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ORIGINAL ARTICLE

Resolution and absolute configuration of some α-aminoacetals: en route to enantiopure *N*-protected α-aminoaldehydes

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Abstract The first successful resolution of *rac*-α-aminoacetals via diastereoisomeric salt formation with optically pure *N*-protected aminoacids is reported. The absolute configuration assignment of α-aminoacetal enantiomers is performed by an entirely non-racemizing chemical correlation method involving *N*-protection and a new efficient hydrolysis step followed by a reduction of the resulting *N*-protected α-aminoaldehyde intermediates. A racemization method of optically enriched α-aminoacetals is exemplified to allow valorisation of both enantiomers.

Keywords Chiral α-aminoalcohols · Chiral α-aminoaldehydes · Chiral HPLC · Resolving agents · Absolute configuration · Chemical correlation method

Introduction

Optically pure α-aminoacetals (**A**) are direct precursors of optically pure α-aminoaldehydes by hydrolysis of the acetal group. Few methods, which are not requiring aminoacids as precursors, have been developed to obtain enantio-enriched α-aminoacetals (Enders et al. 1993; Denmark and Nicaise 1993; Serradeil-Albalat et al. 2008; Bringmann and Geisler 1989) (Scheme 1). Enders et al. (1993) and Denmark and Nicaise (1993) used expensive reactants such as SAMP or RAMP chiral inductors. In other cases, starting materials which are not easily available with the exception of pyruvaldehyde dimethylacetal have been employed (Bringmann and Geisler 1989). We obtained moderate enantioselectivities up to 70% when (1*S*,1′*S*)-1,1′-(4-amino-4*H*-1,2,4-triazole-3,5-diyl)diethanol was used as chiral auxiliary in the asymmetric synthesis of α-aminoacetals (Serradeil-Albalat et al. 2008). These moderate enantioselectivities were in accordance with the lower chiral induction efficiency already noticed for hydrazones bearing an acetal group (Enders et al. 1993; Denmark and Nicaise 1993; Serradeil-Albalat et al. 2008). The acetal group is probably providing detrimental binding sites for the metal during asymmetric alkylation or asymmetric reduction.

Herein, we report on the first successful resolution of *rac*-α-aminoacetals (*rac*-**A**) via diastereoisomeric salt formation. The absolute configuration assignment of α-aminoacetal enantiomers is performed by a completely non-racemizing chemical correlation method involving *N*-protection and a new efficient hydrolysis step followed by a reduction of the resulting *N*-protected α-aminoaldehyde intermediates. A racemization method of optically enriched α-aminoacetals is exemplified to allow valorisation of both enantiomers (Scheme 2).

Results and discussion

Synthesis of racemic α-aminoacetals *rac*-3

The most common synthetic routes for the preparation of racemic α-aminoacetals start from either α-haloacetals

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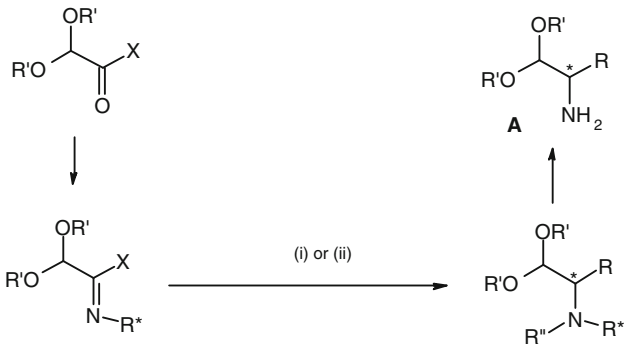
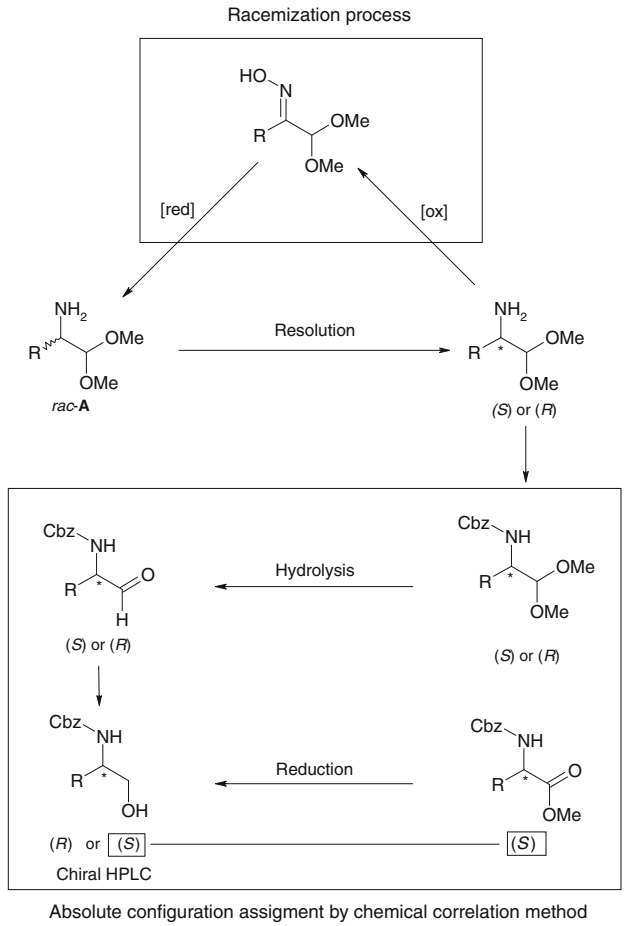
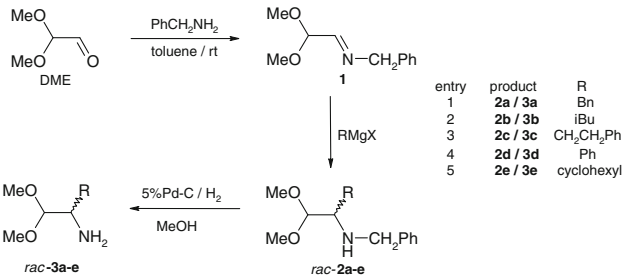


