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OPTICALLY PURE ∝-AMINO ACIDS BY RESOLUTION OF SCHIFF BASES

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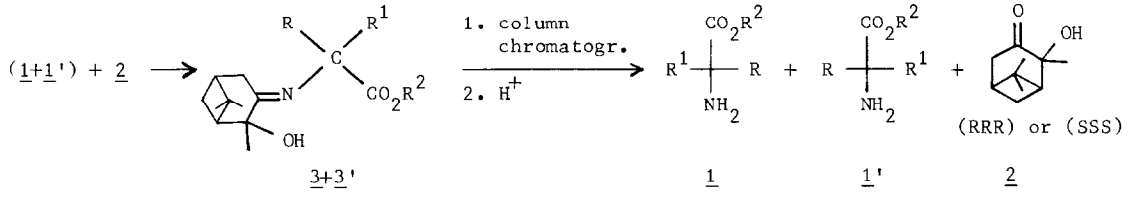
SUMMARY : A new general method of resolution of ∝-amino acids via their Schiff bases with 2-hydroxy pinan-3-ones is described. It complements the asymmetric synthesis of ∝-disubstituted amino acids by alkylation of the Schiff bases.

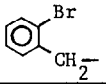
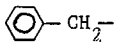
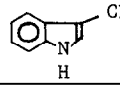
Asymmetric synthesis methods[1,2] seldom give enantiomerically pure amino acids. Thus, a final resolution procedure is almost always necessary, especially if the compounds are to be used in peptide syntheses.
We describe here a new, simple and fast general method for racemic resolution, in connection with our study on the enantioselective alkylation of Schiff bases of ∝-amino esters[3].

Unlike other Schiff bases and particularly those of benzaldehyde, which cleave easily under very mild conditions (they undergo dissociation during a simple column chromatography on silicagel[4]), compounds 3 + 3' formed from methyl or ethyl amino esters 1 + 1'and (+)-(RRR) or (-)-(SSS)-2-hydroxy pinan-3-one (2) are relatively stable. They can be easily chromatographed and gave for all examined compounds a quantitative separation of two diastereoisomers 3 and 3'.



3+3' 1 1' 2

Table 1 - Schiff bases (3,3') separated

3 (3')	R	R^1	R^2	2	Yield %	R_F^a	(éther : hexane)	$[\alpha]_D^{20}$ (c, chloroform)	
a	$n\text{-}C_3H_7$	H	CH_3	+	42	0,43	1:1	+ 71.5°	1,46
b					42	0,22	1:1	- 80,5°	1,70
c	$n\text{-}C_3H_7$	H	CH_3	-	40	0,52	1:2	- 71.0°	1,67
d					40	0,27	1:2	+ 81,0°	1,72
e	$n\text{-}C_3H_7$	CH_3	CH_3	-	65[bc]	0,35	1:2	- 59,5°	3,19
f	$n\text{-}C_3H_7$		CH_3	+	24[b]	0,54	1:2	- 22,5°	1,88
g					38[b]	0,44	1:2	- 3,0°	1,48
h		H	CH_3	+	45	0,50	1:2	+ 83,0°	2,96
i					45	0,19	1:2	- 96,0°	2,98
j	$H_3CO_2C\text{-}(CH_2)_2\text{-}$	H	CH_3	+	35	0,24	1:1	+ 90,5°	1,79
k					35	0,14	1:1	- 86,5°	1,92
l		H	C_2H_5	+	30	0,46	4:1	+ 78,0°	1,58
m					30	0,28	4:1	- 99,0°	1,60

[a] TLC on Merck silica gel 60

[b] prepared by enantioselective alkylation of 3 + 3' (R_1=H)[3]

[c] the (+) isomer was not isolated because of its low content in the crude product mixture before chromatography

In order to avoid any racemisation[5-7], the hydrolysis of Schiff bases is carried out under mild acidic conditions : action of 15% aqueous citric acid at 0—3°C for 72 hours. The optical purity (e.e.> 95%) of the separated amino esters was proved by ^{1}H-NMR spectrometry using d-Eu(hfc)$_3$ as chiral shift reagent[8] and by their specific rotation measurements.

Yields of all the intermediary reactions are good : 60-89% for the Schiff bases preparations and at least 72% for the hydrolysis. The chiral reagents 2 are readily available[9] by permanganate oxidation of respectively (+) or (-)-α-pinene. They do not need to be meticulously purified (to get $[\alpha]_D$ ± 41.2°[9] in chloroform) and we have found that those of $[\alpha]_D$ ± 37-38° can be used successfully ; no other carbonyl compound and no trace (e.e.> 95% based on ^{1}H-NMR spectra with d-Eu(hfc)$_3$) of another enantiomer was detected in 2 used for Schiff bases synthesis. Moreover, there is no epimerisation of 2 and ~70% of it can be recovered after hydrolysis and recycled.

