(*S*)-(−)-1-Amino-2-(siloxymethyl)pyrrolidines: Novel and Efficient Reagents for Chromatographic Resolution of α-Substituted Aldehydes

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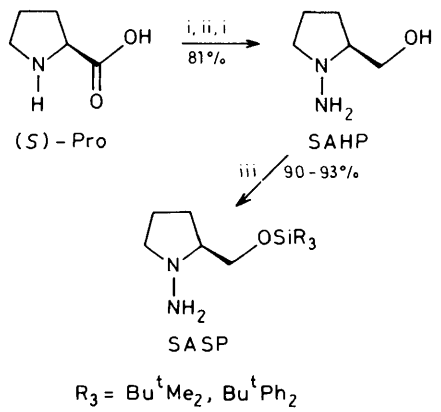
A new aldehyde resolution technique based on the chromatographic separation (preparative h.p.l.c.) of their epimeric (*S*)-1-amino-2-(siloxymethyl)pyrrolidine (SASP)-hydrazones is described.

Aldehydes constitute an important class of compounds in organic chemistry and their pure enantiomers are of increasing interest as chiral building blocks in the synthesis of biologically active substances. For instance, optically active, α-substituted aldehydes (**1**) can be transformed into a variety of other useful compounds without racemization.[1a] Despite their significance, the resolution of aldehydes remains problematic. Although special aldehydes were resolved as early as 1903 *via* their hydrazone and later imine, oxazolidine, or semioxamazone derivatives,[2] practical and general methods are still lacking.

During our work in the field of asymmetric synthesis, we learned that aldehyde resolutions may be possible in principle by separation of their epimeric (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazones,[1] using high perfor-



Scheme 1. i, $LiAlH_4$, tetrahydrofuran (THF); ii, Bu^tONO, THF; iii, R_3SiCl, CH_2Cl_2, Et_3N, 4-*N*,*N*-dimethylaminopyridine (cat.).

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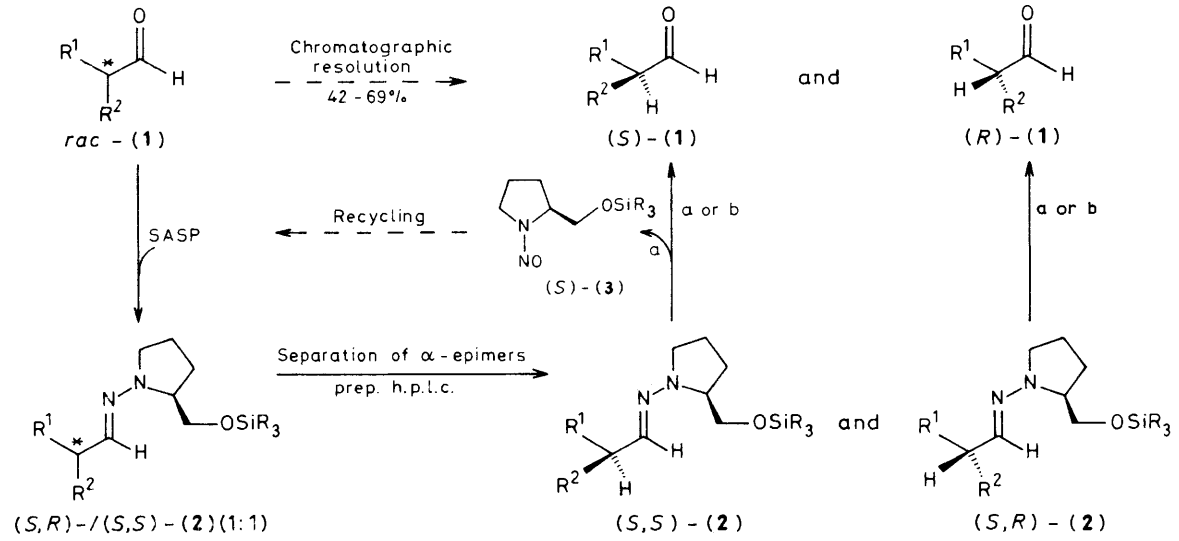

R_3 = Bu^tMe2, Bu^tPh_2

Scheme 2. Method a: O_3, n-pentane, −78 °C. Method b: i, MeI (excess), 60 °C; ii, 3—5 M HCl, n-pentane.

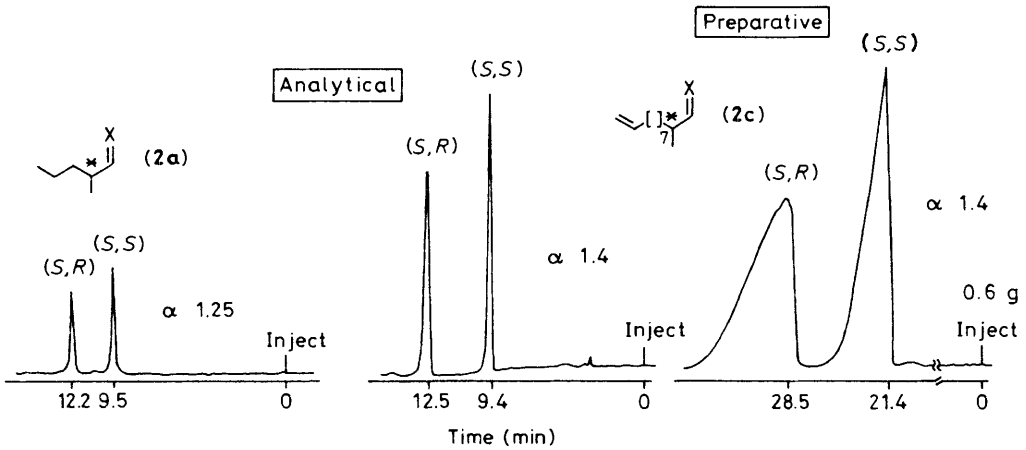

Figure 1. Resolution of aldehydes by chromatographic separation of their SASP-hydrazone epimers using a Du Pont de Nemours h.p.l.c. system 830. Analytical: Zorbax-Sil column (4.6 × 250 mm, 5—6 μm SiO_2), solvent system: light petroleum–THF–diethyl ether (100 : 0.6 : 0.4), pressure 30—55 bar. Preparative: Zorbax-Sil column (2.4 × 50 cm, 10 μm SiO_2), same solvent system, 90—110 bar.