Scheme 1 Literature route to optically active α-aminoacetals **A**. (*i*) X = R [1,2]-asymmetric addition [RM], (*ii*) X = H asymmetric reduction [H], R*= chiral auxiliary like D-(+)- or L-(−)-α-methylbenzylamine, SAMP/RAMP or (1*S*, 1′*S*)-1,1′-(4-amino-4*H*-1,2,4-triazole-3,5-diyl)diethanol, R″ = H or protecting group



Scheme 2 Route to optically active α-aminoacetals, chemical correlation method for the assignment of the absolute configuration and racemization process

(Burtles et al. 1925; Boon 1957; Brumby et al. 2002; Albaugh and Hutchison 1995; Johnson et al. 1947; Walsh et al. 1987; Gall and Kamdar 1981; Upjohn Co 1976) or



Scheme 3 Route to racemic α-aminoacetals *rac*-**3a–e** from glyoxal monoacetal (DME)

α-aminoacids (Narjes et al. 2002; Matassa et al. 1999; Attwood et al. 1998, 1999; Liu et al. 2009).

Racemic α-aminoacetals *rac*-**3** were here obtained by a straightforward route from glyoxal monoacetal (dimethoxyethanal, DME) according to Scheme 3.

Reaction of DME and benzylamine afforded the imine **1** (Terinek and Vasella 2004a). **1** was treated with various Grignard reagents to give racemic *N*-benzyl protected aminoacetals, *rac*-**2a–e** (Enders et al. 1993; Quelet and Chastrette 1959; Chastrette 1962; Kido and Watanabe 1987). Hydrogenolysis of *rac*-**2a–e** with palladium on carbon in methanol, afforded the expected racemic α-aminoacetals, *rac*-**3a–e** (Muralidharan et al. 1994; Bringmann and Geisler 1989; Terinek and Vasella 2004b; Urban and Noe 2003; Winkler et al. 2004). The combined yields in isolated *rac*-**3a–e** from DME after the three chemical steps reported in Scheme 3 and a final purification step by distillation were ranging between 25 and 45% (Albalat et al. 2010). These operating conditions were not further optimized, they provided the starting material for the present study.

Resolution of *rac*-3

rac-1-Benzyl-2,2-dimethoxyethylamine (*rac*-**3a**) and *rac*-1-dimethoxymethyl-3-methyl-butylamine (*rac*-**3b**), were chosen as models compounds to carry out preliminary screening of the resolving agents (Jacques et al. 1981; Sheldon 1993; Baley and Vaidya 1992; Kozma 2002; Rouhi 2003; Sakai et al. 2003, 2006; Hirose et al. 2008). The conventional acidic resolving agents for primary amines (Kozma 2002) such as L-(+)-tartaric acid, D-(+)-dibenzoyltartaric acid, D-(+)-camphor-10-sulfonic acid, L-(−)-di-*p*-toluyltartaric acid, *(S)*-(+)-mandelic acid and L-(−)-*N*-tosylproline, were screened without success in various solvents.

We turned our attention to *N*-protected aminoacids like *N*-acetyl-L-leucine, (*L*)-**4** and *N*-acetyl-L-phenylalanine, (*L*)-**5** which possess some structural similarity with *rac*-**3b** and *rac*-**3a,** respectively, and an acidic N–H prone to enantioselectively interact with the oxygen of the acetal in

the diastereomeric complexes. Both enantiomers of the resolving agent **5** were synthesized by acetylation of commercially available (L)- and (D)-phenylalanine by known method (Huffman and Ingersoll 1951; Synge 1939; Fones 1952; Holland et al. 1953). High yields (85–90%) and high-optical purities (ee ≥ 99.5%, as determined by chiral HPLC analyses on Chiralpak AD-H, hexane-*i*PrOH 90/10) were obtained.

The optically pure salts (*R*)-**3a**.(*L*)-**4,** (*S*)-**3a**.(*L*)-**4,** (*R*)-**3a**.(*L*)-**5** and (*S*)-**3a**.(*L*)-**5** were independently prepared from optically pure (*R*)- and (*S*)-**3a**, provided by preparative chiral HPLC, and their melting points were recorded. The melting points were in the range 149–160°C and the difference in melting points was 2°C for the diastereomeric pair (*R*)-**3a**.(*L*)-**4,** (*S*)-**3a**.(*L*)-**4** and 10°C for the pair (*R*)-**3a**.(*L*)-**5** and (*S*)-**3a**.(*L*)-**5**. (*L*)-**5** which provided a larger difference in the melting points of the diastereoisomeric pair was thus selected for further optimization of the operating conditions.