Table 2 - Amino esters (1,1') by hydrolysis of Schiff bases

Substrate 3 or 3'	Amino ester	Yield %	Config.	$[\alpha]_D^{20a}$ found	(c, solvent) reported or [b]
a	$n\text{-}C_3H_7CH(NH_2)CO_2Me$	82	R	-24.5° (2.2,$CHCl_3$)	-25.5° (1.28,$CHCl_3$)[b]
b		85	S	+25.5° (1.7,$CHCl_3$)	+25.5° (1.20,$CHCl_3$)[b]
c		79	S	-24.5° (1.2,$CHCl_3$)	
d		81	R	+24.0° (2.1,$CHCl_3$)	
e	$n\text{-}C_3H_7C(CH_3)(NH_2)CO_2Me$	95	R	-13.0° (1.5,EtOH)	-12.9° (0.6,EtOH)[13]
h	$C_6H_5CH_2CH(NH_2)CO_2Me$	83	R	-16.5° (1.3,CH_2Cl_2)	-16.5° (1.58,CH_2Cl_2)[b]
i		85	S	+16.5° (1.5,CH_2Cl_2)	+16.9° (2,CH_2Cl_2)[14]
j	$MeO_2CCH(NH_2)(CH_2)_2CO_2Me$	72	R	-17.0° (1.6,$CHCl_3$)	-17.0° (0.95,$CHCl_3$)[b]
k		75	S	+16.5° (1.3,$CHCl_3$)	+17.0° (1.23,$CHCl_3$)[b]
l		91	R	-10.5° (3.4,$CHCl_3$)	-10.5° (1.95,$CHCl_3$)[b]
m		85	S	+10.5° (2.1,$CHCl_3$)	+10.5° (2.20,$CHCl_3$)[b]

[a] $[\alpha]_{578}^{25}$ for h and i

[b] for the amino ester prepared[11,12] from commercially available optically pure amino acid or amino ester hydrochloride

As indicated in the tables, this method of resolution proves to be of general interest. It applies to α-monoalkylated amino acids as well as to the α-dialkylated ones, synthesis of which was recently reported[3]. It gives its full value to the method of synthesis of amino acids by alkylation of Schiff bases[3,10] : regardless of its enantioselectivity, optically pure enantiomers can be easily obtained.

Experimental (general procedure) :

A mixture of the (dl)-α-amino acid, transformed into its methyl or ethyl ester by the usual methods (1; 0,1 mol), 2-hydroxy pinan-3-one[3] (2; 0,12 mol) and a catalytic amount of boron trifluoride etherate in 150 ml of benzene is refluxed for 3 h using a water trap. The solvent is evaporated in vacuo and the oily residue is chromatographed on 70-230 mesh silica gel (30 parts). The first fractions eluted with an ether-hexane (1:3) mixture, give the unreacted 2 almost quantitatively. The polarity of the eluent is increased (1:1 ; the proportions being respectively 3:1 and 5:1 for tryptophan) after collection of the first diastereoisomer. The eluent evaporated, colorless or slighty yellow oils (3 and 3') are pure enough for analyses.

To a stirred solution of the Schiff base 3 (or 3') (0,02 mol) in tetrahydrofuran (100 ml) at 0°C, a 15% aqueous citric acid (75 ml) is added dropwise and stirring is continued for 72 hours at 0-3°C. The solvent is evaporated in vacuo at room temperature and 2 is extracted with 2 x 100 ml of benzene.
The water layer is cooled again to 0°C, basified to pH = 8 with conc. ammonia and immediately extracted with 6 x 100 ml of ether. The etheral phases, after drying with sodium sulphate and evaporation at room temp. give 72-91% yield of pure amino ester 1 (or 1'), which optical purity was established by ^{1}H-NMR spectroscopy (0,15-0,2 M CCl_4/TMS solution in the presence of 0,2 $\longrightarrow$ 0,6 molar equivalent of d-Eu(hfc)$_3$[8]). About 70% of chiral reagent is recovered from the benzenic solution after purification by column chromatography (30 parts of SiO_2 ; ether-hexane 1 : 1).

All compounds described here gave MS and ^{1}H-NMR spectra consistent with their structures. The microanalyses were in satisfactory agreement with the calculated values: C $\pm$ 0,30 ; H $\pm$ 0,20 ; N $\pm$ 0,30.

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