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N-bis-SILYLATION OF α-AMINO ACIDS : "BENZOSTABASES" AS AMINO PROTECTING GROUP

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Amino acid protection; N-Bis-trimethylsilylation; "Stabases"; "benzostabases".

Abstract: N-Bis-trimethylsilylation of α-amino acids using the powerful trimethylsilyl triflate reagent is difficult, and is rendered impossible in the case of bulky side-chains (valine). However, favorable entropy changes resulting from a cyclization reaction allow the formation of "benzostabase" N-diprotections regardless of the side-chain bulk.

Only a few protecting groups stable under strongly basic conditions exist for primary amines; in these cases, both hydrogen atoms need to be blocked (e.g. Schiff-bases). Such N-diprotections are especially useful in the case of α-amino acids.

The phthalimid group[1] is probably the most popular method of N-diprotection, although it is not the unique protecting system in which the nitrogen atom is trapped in a ring[2]. The introduction of two identical substituents in place of each amine hydrogen atom has been reported: N,N-diBoc[3], N,N-dibenzyl[4], N,N-diallyl[5]. However, each of these differing protection groups do not fulfil the following general requirements: easy introduction, stability towards reaction conditions, quantitative removal using mild and selective methods, etc.

The increasing use of organosilicon reagents in organic synthesis, notably as protecting groups[6], has duly introduced studies of N-disilylation as an option for blocking primary amines. N-Disilylated amines are much more stable than their monosilylated analogues. They are resistant to basic and neutral aqueous work-ups, electrophiles, organometallic species (BuLi, LDA...) and to nucleophiles. However, the deprotection can be achieved under extremely mild acidic conditions.

In the field of α-amino acids, the use of N-disilylation in nitrogen protection

could provide two remarquable advantages:

- absence of a carbonyl group on the nitrogen, thus eliminating the main source of racemization from formation of oxazolone intermediates,
- liberation of the free amine under extremely mild conditions.

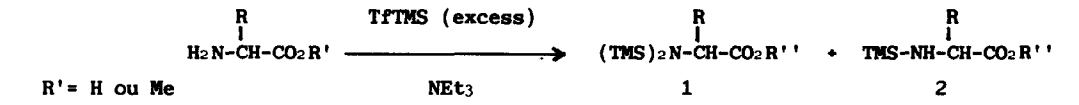
Trimethylsilylation of amino acids has been extensively studied[7-19], revealing the quick silylation of the carboxyl function, followed by monosilylation of the amine group. Side-chain functional groups containing labile hydrogen atoms are also silylated.

N-Bis-trimethylsilylation of α-amino acids has been reported only for the sterically unhindered glycine[13b,10i,20,21]. The N-disilylated "stabase" derivative of glycine was also synthesised by Magnus et al.[22] using the 1,2-bis-chlorodimethylsilyl ethane reagent.

Taking into account the previously mentioned advantages concerning N-disilylated amino acids, we envisaged to develop a new general methodology to obtain these species.

Initially, we attempted to N-bis-trimethylsilylate amino acids using the trimethylsilyl trifluoromethanesulfonate (**TfTMS**) reagent, reported as one of the most powerful silylating reagents[23-25] (Scheme 1). The results are presented in table 1.

Scheme 1



R'= H ou Me

These results show a significant involvement of steric hindrance; for example, glycine where **R=H** may be easily N-bis-silylated. However, larger **R** groups may seriously hinder bis-silylation; the methyl group of alanine and the benzyl group on phenylalanine both decrease the yield of **1**, and likewise the isopropyl on valine impedes N-disubstitution.

The initial difficulties to achieve our purpose even using a reagent as powerful as **TfTMS**, led us to investigate driving forces which could counterbalance steric effects. We considered that the advantage of favourable entropic effect, virtue of a cyclization reaction trapping the nitrogen atom in a cyclic disilylated system (scheme 2), would be a good alternative route. The "stabase" group was first reported by Andrianov et al.[26] and has been further developed by Magnus et al.[22] (scheme 2). It has been employed by Magnus for glycine and by Hegberg et al.[27] for an alanine derivative.

To further increase the rigidity of the cyclic system, and hence the entropic effect and stability, we chose a bicyclic protection (similar to that of Corriu et al.[28] for silylenamines) leading to compounds of type **6**. We designated the nomenclature "benzostabases" by analogy to "stabases" by Magnus. In parallel to our own studies[29], Davis et al.[30] very recently reported the application of this kind of protecting group

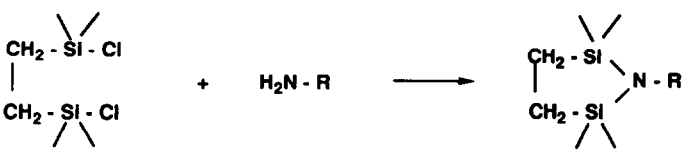
Table 1

Silylation of aminoacids by TfTMS*

Entry	Aminoacid	R	R''	Solvent	Reaction conditions Time (h)	Temp.(°C)	Yields % 1	2
1	Gly	H	$SiMe_3$	C_6H_6	28	20	91	0
2	Ala	Me	$SiMe_3$	C_6H_6	22	20	61	27
3	Ala	Me	Me	C_6H_6	24	20	68	17
4	Phe	Bn	$SiMe_3$	C_6H_6	40	20	6	60
5	Leu	iBu	$SiMe_3$	C_6H_6	45	20	3	57
6	Leu	iBu	$SiMe_3$	CH_2Cl_2	30	20	9	76
7	Leu	iBu	$SiMe_3$	CH_2Cl_2	70	20	40	37
8	Leu	iBu	Me	C_6H_6	24	20	7	70
9	Leu	iBu	Me	CH_2Cl_2	24	20	16	50
10	Leu	iBu	Me	CH_2Cl_2	24	55	24	58
11**	Val	iPr	$SiMe_3$	C_6H_6	24	50	0	92
12	Val	iPr	Me	C_6H_6	24	80	0	80