(*R*)−**3a**.(*L*)−**4** m.p. = 151°C
(*S*)−**3a**.(*L*)−**4** m.p. = 149°C

(*R*)−**3a**.(*L*)−**5** m.p. = 160°C
(*S*)−**3a**.(*L*)−**5** m.p. = 150°C

Preliminary screenings on *rac*-**3a** and *rac*-**3b** showed that optically enriched **3a** and **3b** were indeed obtained but the enantiomeric excess and the yield were depending, as usually, on the solvent, the concentration, the operating conditions and the acidic resolving agent.

The main parameters for diastereoisomeric resolution are the resolving agent, the molar ratio of the resolving agent to racemic substrate, the substrate concentration, the solvent and the temperature. The conditions for the resolution of *rac*-**3** with half molar equivalent amount of (*L*)- or (*D*)-**5** were screened. The detailed resolution process is illustrated in Fig. 1 for *rac*-**3a** with (*L*)-**5**. The resulting diastereoisomeric salt was further enriched in one diastereoisomer by recrystallization or washing.

Selected examples of favorable operating conditions leading to (*S*)- or (*R*)-**3a–d** are reported in Table 1 (Albalat et al. 2009).

High enantioselectivities (ee ≥ 96%) were achieved for all α-aminoacetals **3a–d** with (*L*)- or (*D*)-**5** as resolving agent. The diastereoisomeric purity of the crude salts could be easily further improved by one or several recrystallizations (Table 1).

The R substituent in α-aminoacetals **3** plays a decisive role on the chiroselective molecular recognition: using (*L*)-**5**, the (*R*) enantiomer is collected from the solid diastereoisomer in the case of *rac*-**3a** and *rac*-**3b** (entries 1 and 3, Table 1), while the (*S*) form is obtained in the case of *rac*-**3c** and *rac*-**3d** (entries 5 and 7, Table 1).

rac-**3e** resisted to all resolution attempts using (*L*)- and (*D*)-**5**. A series of resolution tests was performed using *N*-acetyl-(L)-leucine, (*L*)-**4** (Scheme 4; Table 2). It was known from the literature that not all structurally analogous racemates can be resolved under similar conditions (Pallavicini et al. 1997; Loiodice et al. 1995; Albright and Snyder 1959).

Results in Table 2 show that the optical resolution of *rac*-**3e** with (*L*)-**4**, was very instable and was strongly dependent on the operating conditions. In all cases, the ee of the first crop was poor and comprised only between 23 and 50%. The ee can be noticeably improved up to 94% at the expense of the yield by further washing and crystallization. An illuminating proof of the great instability of the system was the occurrence of an unexpected reversal of selectivity in the preferred crystallized diastereoisomer which occurred under very minor changes in operating conditions or solvent (entries 2–3 and 4–5). The change of the configuration of the aminoacetal component in the precipitating salt was firmly established by chiral chromatography for each entry to Table 2. The two diastereoisomeric salts (*D*)-**3e**/(*L*)-**4**

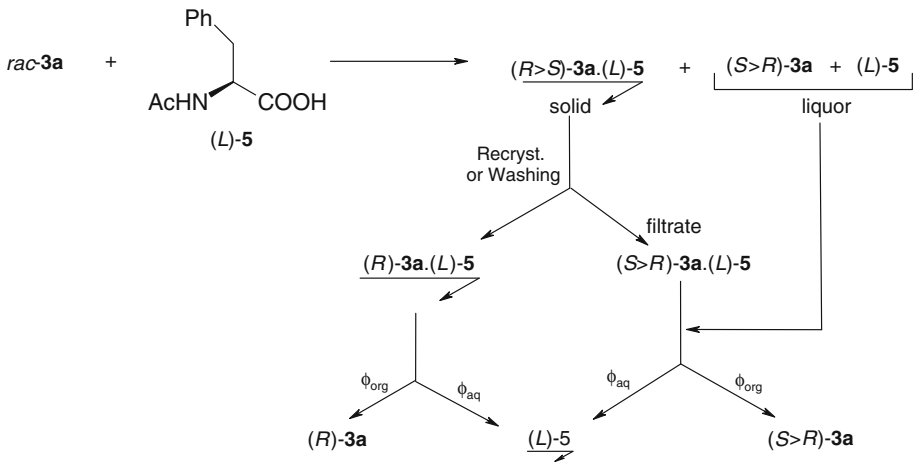


Fig. 1 Flow chart for the resolution of *rac*-**3a** with (*L*)-**5**

Table 1 Resolution of *rac*-**3a–d** with (*L*)- or (*D*)-**5** as resolving agent (RA)

	5	**3**	Solvent (w/w)	Conditions	Yield (ee %)	AC
1	*L*	**3a**	A(6%)	50°C (3 h)/40°C (2 h)/20°C	41[a] (97)	(*R*)
2	*D*	**3a**	A(6%)	50°C (3 h)/40°C (2 h)/20°C	44[a] (99)	(*S*)
3	*L*	**3b**	A/B 13/87 (6%)	50°C (3 h)/19°C	50–55[b] (96)	(*R*)
4	*D*	**3b**	A/B 13/87 (9%)	50°C (3 h)/23°C	50[b] (96)	(*S*)
5	*L*	**3c**	A (6%)	28°C (2 h)/50°C/30°C	19[c] (96)	(*R*)
6	*D*	**3c**	A (6%)	19°C (2 h)/50°C/30°C	23[c] (96)	(*S*)
7	*L*	**3d**	A (6%)	50°C (3 h)/23°C	56[c] (98)	(*S*)
8	*D*	**3d**	A (6%)	50°C (3 h)/23°C	70–75[d] (97)	(*R*)

