MeOH), transacetalization[13,22] with ethylene glycol, then oxidation [DMSO, $(COCl)_2$, Et_3N].[23]

1,1-Dialkoxy-*N*-(1-phenylethyl)-2-propanamines 4; General Procedure: The 1,1-dialkoxy-2-propanone **1** (10 mmol), (*S*)- or (*R*)-1-phenylethylamine [(*S*)- or (*R*)-**2**, 1.21 g, 10 mmol] and a catalytical amount of *p*-toluenesulfonic acid (TsOH) are dissolved in toluene (100 mL) and refluxed using a Dean–Stark water separator. The reaction is monitored by TLC (Note: due to unsatisfactory chromatographical properties of the resulting imines **3**, an analytical amount of the reaction mixture is reduced with $NaBH_4$ in MeOH and then analyzed. After total conver-

Table 1. 1,1-Dialkoxy-*N*-(1-phenylethyl)-2-propanamines **4** Prepared

Product	Yield[a] (%)	de[b] (%)	$[\alpha]_D^{25}$ *c*, CH_2Cl_2	Molecular[c] Formula	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, *J*(Hz)	MS (70 eV) *m/z* (%)
(*S,S*)-**4a**	92 (85)	90	−14.0 *c* = 1.00	$C_{13}H_{21}NO_2 \cdot HClO_4$ (323.8)	3060, 2950, 2930, 1570, 1435, 1070, 765, 700	0.92 [d, 3H, *J* = 6.55, $CH_3CHCH(OCH_3)_2$]; 1.32 (d, 3H, *J* = 6.57, CH_3 at α-C); 1.55 (br s, 2H, NH_2); 2.79 [dq, 1H, *J* = 6.55, 5.22, $CH_3CHCH(OCH_3)_2$]; 3.40 (s, 3H, OCH_3); 3.41 (s, 3H, OCH_3); 3.94 (q, 1H, *J* = 6.57, α-H); 4.14 [d, 1H, *J* = 5.21, $CH(OCH_3)_2$]; 7.26–7.35 (m, $5H_{arom}$)	224 (M − ClO_4, 0.2); 75 (3)
(*R,R*)-**4a**	91 (82)	90	+13.9 *c* = 1.02	$C_{13}H_{21}NO_2 \cdot HClO_4$ (323.8)	same spectroscopical properties as (*S,S*)-**4a**		224 (M − ClO_4, 0.2); 75 (12)
(*S,S*)-**4b**	85 (67)	64	−38.3 *c* = 0.67	$C_{15}H_{25}NO_2$ (251.4)	3315, 2985, 1580, 1445, 1115, 760, 700	0.87 [d, 3H, *J* = 6.53, $CH_3CHCH(OEt)_2$]; 1.14 (t, 3H, *J* = 7.05, OCH_2CH_3); 1.15 (t, 3H, *J* = 7.03, OCH_2CH_3); 1.24 (d, 3H, *J* = 6.56, CH_3 at α-C); 2.69 [dq, 1H, *J* = 6.53, 5.14, $CH_3CHCH(OEt)_2$]; 3.46 (dq, 2H, *J* = 9.33, 7.03, OCH_2CH_3); 3.64 (dq, 1H, *J* = 9.31, 7.05, OCH_2CH_3); 3.65 (dq, 1H, *J* = 9.30, 7.04 (OCH_2CH_3); 3.90 (q, 1H, *J* = 6.56, α-H); 4.23 [d, 1H, *J* = 5.12, $CH(OEt)_2$]; 7.12–7.29 (m, $5H_{arom}$)	251 (M^+, 0.2); 148 (60); 103 (11)
(*S,S*)-**4c**	84 (80)	96	−50.2 *c* = 0.70	$C_{13}H_{19}NO_2$ (221.3)	3410, 2955, 1590, 1443, 1120, 747, 698	0.96 (d, 3H, *J* = 6.67, CH_3CHCH); 1.32 (d, 3H, *J* = 6.60, CH_3 at α-C); 1.54 (br s, 1H, NH); 2.73 (dq, 1H, *J* = 6.68, 3.88, CH_3CHCH); 3.83–4.00 (m, 4H, OCH_2CH_2O); 4.05 (q, 1H, *J* = 6.61, α-H); 4.81 (d, 1H, *J* = 3.87, CH_3CHCH); 7.19–7.33 (m, $5H_{arom}$)	221 (M^+, 0.3); 240 (57); 75 (19)

[a] Of crude diastereoisomeric mixture. Yields of diastereoisomers after purification are given in brackets.
[b] Determined by ^{1}H-NMR [(*S,S*)- and (*R,R*)-**4a**] or by gas chromatography.
[c] Satisfactory microanalyses obtained: C ±0.33, H ±0.29, N ±0.27.
[d] For (*S,S*)-**4b–c**: Film.