*) 3-3.5 eq. of TfTMS and 7-9 eq. of NEt_3 added at -20°C then brought to the temperature indicated in the table.
**)4.5 eq of TfTMS

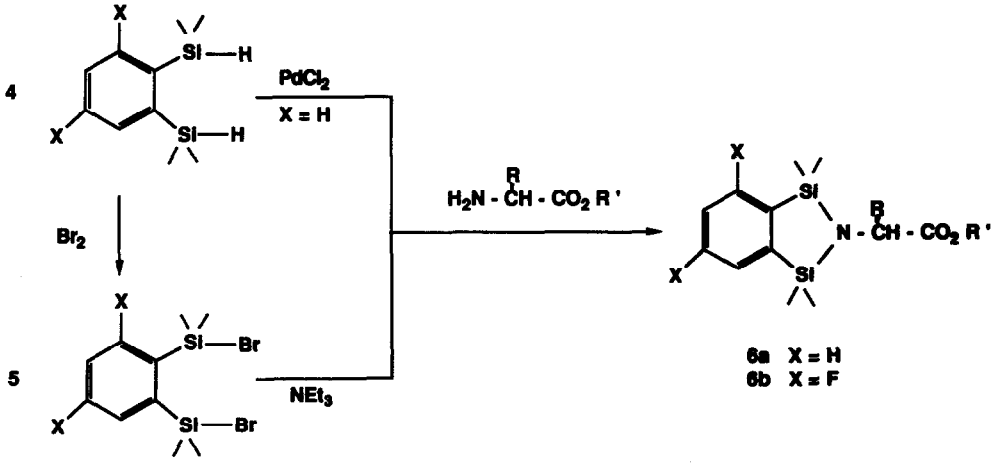
Scheme 2



for varied anilines and benzylamines, and also for two α-amino acids, alanine and phenylalanine. They introduced the "benzostabase" group by deshydrogenative silylation using a rhodium catalyst or palladium chloride. For our part, we investigated the use of the corresponding dibromosilane, a reagent less stable than the hydrogenosilane used by Davis, but which avoids the use of a catalyst (scheme 3).

We synthesized disilanes **4a** and **4b** from the corresponding o-dibromobenzene derivatives, dimethylchlorosilane and magnesium, following the procedure of Fink[31]. Derivative **4b** was prepared due to the low price of the starting material. Dibromoderivatives 5 results from treatment with bromine at 0°C, as described by

Scheme 3



Nametkin et al.[32]. A stream of nitrogen is passed through the mixture to eliminate the hydrobromic acid formed during the course of the reaction, in order to prevent acid induced cleavage of the Si-Ar bonds. Compounds 5 are moisture-sensitive but can be easily stored under a dry nitrogen atmosphere.

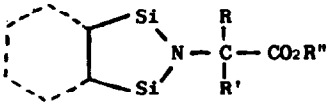
"Benzostabases" of several α-amino acids were synthesized and results were compared with those obtained for "stabases" as described in literature or prepared in our laboratory (table 2).

The data show that the "stabase" system is relatively sensitive to steric hindrance of the amino acid side-chain; glycine (R=H) and alanine (R=Me) gave good yields, leucine (R=iBu) led to a decreased yield and it was impossible to isolate the corresponding valine derivative (R=iPr). However, the bicyclic "benzostabase" system is a lot easier to introduce, being possible for valine derivatives **6a** and **6b** in 62 and 75% yields respectively. The "benzostabase" of α-amino isobutyric acid (R=R'=Me), a very demanding example, was also obtained and with 45% yield. In all the cases studied, the difluorinated reagent **5b** was more reactive that the unsubstitued reagent **5a**.

We confirmed for a single example that the introduction of the "benzostabase" protecting group was free of racemization of the amino acid. NMR spectra of "benzostabases" **6a** and **6b** for L and D,L leucine O-methyl ester derivatives were studied using a chiral shift reagent: with the L component, the methyl ester group gave a single peak whereas with the D,L component, we observed a doublet for the same group.

The adducts **6** are stable to neutral or mild basic work-up; we purified them by

Table 2



3 or 6

R	R'	R"	Yield[a] % 3	Yield[a] % 6a	Yield[a] % 6b
H	H	Et	92[b]		
H	H	Me	78[c]		
Me	H	Y-$CH_2C(Me)_2$	79[d]		
Me	H	Bn	60[e]		
Me	H	CH_2-CH_2-TMS	69[e]		
Me	H	CH_2-CH_2Br	62[e]		
Me	H	Me	80[e]	90[f], 81[g]	93[f]
iBu	H	Me	58[f]	62[f]	85[f]
iBu	H	CH_2-CH_2Br		47[f]	
iPr	H	Me	0[f]	62[f]	75[f]
Bn	H	Me		74[f], 82[g]	
Me	Me	Me		42[f]	

Y = p.Cl-C_6H_4-

[a]) Yields of distillated or chromatographed (neutral Al_2O_3) products [b])ref 22; [c]) CH_2Cl_2, RT, 2h; [d]) ref 27; [e]) CH_2Cl_2, RT, 24h; [f]) C_6H_6, 80°C, 24h; [g]) ref 30.

distillation or by chromatography on neutral alumina without observing any degradation. However, partial degradation was observed on silica gel.

Deprotection is easily achevied in mild acidic media: one equivalent of trifluoroacetic or acetic acid leads to fast and total cleavage.

"Fluorobenzostabases" **6b** seem to be less vulnerable to cleavage than their non-fluorinated analogues **6a**. For example, the protecting group of leucine derivative **6a** is quickly cleaved when treated with a Lewis acid like aluminium chloride, whereas the fluorinated analogue **6b** is stable in the same conditions.