Solvent A = *i*PrOH, B = acetone; Resolving agent/*rac*-**3** = 0.5/1 (molar ratio). Yield with respect to limiting reactant (resolving agent) after salt decomposition. ee determined by chiral HPLC analyses after salt decomposition on free **3a**, **c–d** and on *N*-Cbz-carbamate derivative for **3b**, **e**. For the assignment of the absolute configuration (AC), see text

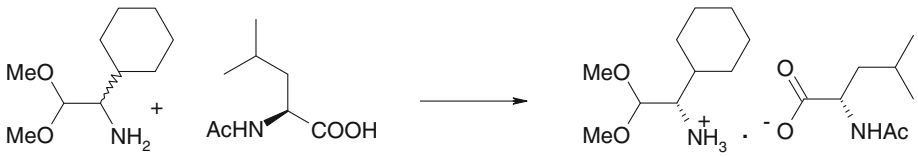
[a] One recrystallization 5.5% w/w in *i*PrOH

[b] Two recrystallizations 7% w/w in *i*PrOH

[c] Two recrystallizations 3% w/w in *i*PrOH

[d] Two recrystallizations 5.5% w/w in *i*PrOH

Scheme 4 Resolution of *rac*-**3e** with (*L*)-**4**



rac-**3e** (*L*)-**4** (*S*>*R*)-**3e**.(*L*)-**4**

and (*L*)-**3e**/(*L*)-**4** should have very similar physical properties.

Racemization/recycling of the undesired enantiomer

The main drawback to any resolution process is the maximal theoretical yield which is limited to 50% in the desired optically pure product in the absence of dynamic kinetic resolution. A way to improve the whole process is to find an efficient racemization method which transforms the undesired enantiomer or a non-racemic mixture of the two enantiomers into a racemic mixture which can be engaged again in the resolution step.

Unfortunately, most of the reported conventional racemization methods for the α-aminoacids and derivatives (catalysis with a base or an acid, formation of a Schiff's base-type intermediate) (Ebbers et al. 1997) or for chiral amines (catalysis with a base, reducing conditions) (Pàmies et al. 2002; Fujino and Sato 2001; Vitt 1980), were not efficient to racemize α-aminoacetals under mild operating conditions.

A sequence of oxidation and reduction on the optically enriched α-aminoacetals **3** (Scheme 5) was explored (Albalat et al. 2008b). Treatment of α-aminoacetals **3a–b** with aqueous hydrogen peroxide and catalytic amount of sodium tungstate ($Na_2WO_4{\cdot}2H_2O$) at room temperature in a mixture of methanol and water, afforded the corresponding oximes **6a–b** in good yields (70–90%) (Kahr and Berther 1960; Kahr 1956; Synthese-Chemie GmbH 1956). The reduction of the resulting oximes **6a–b** to yield *rac*-**3a–b** was successfully accomplished using catalytic hydrogenation (20–50 bar H_2) with Raney nickel as catalyst in ethanol at room temperature (crude yield = 75–90%) (Nielsen and Lies 1990; Paul 1937; Shivers and Hauser 1974; Ikeda et al. 1977).

An efficient resolution process of α-aminoacetals **3** has been developed with *N*-acetyl-phenylalanine, **5**, or with *N*-acetyl-leucine, **4**. High selectivities (ee ≥ 94%) were achieved thanks to recrystallization and both enantiomers of *rac*-**3** can be obtained. The recycling of the unresolved enantiomer in the starting racemic material was developed on two examples.

Determination of ee's and absolute configuration of enantiomers of 3a–e isolated during the resolution process

The ee's of the enriched **3a** and **3c–d** resulting from the resolution process were determined by liquid chromatography on chiral support without additional derivatization. Ee's of **3b** and **3e** were determined on the corresponding *N*-Cbz-protected forms. It is worth noting that excellent

Table 2 Resolution of *rac*-**3e** with (*L*)-**4** (0.5 mol.eq.)

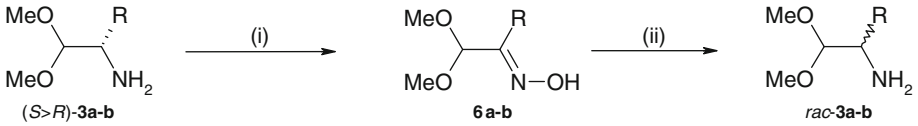
	Solvent (w/w)	Conditions	Yield	Ee%	AC
1	Acetone (3.6%)	19°C (2 h)/reflux (1 h)/filtration (30°C)	96	30	(*S*)
2	THF (3.6%)	21°C (2 h)/56°C (1 h)/filtration (21°C)	72	29	(*R*)
3	THF (3.6%)	19°C (2 h)/reflux/filtration (30°C)	88	45	(*S*)
4	THF/CH_3CN (50/50) (3.5%)	19°C (2 h)/reflux/filtration (30°C)	64	27	(*R*)
5	THF/AcOEt (50/50) (3.5%)	19°C (2 h)/reflux/filtration (30°C)	88	32	(*S*)
6	THF/acetone (75/25) (3.5%)	19°C (2 h)/reflux/filtration (22°C)	93	50	(*S*)
			32[a]	91	(*S*)
7	THF/acetone (75/25) (3.5%)	19°C (2 h)/Δ (62°C→40°C/seeding/filtration (22°C)	70[b]	23	(*S*)
			21[c]	84	(*S*)
			6[d]	94	(*S*)