Table 1. α-Substituted aldehydes (**1**) prepared by chromatographic resolution (h.p.l.c.) *via* their SASP-hydrazones (**2**) (R_3 = Bu^tMe_2, cleavage method b).

	R^1	R^2	B.p.(°C/Torr)[a]	% Yield[b]	α[c]	$[\alpha]_D^{20}$ (*c*, solvent)	% e.e.[d]
(*S*)-(**1a**)	n-C_3H_7	CH_3	110	48	1.25	+30° (0.5, acetone)	*ca.* 100
(*R*)-(**1a**)	n-C_3H_7	CH_3		36		−29.7° (0.75, acetone)	≥99[e]
(*S*)-(**1b**)	n-C_4H_9	C_2H_5	130	54	1.24	+4.6° (0.3, $CHCl_3$)	98.5
(*R*)-(**1b**)	n-C_4H_9	C_2H_5		50		−4.5° (0.6, $CHCl_3$)	96.4
(*S*)-(**1c**)	H_2C=CHC_7H_{15}-n	CH_3	85/0.1	71	1.42[f]	+23.6° (0.7, $CHCl_3$)	*ca.* 100
(*R*)-(**1c**)	H_2C=CHC_7H_{15}-n	CH_3		63		−23.4° (1.4, $CHCl_3$)	99.2
(*S*)-(**1d**)	C_6H_5	CH_3	85/5	73	1.21[g]	+314.6° (0.45, C_6H_6)[h]	99.4
(*R*)-(**1d**)	C_6H_5	CH_3		65		−288.3° (0.5, C_6H_6)	91[i]

[a] Data of shortpath distillation. [b] Overall resolution yield. [c] Separability factor. [d] Enantiomeric excess, determined by analytical h.p.l.c. (see Figure 1 and text) by retransformation of at least one of the enantiomers (**1**) to the SASP-hydrazone (**2**). [e] Also confirmed by comparison with an authentic sample prepared by the SAMP-/RAMP-hydrazone method having $[\alpha]_D^{20}$ 26.8° (*c* 0.9, acetone) of *ca.* 90% e.e. (n.m.r. shift experiment). [f] Using SASP (R_3 = Bu^tPh_2); α 1.6 is reached. [g] Using SASP (R_3 = Bu^tPh_2); α 1.27 is reached. [h] Max. calculated optical rotation: $[\alpha]_D^{21}$ 315.8° (*c* 1.5, C_6H_6), ref. 6. [i] Owing to tailing off (*S*,*S*)-(**2d**) not base line separated.

mance liquid chromatography (h.p.l.c.).[3—5] However, the separability factors, α, were not large enough for preparative purposes.

In this communication we report that the enantiomerically pure hydrazines [(*S*)-(−)-1-amino-2-(siloxymethyl)pyrrolidines] SASP, {R_3 = Bu^tMe_2, b.p. 86—88 °C/1.3 Torr; $[\alpha]_D^{20}$ −49° (neat), or Bu^tPh_2, $[\alpha]_D^{20}$ −15.4° (*c* 1.7, C_6H_6)}, easily prepared in 4 steps from (*S*)-proline, Scheme 1, can serve as efficient reagents for the chromatographic resolution of α-substituted aldehydes (**1**) in gram quantities.

As depicted in Scheme 2, the racemic aldehydes, *rac*-(**1**), are transformed into 1 : 1 mixtures of their epimeric SASP-hydrazones [(*S,S*)- and (*S,R*)-(**2**)] (SASP, benzene, Na_2SO_4, 20 °C), which are separated by h.p.l.c. As is shown in Figure 1 in the case of the typical examples (**2a**) and (**2c**), separability factors of α 1.25—1.6 are reached under analytical and preparative conditions (up to 0.6 g per injection). Finally, the pure diastereoisomers [(*S,S*)-(**2**) and (*S,R*)-(**2**)] are cleaved either by ozonolysis [method a, (*S*)-(**3**) (R_3 = Bu^tPh_2) precipitates and allows the recycling of SASP (Bu^i_2AlH, THF, 0 °C, not optimized)] or by acidic hydrolysis (method b), affording both enantiomers [(*S*)-(**1**) and (*R*)-(**1**)] of high enantiomeric purity and in good overall resolution yields (Table 1). In this way, for instance, the very sensitive 2-phenylpropanal [(*S*)-(**1d**)] was obtained for the first time in enantiomerically pure form (Table 1).

Although it is too early to discuss a chiral recognition model correlating elution orders and α values with stereostructure, the consistent elution orders [the (*S,S*)-diastereoisomer always elutes first] can be used to indicate the absolute configurations of aldehydes (**1**). Another advantage is the fact that enantiomerically enriched aldehydes (**1**) can be transformed into their SASP-hydrazones without racemization. This enables the accurate assay of enantiomeric purity of these important compounds on small amounts of sample (see Table 1, footnote d).‡

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‡ All new compounds exhibited satisfactory spectra (n.m.r., i.r., mass) and elementary analyses.