We finally investigated the use of "benzostabases" **6** in peptide synthesis. Initially we tried to generate the carboxylate derivative (but not the free carboxylic acid group which would induce rapid N-deprotection) from the respectives methyl ester species. The methyl ester derivatives of alanine, leucine and phenylalanine "benzostabases" remained intact when submitted to classical saponification conditions (KOH or NaOH in methanol , 4 to 24 hours at room temperature, table 3, entries 1-4).

Bases in aqueous alcoholic media (entry 5) or increasing the reaction temperature led to a little or a significant cleavage of the N-protecting group which in all cases occurred before complete hydrolysis of the methyl ester function. Such findings

may be connected to the strong steric interference due to the "benzostabase" group. Consequently, we tried to saponify the phenylalanine "benzostabase" using lithium iodide in DMF (entry 6) following the procedure reported by Dean[33] for hindered methyl esters. We observed a full recovery of the free amine. Trimethylsilyl iodide under the conditions used by Young and Lyster[34] left the phenylalanine "benzostabase" intact (entry 7).

Table 3
Deprotection conditions

Entry	Reagents	T	Time	N-Si clivage	CO_2R clivage
1	KOH/MeOH	R.T.	4h	-[a]	-[c]
2	NaOH/MeOH	R.T.	4h	-[a]	-[c]
3	KOH/MeOH	R.T.	24h	-[a]	-[c]
4	NaOH/MeOH	R.T.	24h	-[a]	-[c]
5	KOH/MeOH/H_2O	R.T.	16h	+[a]	+[c]
6	LiI/DMF	90°	2h	+[a]	+[c]
7	$ISiMe_3$	50°	48h	-[a]	-[c]
8	H/Pd/C/MeOH/NEt_3	R.T.	2h	+[b]	+[d]
9	CsF/CH_2Cl_2	R.T.	18h	-[b]	-[e]
10	KF/MeOH/THF	R.T.	18h	-[b]	-[e]
11	$NBu_4^+F^-$/THF	R.T.	30mn	+/-[b]	+/-[e]
12	Zn/EtOH/H_2O	60°	12h	-[a,b]	-[f]
13	Mg/THF	60°	12h	-[a,b]	-[f]
14	Na/THF	R.T.	2h	+[a]	+[f]

a) "Benzostabase" protecting group 6. b) "Stabase" protecting group 3.
c) R = CH_3. d) R = CH_2-C_6H_5. e) R = CH_2-CH_2-$SiMe_3$. f) R = CH_2-CH_2-Br.

On account of the difficulties we observed for selective saponification of methyl esters, we investigated other kind of esters. The benzyl ester of the alanine "stabase" when submitted to classical deprotection conditions (Pd/C, cyclohexadiene, MeOH,NEt_3[35] or Pd/C, ammonium formate[36,37], entry 8) led in several instances to the fully deprotected compound.

We then tried esters which could be liberated by a ß-elimination mecanism, such as ß-trimethylsilylethyl esters, sensitive to fluoride ions[38], or ß-bromoethyl esters cleaved by metals[39,40]. The trimethylsilylethyl ester of the alanine "stabase" was stable to CsF (entry 9) and to KF (entry 10) even after long reaction times (18

hours); however, anhydrous tetrabutylammonium fluoride in THF led after 30 minutes to a complex mixture showing partial amine and ester deprotections (entry 11).

Zinc or magnesium did not affect the ß-bromoethyl esters derivatives (entries 12,13), whereas sodium in THF led to full deprotection of both functions (entry 14).

Hence, we have not succeeded in the selective deprotection of the acid function of "stabases" or "benzostabases" and therefore they cannot be used for the moment in a racemization-free peptide synthesis. However, these N-diprotected amino acid derivatives could be useful for other applications, notably for the synthesis of chiral amino alcohols by reduction of the ester function as reported by Bonar-Law et al.[30b].

Experimental

Melting points were taken on a Büchi apparatus and are uncorrected.

^{1}H NMR spectra were recorded on Varian EM 390 or Brüker WP 200 spectrometers by the "Laboratoire de Mesures Physiques de l'Universisté de Montpellier II"; chemical schifts are quoted in ppm (δ) relative to tetramethylsilane as internal standard, or relative to Si-Me signals for molecules containing this group. Mass spectra were determinated with a Jeol JMS DX 300 instrument.

Elemental analyses were carried out by the "Laboratoire de microanalyse du CNRS" (Vernaison).

Merk neutral aluminium oxyde (70-230 mesh, activity 1) was used for preparative chromatography with ethylether/hexane (1/1) as eluent.

Moisture and air-sensitive reactions were carried out under a dry nitrogen atmosphere. Anhydrous solvents were prepared using standard methods. The methylene chloride used was stabilised with amylene and not ethanol (from SDS, France).

All amino acids used were of L-configuration unless otherwise stated.

Esterification of amino acids

Methyl esters of alanine, glycine, leucine, phenylalanine and valine were commercially available.

Other amino ester were synthesized according to the procedure of Brook and Chan[41], from chlorotrimethylsilane, the amino acid and the appropriate alcohol, alone or mixed with THF. The ester hydrochlorides were correctly identified from their NMR spectra and melting points.

Aib-OMe,HCl: Yield:80%; mp=152-154°C (Lit.[42]: 140°); NMR (D_2O) δ : 1.6 (s,6H,2 CH_3); 3.8 (s,3H,OCH_3).

Ala-OBn,HCl: Yield: 90%; mp=139-140°C (Lit.[43]: 140°); NMR (D_2O) δ : 1.14

(d,J=7Hz,3H,CH-$\underline{CH_3}$); 4.0 (q,J=7Hz,1H,CH); 5.0 (s,2H,CH_2); 7.15 (s, 5H,C_6H_5).