[a] Two recrystallizations 4% w/w in THF/acetone (75/25)

[b] Washing with THF/acetone (75/25)

[c] One recrystallization 4% in THF/acetone (75/25) and washing with THF/acetone (75/25)

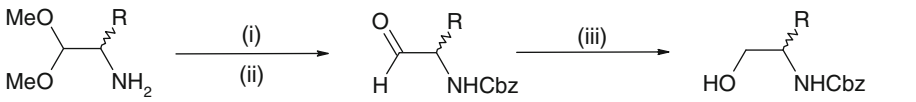
[d] Two recrystallizations 4% in THF/acetone (75/25)



(*S*>*R*)-**3a-b** **6a-b** *rac*-**3a-b**

Scheme 5 Tandem oxidation and reduction to recycle the unresolved α-aminoacetal **3**. (*i*) 30% $H_2O_2/Na_2WO_4.2H_2O$/MeOH. (*ii*) Raney-Ni/H_2/EtOH

Scheme 6 Process for chemical correlation to assign the absolute configuration of α-aminoacetal **3a–e**. Step one: chromatographic data acquisition for ***rac*-9a–e**. (*i*) Cbz *N*-protection, (*ii*) HCO_2H, H_2O, (*iii*) metal hydride reduction



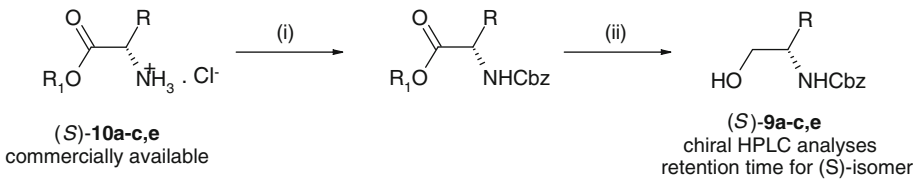
rac-**3a-e** *rac*-**8a-e** *rac*-**9a-e**
chiral HPLC analyses
retention time for (*S*)- and
(*R*)-isomers

separations were obtained for all the *N*-Cbz-protected α-aminoacetals (see Supporting Information).

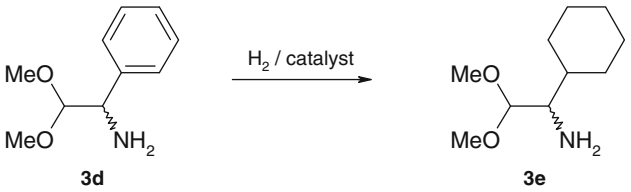
The assignment of the absolute configuration of the enantiomers of **3a–e** was envisioned by the adaptation of the chemical correlation method to modern chiral chromatography. The classical chemical correlation method refers to a series of non-racemizing chemical transformations leading to an enantiomer of known configuration associated to a sign of the optical rotation. The chemical correlation method involving chiral chromatography requires the comparison of the retention time of the enantiomer resulting from a series of non-racemizing chemical transformations with the retention times of the enantiomers of known absolute configuration of the corresponding racemate. The chemical correlation we used is reported in Scheme 6 for its racemic version. α-Aminoacetals **3a–e** were *N*-Cbz-protected yielding **7a–e**, acetal hydrolysis afforded *N*-protected α-aminoaldehydes **8a–e**, and metal hydride reduction gave the *N*-protected α-aminoalcohols **9a–e**.

In a first step the analytical conditions (column, mobile phase) which gave a baseline separation of the enantiomers of *rac*-*N*-protected α-aminoalcohols **9a–e** were screened (see Supporting Information). In a second step, the injection of the pure (*S*)-enantiomer of **9a–c**, **e**, obtained from commercially available ester of (*S*)-α-aminoacids **10a–c**, **e** according to Scheme 7, allowed the assignment of the order of elution. Chiroptical detection (polarimeter on-line) offered additional validation of the assignments.

The metal hydride reduction of the ester of (*S*)-phenyl glycine **10d** produced in our hands *rac*-**9d** precluding the assignment of the order of elution for **9d**. The absolute configuration of the enantiomers of **3d** should be assigned by another chemical correlation method. We decided to explore the reduction of **3d** into **3e** (Scheme 8) to catch up with the chemical correlation scheme already established for **3e**.