Table 2. 1,1-Dialkoxy-2-propanamines **5** Prepared

Product	Yield (%)	ee[a] (%)	$[\alpha]_D^{25}$ *c*, solvent	Lit. $[\alpha]_D^{25}$	IR (Film) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, *J*(Hz)	MS (70 eV) *m/z* (%)
(*S*)-**5a**	96	92 (97)	+3.7 *c* = 1.6, MeOH	+3.7[5] *c* = 1.7, MeOH	3360, 1590, 1450, 1105	1.06 (d, 3H, *J* = 6.50, 3-H); 1.61 (br s, 2H, NH_2); 2.98 (dq, 1H, *J* = 6.51, 6.00, 2-H); 3.38 (s, 3H, OCH_3); 3.41 (s, 3H, OCH_3); 3.96 (d, 1H, *J* = 6.00, 1-H)	119 (M^+, 0.2); 75 (90)
(*R*)-**5a**	98	93 (98)	−4.0 *c* = 1.6, CH_3OH	–	same spectroscopic properties as (*S*)-**5a**		119 (M^+, 0.3); 75 (90)
(*S*)-**5b**	88	94 (99)	+21.0 *c* = 0.7, 0.1 N HCl	+17.8[6] *c* = 1.32, 0.1 N HCl	3360, 1580, 1445, 1118	1.02 (d, 3H, *J* = 6.55, 3-H); 1.15 (t, 3H, *J* = 7.05, OCH_2CH_3); 1.17 (t, 3H, *J* = 7.05, OCH_2CH_3); 1.38 (br s, 2H, NH_2); 2.90 (dq, 1H, *J* = 6.55, 5.84, 2-H); 3.47 (dq, 1H, *J* = 9.33, 7.06, OCH_2CH_3); 3.48 (dq, 1H, *J* = 9.33, 7.06, OCH_2CH_3); 3.64 (dq, 1H, *J* = 9.33, 7.13, OCH_2CH_3); 3.68 (dq, 1H, *J* = 9.33, 7.11, OCH_2CH_3); 4.04 (d, 1H, *J* = 5.80, 1-H)	148 (M^+ + H, 0.1); 103 (63)
(*S*)-**5c**	82	91 (96)	+4.0[b] *c* = 0.72, CH_2Cl_2	+16.3[6] *c* = 1.32, 0.1 N HCl	3370, 1591, 1452, 1115	1.05 (d, 3H, *J* = 6.73, 3-H); 1.45 (br s, 2H, NH_2); 2.87 (dq, 1H, *J* = 6.72, 3.80, 2-H); 3.81–3.95 (m, 4H, OCH_2CH_2O); 4.57 (d, 1H, *J* = 3.81, 1-H)	117 (M^+, 0.5); 73 (45)

[a] The enantiomeric excess based on the optical purity of the chiral auxiliary (ee = 95%) are given in brackets.
[b] Optical rotation could not be measured under literature conditions.

sion of the starting materials (36–72 h), the solvent is evaporated *in vacuo*; a solution of the residue in dry EtOH (100 mL) is transferred into a nitrogen-flushed hydrogenation vessel. After addition of EtOH-washed Raney-Ni W2 (0.5 g), hydrogenation is carried out in a Parr shaker at a H_2 pressure of 5 bar at room temperature. After 24 h, the catalyst is filtered, and the filtrate is evaporated *in vacuo*. In the case of **4a**, the residue is dissolved in MeOH (30 mL) and titrated with 70% aq. $HClO_4$ to neutrality. The solvent is distilled, and the resulting solid is recrystallized twice from CH_2Cl_2/petroleum ether, to give the diastereoisomerically pure secondary amines (*S,S*)-**4a** and (*R,R*)-**4a** as their hydroperchlorate salts. For **4b–c**, the main diastereoisomer is isolated by column chromatography of the residue (silica gel deactivated with 10% NH_3, using Et_2O/petroleum ether, 1:2, as eluent). Yields and properties of the diastereoisomerically pure amines **4** thus obtained are compiled in Table 1.

1,1-Dialkoxy-2-propanamines 5; General Procedure:

In a flame dried, nitrogen-flushed, three-neck flask, fitted with reflux condenser, stirrer and bubble-counter, the appropriate secondary amine **4** (5 mmol) is dissolved in dry MeOH (50 mL). After addition of HCO_2NH_4 (1.27 g, 20 mmol) and 10% Pd–C (100 mg), the reaction mixture is refluxed until TLC control indicates total conversion (0.5–1 h). The catalyst is filtered, and the filtrate is concentrated to a volume of about 5 mL. After addition of 2N NaOH (50 mL), the resulting emulsion is continuously extracted with Et_2O for 36 h. The Et_2O phase is carefully dried (K_2CO_3) the solvent is evaporated *in vacuo*, and the residue is distilled (Kugelrohr) for further purification, giving the primary amines **5** as colorless oils. Yields and properties of compounds **5** are given in Table 2.

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