Ala-O-CH_2-CH_2-TMS : as crystallization failed, the free amino ester was obtained as an oil by bubbling ammonia in diethyl ether at 0°C. Yield:75%; NMR ($CDCl_3$) δ : 0 (s,9H,$Si(CH_3)_3$) (as internal standard), 1.0 (m,2H,Si-CH_2); 1.33 (d,J=7Hz,3H,CH-$\underline{CH_3}$); 1.53 (broad s,2H,NH_2); 3.5 (q, J=7Hz,1H, CH); 4.16 (m,2H,O-CH_2).

Ala-O-CH_2-CH_2Br,HCl: Yield:95%; mp = 90-93°C; NMR (D_2O) δ : 1.6 (d,J=7Hz,3H,CH-$\underline{CH_3}$); 3.8 (m,2H,O-CH_2); 4.2 (m,1H,CH); 4.6 (m,2H,CH_2Br).

Leu-O-CH_2-CH_2Br,HCl: Yield:100%; mp=142-145°C; NMR (D_2O) δ: 1.06 (d,J=7hz,6H,CH($\underline{CH_3}$)$_2$); 2.1 (m,3H,$\underline{CH_2}$-$\underline{CH}(CH_3)_2$); 3.6 (d,J=7Hz,2H,O-CH_2); 4.3 (m,1H,N-CH); 4.6 (d,J=7Hz,2H,CH_2Br).

1,2-bis-dibromodimethylsilyl) benzenes 5

- 1,2-Bis(dimethylsilyl) benzenes 4

A solution of 1,2-dibromobenzene (100mmol) (or 1,2-dibromo-3,5-difluorobenzene) in anhydrous THF (100ml) was added slowly (1 hour) to a stirred mixture of magnesium (5,3g, 210mmol) and chlorodimethylsilane (23,5ml, 210mmol) in anhydrous THF (15ml). In some instances iodine was necessary to initiate the reaction. The mixture was refluxed for one hour before cooling to room temperature. On cooling a precipitate settled. After trituration of the solid with a large amount of hexane followed by filtration and then concentration *in vacuo* at 30°C, an oil was obtained which was further purified by distillation under reduce pressure.

1,2-Bis(dimethylsilyl) benzene **4a**: Eb_8=75-80°C (Lit.[31]: Eb_{10}=93°). Yield:75%. NMR (CCl_4) δ : 0 (d,12H,Si-CH_3); 4.3 (m,2H,SiH); 7.03 (m,4H,C_6H_4).

1,2-Bis(dimethylsilyl)-3,5- difluoro benzene **4b**: Eb_{10}=70-75°C. Yield:70%. NMR (CCl_4) δ : 0 (d, J = 3,5Hz, 12H, Si-CH_3); 4.23 (m, 2H, SiH); 6.33 et 6.66 (m,2H arom.).

-1,2-Bis(bromodimethylsilyl) benzenes 5

A solution of the reagent 4 (77mmol) in CCl_4 (90ml) was added over 45min. to a ice-bath cooled solution of bromine (9ml, 175mmol) in CCl_4 (90ml) whilst maintaining nitrogen atmosphere. Nitrogen gas was bubbled through the mixture for a further 30min. before removing the solvent *in vacuo* at room temperature. The residual oil was purified by distillation under reduced pressure.

1,2-bis(bromodimethylsilyl) benzene **5a**: Eb_{15}=160-170°C; Yield:80%. NMR (CCl_4) δ : 0 (s,12H,2 $Si(CH_3)_2$; 6.63 (m,4H,C_6H_4).

1,2-bis(bromodimethylsilyl) 3,5-difluoro benzene **5b**: Eb_{15}=115-120°C; Yield:60%. NMR (CCl_4) δ : 0 (m,12H,2 $Si(CH_3)_2$); 5.8 and 6.66 (m,2H, C_6H_2).

Trimethylsilylation of amino acids and amino esters

Maintaining a nitrogen atmosphere, **TfTMS** (5ml, 25mmol) was added slowly to a cooled solution (-20°C) of the amino ester or amino acid (7.2mmol) and triethylamine (7ml, 50mmol) in benzene or methylene chloride (20ml). With stirring (time and temperature indicated in table 1) the mixture separated into two distinct layers. When methylene chloride was used as solvent, it was then removed under reduced pressure replacing it afterwards by benzene (20ml). The upper benzene layer, after concentration *in vacuo* (160mm Hg), afforded an oily residue which was distillated under reduced pressure (10-15mm Hg). As the N-disilylated derivatives have higher boiling points than the monosilylated analogues, it was possible to isolate a pure fraction of the N-disilylated product. Structures were confirmed by NMR and mass spectroscopy. NMR spectra of the residue prior to distillation gave the percentage of both derivatives. Yields and NMR spectra are given in tables 1 and 4 respectively.

Stabases and benzostabases of amino esters:

The dihalosilylated reagent **5a** or **5b** or 1,2-bis(chlorodimethylsilyl ethane (10.5mmol) and triethylamine (6 eq., 7ml) were added to a stirred suspension of the amino ester hydrochloride (8mmol) in an appropriate solvent (40ml, benzene or methylene chloride) under a nitrogen atmosphere. The mixture was stirred under the conditions (time and temperature) given in table 2. The mixture was then diluted with diethyl ether (100ml) and the precipitate was filtered off. Evaporation of the filtrate under reduced pressure afforded an oil which was purified by distillation or chromatography. All the structures were confirmed by ^1H NMR and mass spectroscopy. Elemental analysis were performed on two crystallized products.

Stabase of Gly-OMe: Yield:78%; Eb_{15}=70-73°C; NMR (CCl_4) δ : 0 (s,12H,2 $Si(CH_3)_2$); 0.66 (s,4H,CH_2-CH_2); 3.3 (s,2H,CH_2); 3.53 (s,3H,OCH_3).