Scheme 7 Synthesis of (*S*)-**9a–c** and (*S*)-**9e** from optically pure α-aminoesters chlorhydrate salt (*S*)-**10a–c** and (*S*)-**10e**. (*i*) Cbz *N*-protection, (*ii*) metal hydride reduction



Scheme 8 Aromatic ring hydrogenation of **3d** on Ru or Rh catalyst. The reduction proceeded without any racemization

Inspection of the literature provided several examples of the selective and non-racemizing catalytic hydrogenation of a phenyl group in phenylglycine, phenylalanine or phenethylamine and analogues using ruthenium on carbon or rhodium on Al_2O_3 (Sato et al. 1998; Herlinger et al. 1967; Strotmann and Butenschön 2000; Nugent 2002; Minnaard et al. 1999; Hayashi et al. 1983). These methods when applied to the hydrogenation of **3d** on Rh/Al_2O_3 or Ru/C catalyst gave quantitatively **3e**. Furthermore, starting from diversely enantio-enriched samples of **3d**, the corresponding enriched **3e** was obtained without any detectable racemization according to chiral HPLC on the *N*-Cbz-protected forms.

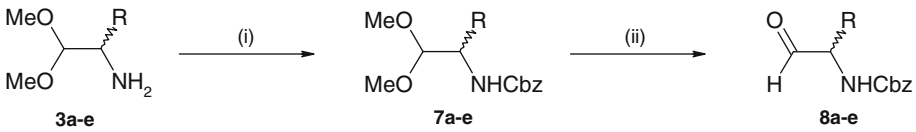
The acetal hydrolysis step in Scheme 6 which leads to the corresponding *N*-protected α-aminoaldehydes was highly critical in terms of chemical stability and racemization risk. The literature procedures to obtain optically active *N*-protected α-aminoaldehydes from optically active *N*-protected α-aminoacetals, were not encouraging. Denmark and Nicaise (1993) reported that the deacetalization step of *N*-Boc-α-aminoacetals with 3 molar equivalents of trimethylsilyl iodide, led to a substantial loss of optical purity for most of the tested products. Severe operating conditions (reflux in aqueous DMSO), followed by flash chromatography purification, were used to hydrolyze chiral *N*-benzyloxycarbonyl-α-aminoacetals without racemization (Muralidharan et al. 1994). We found that *rac*-**7a–e** were efficiently hydrolyzed using 95% formic acid to give *N*-protected α-aminoaldehydes *rac*-**8a–e** under very mild conditions (Albalat et al. 2008a) (Scheme 9).

Optically enriched *N*-Cbz-α-aminoacetals **7a** and **7b** were used as model compounds to study the configuration stability during the acetal hydrolysis step. They were prepared from optically pure α-aminoacid derivatives according to the literature (Enders et al. 1993; Attwood et al. 1998; Guillaumie et al. 2000; Iqbal et al. 1996; Edwards et al. 1988; Trainor and Stein 1987; Gacek and Undheim 1974) or from the optically pure α-aminocetals obtained by the resolution process here described. Hydrolysis of optically enriched **7a** and **7b** were performed using 95% formic acid and the isolated *N*-protected α-aminoacetals **8a**, **b** were acetalized with methanol to restore **7a** and **7b,** respectively. The ee's of compounds **7a–b** after ketalization showed no appreciable changes when compared with the ee's of compounds **7a–b** before the acetal hydrolysis with formic acid. It is worth noting that the very mild procedure to obtain *N*-protected-α-aminoaldehydes through the corresponding acetal hydrolysis without detectable racemization constitutes a valuable route to these useful chiral building blocks (Jurczak and Golebiowski 1989; Reetz 1999, 1991; Gryko et al. 2003; Hili et al. 2008; Baktharaman et al. 2008; Izawa and Onishi 2006; Garner and Park 1987; Chowdari et al. 2003; Tokuyama et al. 2002; Dias et al. 2003; Kwon and Myers 2005; Wen and Crews 1998; Hili and Yudin 2006; Myers et al. 2000; Diness et al. 2004).

The various steps described in Scheme 6 when applied to optically pure **3a–e** allowed a very safe assignment of the absolute configuration of **3a–e** and all the intermediates **7a–e** and **8a–e**. Furthermore, chiral HPLC analysis revealed that all the steps described in Scheme 6 proceeded without any noticeable change in the ee's.

Conclusion

Resolution of racemic α-aminoacetals via diastereoisomeric salt formation was successfully achieved for the first time. A careful chemical correlation method was



Scheme 9 Protection and hydrolysis of compounds *rac*-**3a–e** into *N*-Cbz-α-aminoaldehydes *rac*-**8a–e**. (*i*) $CbzCl/K_2CO_3/MTBE/H_2O$, (*ii*) HCO_2H/H_2O

established to assign the absolute configuration of the isolated enantiomers. Furthermore, a method for the racemization of enantio-enriched α-aminoacetals and a non-racemizing hydrolysis of *N*-protected α-aminoacetals to give *N*-protected α-aminoaldehydes were exemplified. The method using *N*-protected amino-acids as resolving agents has been used with success to resolve some undisclosed proprietary α-aminoacetals related to non-natural amino-acids with the usual case by case optimization of the resolution step conditions.

Experimental section

Experimental details: the full experimental details and product characterizations are reported in the Supporting Information.

Optical resolution of racemic 1-benzyl-2,2-dimethoxyethylamine *rac*-3a with N-acetyl (L)-phenylalanine (*L*)-5:

In a 250-mL three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer, racemic 1-benzyl-2,2-dimethoxyethylamine *rac*-**3a** (6 g, 30.8 mmol) and *N*-acetyl-(L)-phenylalanine (*L*)-**5** (3.18 g, 15.4 mmol) were added to *i*PrOH (94 g, 6% solution). The medium was stirred and heated at 50°C for 3 h, and then kept at 40°C for 2 h. Heating was switched off and stirring was maintained overnight.