Stabase of Ala-OMe: Yield:80% after chromatography (Rf=0.7); NMR ($CDCl_3$) δ : 0 (s,12H,2 $Si(CH_3)_2$); 0.6 (s,4H,CH_2-CH_2); 1.2 (d,J=7Hz,3H,C-CH_3); 3.5 (s,3H,OCH_3); 3.7 (q,J=7Hz,1H,CH).

Stabase of Ala-OBn: Yield:60% after chromatography (Rf=0.65). NMR ($CDCl_3$) δ : 0 (d,12H, $Si(CH_3)_2$; 0.6 (s,4H,CH_2-CH_2); 1.3 (d,J=7Hz,3H,C-CH_3); 3.7 (q,J=7Hz,1H,CH); 5.0 (s,2H,CH_2O); 7.2 (s,5H,C_6H_5).

Stabase of Ala-OCH$_2$-CH$_2$TMS: Yield:69% after chromatography (Rf=0.76). NMR ($CDCl_3$)

δ: 0 (s,9H, $Si(CH_3)_3$); 0.06 (d,12H,2 $Si(CH_3)_2$); 0.67 (s,4H,Si-CH_2-CH_2-Si); 0.97 (m,2H,-CH_2-Si); 1.30 (d,J=7Hz,3H,C-CH_3); 3.67 (q,J=7Hz,1H,CH); 4.10 (m,2H,OCH_2).

Stabase of Ala-OCH_2-CH_2Br: Yield:62% after chromatography (Rf=0.95). NMR ($CDCl_3$) δ: 0 (s,12H,2 $Si(CH_3)_2$); 0.63 (s,4H,Si-CH_2-CH_2-Si); 1.23 (d,J=7Hz,3H,C-CH_3); 3.4 (t,J=7Hz,CH_2Br); 3.7 (q,1H,CH); 4.2 (t,J=7Hz,OCH_2).

Stabase of Leu-OMe: Yield:58%; Eb_{10-15}=80-82°C. NMR ($CDCl_3$) δ : 0 (t,12H,2 $Si(CH_3)_2$); 0.8 (m,6H,$C(CH_3)_2$); 1.37 (m,2H,CH_2); 1.7 (m,1H,$\underline{CH}(CH_3)_2$); 3.57 (s,3H,OCH_3); 3.58 (m,1H,CH).

Benzostabase of Ala-OMe: Yield:90%; Eb_{10-15}=120-125°C. NMR (CCl_4) δ: 0 (d,12H,2 $Si(CH_3)_2$); 1.1 (d,J=7Hz,3H,C-CH_3); 3.3 (s,3H,OCH_3); 3.5 (q,J=7hz,1H,CH); 7 (m,4H Arom.).

Benzostabase of Leu-OMe: Yield:62%; Eb_{10-15}=112-118°C; mp=40°C. Anal.: $C_{17}H_{29}NO_2Si_2$. NMR ($CDCl_3$) δ : 0 (d,12H, 2 $Si(CH_3)_2$); 0.6 (d,6H,$C(CH_3)_2$); 1.2 (m,2H,CH_2); 1.6 (m,1H,CH); 3.4 (s,3H,OCH_3); 3.5 (t,J=7Hz,1H,CH); 7.2 (m,4H Arom.).

Benzostabase of Leu-OCH_2-CH_2Br: Yield:47% after chromatography (Rf=0.77). NMR ($CDCl_3$) δ : 0 (d,12H,2 $Si(CH_3)_2$); 0.63 (d,J=7Hz,6H,$C(CH_3)_2$); 1.33 (m,3H,CH_2-CH); 3.16 (t,J=7Hz,2H,CH_2Br); 3.5 (q,J=7Hz,1H,CH); 4.1 (t,J=7Hz,2H,OCH_2); 7.16 (m,4H Arom.).

Benzostabase of Val-OMe: Yield:62%; Eb_{10-15}=120-122°C. NMR ($CDCl_3$) δ : 0 (d,12H,2 $Si(CH_3)_2$); 0.63 (m,6H,$C(CH_3)_2$); 1.8 (m,1H,CH); 3.3 (s,3H,OCH_3); 7.1 (m,4H Arom.).

Benzostabase of Phe-OMe: Yield:74% after chromatography (Rf=0.76). NMR (CCl_4) δ: 0 (d,12H,2 $Si(CH_3)_2$); 2.9 (m,3H,CH-CH_2); 3.2 (s,3H,OCH_3); 6.8 (s,5H,C_6H_5); 7 (m,4H Arom.).

Benzostabase of Alb-OMe: Yield:42% after chromatography (Rf=0.78). NMR ($CDCl_3$) δ: 0 (d,12H, 2 $Si(CH_3)_2$); 1.3 (s,6H,$C(CH_3)_2$); 3.3 (s,3H,OCH_3); 7 (m,4H Arom.).

Difluorobenzostabase of Ala-OMe: Yield:93% after chromatography (Rf=0.80). NMR (CCl_4) δ : 0 (t,12H,2 $Si(CH_3)_2$); 1.06 (d,J=7Hz,3H,C-CH_3); 3.3 (s,3H,OCH_3); 6.33 and 6.63 (m,2H Arom.).

Difluorobenzostabase of Leu-OMe: Yield:85% after chromatography (Rf=0.85). NMR ($CDCl_3$) δ : 0 (t,12H,2 $Si(CH_3)_2$); 1.26 (m,3H,CH_2-CH); 3.33 (s,3H,OCH_3); 3.4 (q,J=7Hz,1H,CH); 6.33 and 6.63 (m,2H Arom.).

Difluorobenzostabase of Val-OMe: Yield:75% after chromatography (Rf=0.85). mp. = 30°C. Anal.: $C_{16}H_{24}F_2NO_2OSi_2$. NMR ($CDCl_3$) δ : 0 (t,12H,2 $Si(CH_3)_2$); 0.56

(m,6H,C(CH_3)$_2$); 1.73 (m, 1H,CH); 3.33 (s,3H,OCH_3); 6.3 and 6.63 (m,2H Arom.).

Confirmation of the optical purety of benzostabases

The methyl esters of D,L leucine benzostabase and difluorobenzostabase were prepared according to the previously described procedure for L amino esters.

NMR spectra using a chiral schift reagent were recorded on a 90MHz Varian spectrometer, between repeated additions of tris (heptafluorobutyryl-3 d-camphorato) Europium^{III} (**EU(hfc)$_3$**) (0.1 eq) to the respective compound (50 mol) in $CDCl_3$ (0.5ml). When the concentration of **Eu(hfc)$_3$** reached 0.7 eq. (42mg), the doublet of the **D,L OMe** group gave a 4 to 5Hz enantiomeric schift separation ($\Delta\Delta\delta$). Integration of the two signals allowed accurate determination of a 50/50 mixture of L and D enantiomers. Under the same conditions, the L leucine derivative gave a single peak for the **OMe** group.

Deprotection attemps of the acid function of "stabases" 3 and "benzostabases" 6.

- Saponification of methyl esters (Table 3; entries 1-5)

A solution of base (2mmol) in a small amount of solvent was added to a solution of the methyl ester (2mmol) in an appropriate solvent (4ml). The reaction was carried out under conditions (solvent, temperature, time) given in table 3. The solvents were then evaporated under reduced pressure, and the residue was taken up in diethyl ether. The precipitate was isolated by filtration and the diethyl ether filtrate was concentrated. Both residues were analyzed by CCM and ^1H NMR.

Examples:

*- Saponification of the Ala-OMe benzostabase using **KOH/MeOH** (Table 3, entry 1; 4 hours, R.T.): alanine was absent in the NMR spectrum of the isolated precipitate (D_2O). NMR spectrum ($CDCl_3$) of the residue from diethyl ether concentration was identical to that of the starting material. The latter was fully recuperated.

*- Saponification of the Phe-OMe benzostabase using **KOH/MeOH/H_2O** (Table 3, entry 5; 16 hours, R.T.): the potassium salt of the N-deprotected **Phe** only was identified by NMR spectrum of the precipitate in D_2O. NMR spectrum of the concentrate in $CDCl_3$ showed signals corresponding to the siloxane: δ: 0.2 (s,12H,2 Si(Me_3)$_2$); 7.3 (m,4H Ar).

- Saponification following the procedure of Dean[33] (Table 3, entry 6)

A solution of **LiBr** (2.6mmol) in dry acetonitrile was quickly added to a solution of **NaI** (2.6mmol) in 3ml of dry acetonitrile. **NaBr** formed and was filtered off. A solution of "benzostabase" of Phe-OMe (2.5mmol) in **DMF** (5ml) was then added to the filtrate. The mixture was stirred for two hours at 90°C before evaporation of the

solvent *in vacuo*. Concentration afforded a whitish solid which was then taken up in a mixture of D_2O and $CDCl_3$ (1/1). N-deprotected methyl ester of phenylalanine was present in the $CDCl_3$ layer as shown by NMR spectrum (100% recovery).

- Cleavage using $ISiMe_3$/triethylamine (Table 3, entry 7).

Trimethylsilyl iodide (2.4mmol) was added via syringe to a solution of triethylamine (0.1ml) in CCl_4 (10ml) under a nitrogen atmosphere. A solution of the "benzostabase" of Phe-OMe (2mmol) in CCl_4 (10ml) was then added. the mixture was stirred at room temperature for 1.5 hour followed by 48 hours at 55°C. After concentration *in vacuo* at 40°C, CCM and NMR analysis showed the residue to be unreacted starting materials (90% recovery).

-Hydrogenolysis of benzylic esters (Table 3, entry 8)

Pd/C 10% (1g), ammonium formate (5mmol) (or cyclohexadiene, 10mmol and triethylamine, 1mmol) were added to a solution of the "stabase" of Ala-OBn (1mmol) in methanol (15ml). A gas evolved and after stirring for two hours at R.T., the mixture was filtered through a filter paper with cotton (celite cleaves Si-N bonds). Evaporation of the solvent afforded a white residue which was identified as free alanine (NMR in D_2O; 100% recovery).

- Cleavage of trimethylsilylethyl esters with F^- ions (Table 3, entries 9-11)

A solution of stabase of Ala-OCH2-CH2SiMe3 (1,5mmol) in THF or methylene chloride (2ml) was added to a stirred solution of KF (1.5mmol) or a slurry of CsF (1.5mmol) in a mixture of methanol (4ml) and THF (3ml). After stirring for 18 hours at R.T., the solvents were evaporated *in vacuo* at 40°C. The residue was taken up in diethyl ether and the precipitate was filtered off. The filtrate, after evaporation of the solvent under reduced pressure, afforded a solid which on analysis (CCM and NMR spectrum) was confirmed to be the unreacted starting stabase (94% recovery).

A similar procedure was carried out on the same substrate using a commercial solution of 1M tetrabutylammonium fluoride in THF dried by molecular sieves. After stirring for 30min. at R.T., a white precipitate appeared. The NMR spectrum of the solid showed the NBu_4^+ and free alanine signals. The filtrate, on concentration provided a complex NMR spectrum ($CDCl_3$) revealing a mixture of starting material and siloxane.

- Cleavage of the bromoethyl esters (Table 3, entries 12-14)

-Using Zn or Mg

A mixture of the stabase of Ala-OCH_2-CH_2Br (1mmol) and Zn or Mg (1.1 eq.) in EtOH-H_2O (5ml), was stirred for 12 hours at 60°C. Evaporation of the solvent under reduced pressure afforded the unreacted starting component.