Isolation of (R)-1-benzyl-2,2-dimethoxyethylamine (R)-3a The precipitate was filtered off, washed with cyclohexane (ca 100 mL) (filtrate 1), and then oven-dried at 40°C under vacuum. (*R*)-1-benzyl-2,2-dimethoxyethylammonium *N*-acetyl-(L)-phenylalaninate, (*R*)-**3a**.(*L*)-**5**, was obtained as a white solid (3.06 g, 50% relative to the *N*-acetyl-(L)-phenylalanine (*L*)-**5**); m.p. 159°C; $[\alpha]_D^{25} = +42.2$ ($c = 1$ in MeOH); ^{1}H NMR (200 MHz, [D_6] DMSO, TMS): $\delta = 1.78$ (s, 3 H), 2.63–2.74 (AB syst., 1 H), 2.85 (m, 2 H), 3.05–3.14 (AB syst., 1 H), 3.2–3.4 (m, 1 H), 3.33 (s, 3 H), 3.38 (s, 3 H), 4.2 (d, 1 H, $J = 4.8$ Hz), 4.32 (m, 1 H), 7.1–7.4 (m, 10 H), 7.86 ppm (d, 1 H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, [D_6] DMSO, TMS): $\delta = 22.56, 36.06, 37.31, 53.36, 54.51, 54.85,$ 55.12, 105.25, 125.95, 126.23, 127.88, 128.27, 129.16, 129.29, 137.96, 138.59, 168.66, 173.71 ppm; HRMS (ESI): for $C_{11}H_{17}NO_2$ $[M+H]^+$: calcd. 196.1338; found 196.1337 and for $C_{11}H_{12}NO_3$ $[M+H]^+$: calcd. 208.0974; found 208.0973.

The salt (*R*)-**3a**.(*L*)-**5** was triturated in *i*PrOH (53 g, solution at 5.5%) and the medium was heated at 50°C for approximately 1.5 h. Heating was switched off and stirring was maintained overnight. The resulting solid was filtrated, washed with cyclohexane (50 mL), oven-dried (40°C) and then treated with an aqueous solution of sodium hydroxide. The aqueous phase was extracted with CH_2Cl_2. After solvent concentration, (*R*)-1-benzyl-2,2-dimethoxyethylamine was obtained (1.23 g, 41% relative to (*L*)-**5**, $ee_{(R)} = 97\%$ determined by chiral HPLC).

Isolation of enriched (S)-1-benzyl-2,2-dimethoxyethylamine (S)-3a

Filtrate 1 was concentrated and the solid residue was triturated in cyclohexane (ca 100 mL), filtered under vacuum and washed with cyclohexane (60 mL). After drying and treatment with an aqueous solution of sodium hydroxide, enriched (*S*)-1-benzyl-2,2-dimethoxyethylamine was obtained (1.29 g, 43% relative to (*L*)-**5**, $ee_{(S)} = 74\%$ determined by chiral HPLC).

Optical resolution of racemic 1-benzyl-2,2-dimethoxyethylamine *rac*-**3a** with *N*-acetyl-(*D*)-phenylalanine (*D*)-**5** was performed according to a mirrored experimental procedure and yielded (*S*)-1-benzyl-2,2-dimethoxyethylamine (1.32 g, 44% relative to (*D*)-5 $ee_{(S)} \geq 99\%$ determined by chiral HPLC).

(*S*)-1-benzyl-2,2-dimethoxyethylammonium *N*-acetyl-(D)-phenylalaninate: m.p. 159°C; $[\alpha]_D^{25} = -39.6$ ($c = 1$ in MeOH); ^{1}H NMR (200 MHz, [D_6] DMSO, TMS): $\delta = 1.78$ (s, 3 H), 2.63–2.74 (AB syst., 1 H), 2.85 (m, 2 H), 3.05–3.14 (AB syst., 1 H), 3.2–3.4 (m, 1 H), 3.33 (s, 3 H), 3.38 (s, 3 H), 4.2 (d, 1 H, $J = 4.8$ Hz), 4.32 (m, 1 H), 7.1–7.4 ppm (m, 10 H), 7.86 (d, 1 H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, [D_6] DMSO, TMS): $\delta = 22.56, 36.06, 37.31, 53.36, 54.51, 54.85, 55.12, 105.25, 125.95, 126.23, 127.88, 128.27, 129.16, 129.29, 137.96, 138.59, 168.66, 173.71$; HRMS (ESI): for $C_{11}H_{17}NO_2$ $[M+H]^+$: calcd. 196.1338; found 196.1337 and for $C_{11}H_{12}NO_3$ $[M+H]^+$: calcd. 208.0974; found 208.0973.

1-Benzyl-2,2-dimethoxyethylamine **3a** (Guillaumie et al. 2000; Gacek and Undheim 1974; Grobelny and Galardy 1986) *rac*-**3a**: colorless oil (58.2 g, 45%); b.p. 115–120°C/5 mmHg; GC t_R=13.65 min; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.3$ (s, 2 H), 2.5 (m, 1 H), 3 (m, 1 H), 3.15 (m, 1 H), 3.49 (s, 6 H), 4.14 (d, 1 H, $J = 5.6$ Hz), 7.19–7.4 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 38.7, 54.2, 55.05, 55.19, 107.9, 126.3, 128.3, 128.56, 129.1, 129.4, 139.1$ ppm; EI MS: *m/z* (%): 164 (M-31, 11), 120 (M-75, 96), 104 (M-91, 39), 91 (62), 75 (100).