Table 4

N-Silyl Aminoesters

Compound	Eb_{10-15}	^1H NMR ($CDCl_3$), ppmm
N-$(TMS)_2$ Gly-OTMS	75	0 (s,18H,$(TMS)_2$); 0.18 (s,9H,O-TMS); 3.83 (s,2H,CH_2).
N-$(TMS)_2$ Ala-OTMS	57-67	0 (s,18H,$(TMS)_2$); 0.17 (s,9H,O-TMS); 1.93 (d, J=7Hz,3H,CH_3); 3.58 (q,J=7Hz,1Hz,CH).
N-TMS Ala-OTMS*	32-57	0 (s,9H,N-TMS); 0.17 (s,3H,O-TMS); 1.20 (t,3H, CH_3); 3.60 (m,1H,CH); 5.08 (m,1H,NH).
N-$(TMS)_2$ Ala-OMe	60-83	0 (s,18H,$N(TMS)_2$); 1.3 (d,3H,C-CH_3); 3.55 (m,1H CH); 3.56 (s,3H,O-CH_3).
N-TMS Ala-OMe*	50-60	0 (s,9H,N-TMS); 1.22 (t,3H,CH_3); 3.57 (m,1H,CH) 3.58 (s,3H,OCH_3).
N-$(TMS)_2$ Phe-OTMS* + N-TMS Phe-OTMS*	110-120	0 (s,N-TMS); 0.13 (s,$N(TMS)_2$); 0.26 (s,O-TMS); 2.80 (m,CH_2); 3.53 (m,CH); 7.1 (m,C_6H_5).
N-$(TMS)_2$ Leu-OTMS* + N-TMS Leu-OTMS*	75-80	0 (s,N-TMS); 0.12 (s,$N(TMS)_2$); 0.26 (s,O-TMS); 0.9 (m,C-CH_3); 1.53 (m,CH-CH_2); 3.45 (m,CH).
N-$(TMS)_2$ Leu-OMe* + N-TMS Leu-OMe*	65-70	0 (s,N-TMS); 0.10 (s,$N(TMS)_2$); 0.88 (m,CH_3); 1.48 (CH-CH_2); 3.23 (m,CH); 3.60 (s,O-CH_3).
N-TMS Val-OTMS	69-70	0 (s,9H,N-TMS); 0.27 (s,9H,O-TMS); 0.87 (m,6H, $(CH_3)_2$); 1.83 (m,1H,CH); 3.08 (m,CH).
N-TMS Val-OMe	58-60	0 (s,9H,N-TMS); 0.88 (m,$(CH_3)_2$); 1.20 (s,1H,NH) 1.88 (m,1H,CH); 3.20 (m,1H,CH);3.88 (s,3H,OCH_3)

*) Fractions of distillation containing a mixture of mono and bis-silylilated compounds.

-Using Na

A mixture of the stabase of Ala-OCH_2-CH_2Br (1mmol) and **Na** (1eq.) in **THF** (5ml) was stirred for two hours at R.T.. Evaporation of the solvent afforded a solid which was washed with diethyl ether. The NMR spectrum (D_2O) of the solid correspond to the sodium salt of alanine (100% recovery).

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References

1a. Sheehan, J.C.; Frank, V.S. *J. Amer. Chem. Soc.* **1949**, *71*, 1856-1861. 1b. Neflenks, G.H.L.; Tesser, G.I.;Nivar, R.J.F. *Rec. Trav. Chim.* **1960**, *79*, 688-698. 1c. Neflenks, G.H.L. *Nature* **1960**, 309-310. 1d. Hoogwater, D.A.; Reinhout, D.N.; Lie, T.S.; Guneweg, J.J.; Beyerman, H.C. *Rec. Trav. Chim.* **1973**, *92*, 819-825. 1e. Kukolja, S.; Lammert, S.R. *J. Amer. Chem. Soc.* **1975**, *97*, 5582-5583. 1f. Dikshit, A; Chadda, M.; Singh, R.K.; Misra, K. *Canad. J. Chem.* **1988**, *66*, 2989-2994.

2a. Keller, O.; Rudinger, J. *Helv. Chim. Acta* **1977**, *58*, 531-541. 2b. Zehavi, U. *J. Org. Chem.* **1977**, *42*, 2819-2821. 2c. Zalipsky, S.; Albericio, F.; Slomczynska, U.; Barany, G. *Int. J. Pept. Prot. Res.* **1987**, *30*, 740-783. 2d. Sheehan, J.C.; Gusiec, F.S. *J. Org. Chem.* **1973**, *38*, 3034-3040. 2e. Panetta, C.A.; Pesh-Imam, M. *J. Org. Chem.* **1972**, *37*, 302-304. 2f. Matsumura, E.; Ariga, M.; Thoda, Y.; Kawashima, T. *Tetrahedron Letters* **1981**, *22*, 757-758. 2g. Bruekelman, S.P.; Leach, S.E.; Meakins, G.D.; Tirel, M.D. *J. Chem. Soc. Perkin Trans. I* **1984**, 2801-2807.

3a. Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1985**, *24*, 510. 3b. Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275-276. 3c. Gunnarsson, K.; Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1988**, *27*, 400-401.

4. Reetz, M.T.; Drewes, M.W.; Schmitz, A. *Angew. Chem. Int. Ed.* **1987**, *26*, 1141-1143.

5. Laguzza, B.C.; Ganem, B. *Tetrahedron Letters* **1981**, *22*, 1483-1486.

6. Lalonde, M.; Chan, T.H. *Synthesis* **1985**, 817-845.

7. Pierce, A.E. in *Silylation of organic compounds*; Pierce Chemical Co., Rockford III, **1968**, 218-243.

8. Kashutina, M.V.; Ioffe, S.L.; Tartakowskii, V.A. *Russian Chem. Rev.* **1975**, *44*, 733-747.

9a. Birkofer, L.; Ritter, A. *Angew. Chem.* **1956**, *68*, 461-462. 9b. Birkofer, L.; Ritter, A. *Chem. Ber.* **1960**, *93*, 424-427. 9c. Birkofer, L.; Ritter, A.; Neuhausen, P. *Liebigs Ann. Chem.* **1962**, *659*, 190-199.

10a. Rühlmann, K. *J. Prakt. Chem.* **1959**, *9*, 86-91. 10b. Rühlmann, K. *Chem. Ber.* **1961**, *94*, 1876-1878. 10c. Rühlmann, K.; Kaufman, U. *Liebigs Ann. Chem.* **1962**, *656*, 22-23. 10d. Rühlmann, K.; Hils, J. *Liebigs Ann. Chem.* **1965**, *683*, 211-215. 10e. Rühlmann, K.; Michael, G. *Bull. Soc. Chim. Biol.* **1965**, *47*, 1467-1475. 10f; Rühlmann, K.; Hils,; Graubaum, H.J. *J. Prakt. Chem.* **1966**, *32*, 37-42. 10g. Rühlmann, K.; Liebsch, K.; Michael, C. *J. Prakt. Chem.* **1966**, *32*, 225-229. 10h. Rühlmann, K.; Simon, H.; Becker, *Chem. Ber.* **1966**, *99*, 780-781. 10i. Rühlmann, K.; Kuhrt, K. *Angew. Chem. Int. Ed.*, **1968**, *7*, 809.

11. Klebe, J.F.; Finkbeiner, H.; White, D.M. *J. Amer. Chem. Soc.* **1966**, *88*, 3390-3395.

12. Mason, P.S.; Smith, E.D. *J. Gas Chrom.* **1966**, *4*, 398-400.

13a. Hils, J.; Rühlmann, K. *Chem. Ber.* **1967**, *100*, 1638-1645. 13b. Hils, J.; Hagen, V.; Rühlmann, K. *Chem. Ber.* **1966**, *99*, 776-779.

14. Venkateswaran, P.S.; Bardos, T.J. *J. Org. Chem.* **1967**, *32*, 1256-1257.

15. Stalling, D.L.; Gehrke, C.W.; Zumwalt, R.W. *Biochem. Biophys. Res. Comm.* **1968**, *31*, 616-622.

16. Smith, E.D.; Shewbart, K.L. *J. Chrom. Sci.* **1969**, *7*, 704-707.

17a. Kricheldorf, H.R. *Synthesis* **1970**, 592-593. 17b. Kricheldorf, H.R. *Liebigs Ann. Chem.* **1972**, *773*, 17-38.

18. Rogozhin, S.V.; Davidovitch, Y.A.; Andreev, S.M.; Mironova, N.V.; Yurtanov, A.I. *Bull. Acad. Sci. USSR* **1974**, *23*, 1789-1792.

19. Anteunis, M.J.O.; Becu, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 119-130.

20. Bergstrom, K.; Gurtler, J.; Blomstrand, R. *Anal. Biochem.* **1970**, *34*, 74-87.

21. Leimer, K.R.; Rice, R.H.; Gehrke, C.W. *J. Chrom.* **1977**, *141*, 355-375.

22. Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Letters* **1981**, *22*, 1787-1790.

23. Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H.H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Dteppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1-21.

24a. Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* **1982**, 85-126. 30b. Simchen, G. in Larson, G., Advances in Silicon Chemistry, Vol. 1, p. 189, JAI Press Inc., Greenwich, Conn. - LONDON 1991.

25. Bassindale, A.R.; Stout, T. *Tetrahedron Letters* **1985**, *26*, 3403-3406.

26. Andrianov, K.A.; Kotrelev, K.V.; Kononov, A.M.; Prudnik, I.M. *J. Gen. Chem. USSR* **1974**, *44*, 2108-2111.

27. Hogdberg, T.; Strom, P.; Lendberg, U.H. *Acta Chem. Scand.*, **1985**, *B 39*, 414-416.

28a. Corriu, R.J.P.; Moreau, J.J.E.; Pataud-Sat, M. *J. Org. Chem.* **1981**, *46*, 3372-3374. 28b. Corriu, R.J.P.; Huynh, V.; Moreau, J.J.E.; Pataus-Sat, M. *Tetrahedron Letters* **1982**, *23*, 3257-3260.

29 Paladino, J. *Thèse de Doctorat* **1989**, Université de Montpellier II - France.

30a. Bonar-Law, R.P.; Davis, A.P.; Dorgan, B.J. *Tetrahedron Letters*, **1990**, *31*, 6721-6724. 30b. Bonar-Law, R.P.; Davis, A.P.; Dorgan, B.J.; Reetz, M.T.; Wehrsig, A.

Tetrahedron Letters, **1990**, *31*, 6725-6728.

31. Fink, W. *Helv. Chim. Acta* **1974**, *57*, 1010-1015.
32. Nametkin, N.S.; Chernisheva, T.I.; Pritula, N.A.; Genevian, M.I. *Dokl. Akad. Nauk. SSSR* **1964**, *155*, 1126-1129; C.A. *61*, 1887 b.
33. Dean, P.D.G. *J. Chem. Soc.* **1965**, 6655.
34. Young, M.E.; Lyster, M.A. *J. Amer. Chem. Soc.* **1977**, *99*, 968-969.
35. Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194-4196.
36. Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91-102.
37. Weir, J.R.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* **1980**, *45*, 4926-4931.
38. Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711-2716.
39. Schubert, W.M.; rabinovitch, B.S.; Larson, N.R.; Sims, V.A. *J. Amer. Chem. Soc.* **1952**, *74*, 4590-4592.
40. House, H.O.; Ro, S.R. *J. Amer. Chem. Soc.* **1958**, *80*, 182-187.
41. Brook, M.A.; Chan, T.H. *Synthesis* **1983**, 201-203.
42. Pastuszak, J.; Gardner, J.H.; Singh, J.; Rich, D.H. *J. Org. Chem.* **1982**, *47*, 2982-2987.
43. Erlanger, B.F.; Brand, E. *J. Amer. Chem. Soc.* **1951**, *73*, 3508-3510.