(S)-(−)-**3a**: chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): $t_R = 5.6$ min; Optical rotation: $[\alpha]_D^{25} = -27.7$ ($c = 1$ in MeOH).

(*R*)-(+)-**3a**:chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): t_R= 6.5 min; Optical rotation: $[\alpha]_D^{25} = +27.6$ ($c = 1$ in MeOH).

1-Dimethoxymethyl-3-methyl-butylamine **3b** *rac*-**3b**: colorless oil (32.2 g, 30%); b.p. 75°C/10 mmHg; GC $t_R = 8.65$ min; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 0.85$ (dd, 6 H, $J = 6.4$ Hz, $J = 6.6$ Hz), 1.2 (m, 4 H), 1.7 (m, 1 H), 2.8 (m, 1 H), 3.33 (s, 3 H), 3.36 (s, 3 H), 3.9 ppm (d, 1 H, $J = 5.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 21.5$, 23.97, 24.5, 41.5, 50.6, 54.8, 55.2, 108.9 ppm; EI MS: *m/z* (%): 130 (M-31, 7), 86 (M-75, 100), 75 (67), 43 (80); HRMS (ESI): for $C_8H_{19}NO_2$ $[M+H]^+$: calcd. 162.1494; found 162.1482.

(*S*)-(−)-**3b**: Optical rotation: $[\alpha]_D^{25} = -20.4$ ($c = 1$ in MeOH).

(*R*)-(+)-**3b**: optical rotation: $[\alpha]_D^{25} = +20.9$ ($c = 1$ in MeOH).

1-(2-Phenylethyl)-2,2-dimethoxyethylamine **3c** *rac*-**3c**: colorless oil (20.7 g, 43%); b.p. 100°C/0.5–1 mmHg; GC $t_R =$ 14.4 min; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.4$ (s, 2 H), 1.5 (m, 1 H), 1.8 (m, 1 H), 2.6 (m, 1 H), 2.8 (m, 2 H), 3.29 (s, 3 H), 3.34 (s, 3 H), 3.97 (d, 1 H, $J =$ 5.4 Hz), 7–7.3 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 32.5$, 34.2, 52.5, 54.97, 55.15, 108.5, 125.9, 128.43, 128.48, 142.3 ppm; HRMS (ESI): for $C_{12}H_{19}NO_2$ $[M+H]^+$: calcd. 210.1494; found 210.1494.

(*S*)-(−)-**3c**: chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): $t_R = 6.9$ min, Optical rotation: $[\alpha]_D^{25} = -18.0$ ($c = 1$ in MeOH).

(*R*)-(+)-**3c**: chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): $t_R = 9.9$ min; Optical rotation: $[\alpha]_D^{25} = +17.8$ ($c = 1$ in MeOH).

1-Phenyl-2,2-dimethoxyethylamine **3d** (Boon 1957; Suzuki and and Ishida 1998) *rac*-**3d**: colorless oil (5.3 g, 46%); b.p. 118°C/5 mmHg; GC $t_R =$ 12.3 min; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.5$ (s, 2 H), 3.2 (s, 3 H), 3.45 (s, 3 H), 4.0 (d, 1 H, $J = 6.2$ Hz), 4.3 (d, 1 H, $J = 6.2$ Hz), 7.15–7.45 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 55.3$, 55.65, 58.05, 108.9, 127.4, 127.7, 128.3, 141.5 ppm.

(*S*)-(+)-**3d**: chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): t_R= 6.7 min; Optical rotation: : $[\alpha]_D^{25} = +9.1$ ($c = 1$ in MeOH).

(*R*)-(−)-**3d**: chiral HPLC (Chiralcel OD-H, hexane/*i*PrOH 90/10 v/v, 1 mL/min): t_R= 8.2 min; Optical rotation: $[\alpha]_D^{25} = -8.9$ ($c = 1$ in MeOH).

1-Cyclohexyl-2,2-dimethoxyethylamine **3e** *rac*-**3e**: colorless oil (18.1 g, 24%); b.p. 100–110°C/5 mmHg; GC $t_R = 12.2$ min; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.1$ (s, 2 H), 1.05–1.25 (m, 6 H), 1.45–1.75 (m, 5 H), 2.6 (dd, 1 H, $J = 5.8$ Hz, $J = 6$ Hz), 3.3 (s, 3 H), 3.34 (s, 3 H), 4.1 ppm (d, 1 H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 26.4$, 26.6, 26.7, 27.4, 30.7, 39.15, 54.6, 54.74, 57, 106.4 ppm; HRMS (ESI): for $C_{10}H_{21}NO_2$ $[M+H]^+$: calcd. 188.1645; found 188.1646.

(*S*)-(+)-**3e**: Optical rotation: $0 < [\alpha]_D^{25} < 1$ ($c = 15$ in MeOH).

(*R*)-(−)-**3e**: optical rotation: $-1 < [\alpha]_D^{25} < 0$ ($c = 15$ in MeOH).

Conflict of interest The authors declare that they have no conflict of interest.

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