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DIBENZYLAMINOACETATES AS USEFUL SYNTHETIC EQUIVALENTS OF GLYCINE IN THE SYNTHESIS OF α-AMINO-β-HYDROXYACIDS[1]

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Summary: The stereochemical course of three new simple methodologies for the preparation of α-amino-β-hydroxyacids starting from dibenzylaminoacetates as synthetic equivalents of glycine is described. While the aldol-type condensation *via* lithium enolates gave results highly dependent on the aldehyde employed, producing in some cases diastereoselectivities up to 5:1 for the *anti* isomers, the acid-catalysed aldol condensation of silyl ketene acetals yielded predominantly *syn* adducts with selectivities from 5:1 to 32:1. Finally the acylation-reduction procedure gave the best results in terms of yields and stereoselectivities, affording *syn* isomers with excellent induction (≥ 13 : 1).

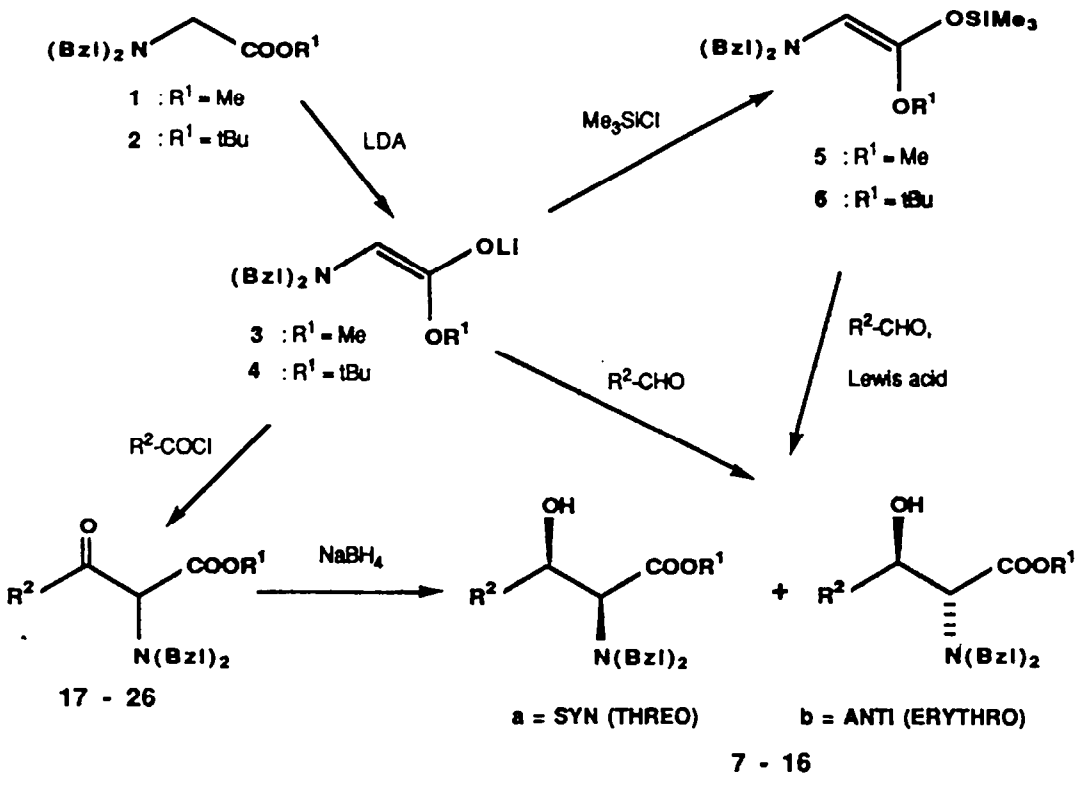
α-Amino-β-hydroxyacids are important derivatives both as enzymatic inhibitors and as precursors to β-lactam antibiotics[2] and related compounds. Although a number of methods for their stereoselective preparation were already known when we started this research,[3] they all suffered from some drawbacks, like low practicity and generality, poor stereoselectivity, or drastic conditions.[4]

In the course of a project directed towards the synthesis of new monocyclic β-lactam antibiotics[5] we decided to search a new methodology for the stereoselective synthesis of *syn* or *anti* α-amino-β-hydroxyacids which would fulfill these requirements: a) the shortest number of steps; b) high stereoselectivity; c) mild reaction conditions and hence wide generality; d) employment of easy accessible and inexpensive reagents.

Among the various possible ways to construct the α-amino-β-hydroxyacid structure, the condensation of a glycine synthetic equivalent with an oxygenated functionality is probably the most straightforward. In principle this can be accomplished either *via* aldol-type condensation with aldehydes (under basic or acidic conditions), or by acylation with an activated carboxylic acid derivative (e.g. an acyl chloride), followed by reduction of the resulting α-amino-β-ketoester (Scheme 1).[6] While the first method is more direct, the acylation-reduction procedure has been shown by us[7] and others[8] to be sometimes superior from the point of view of stereoselectivity. Moreover it should be pointed out that, in some particular cases, activated carboxylic acid derivatives could be more easily accessible than the corresponding aldehydes.[9]

We report here our results employing all these strategies, using the esters of dibenzylaminoacetic acid **1** and **2** as glycine synthetic equivalents. The advantage of these synthons is that a) they are easily obtained from inexpensive precursors; b) the dibenzyl protecting group is stable under a variety of conditions, but can be cleaved by hydrogenolysis under neutral conditions; c) the NH_2 group is fully protected, that is there are no acidic protons on nitrogen which could interfere with the condensation

SCHEME 1



Compounds	7, 17	8, 18	9, 19	10, 20	11, 21	12, 22	13, 23	14, 24	15, 25	16, 26
R^1	Me	Me	Me	Me	Me	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu
R^2	Me	Ph	*n*-Hex	*cy*-Hex	*t*-Bu	Me	Ph	*n*-Hex	*cy*-Hex	*t*-Bu

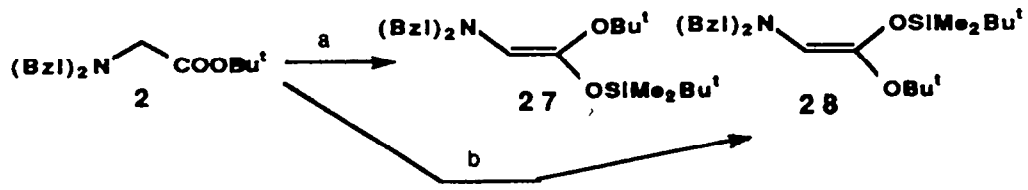
reactions; d) the bulkiness of the substituents at nitrogen can be valuable in directing the stereoselectivity of the process.

Aldol- type condensation of enolates 3 & 4 with aldehydes

As shown in table 1, the condensation of lithium enolates 3 and 4 with a series of aldehydes proceeds with excellent yields, with the exception of sterically encumbered pivaldehyde. Unfortunately the asymmetric induction is usually low although by increasing the bulkiness of the R^2 group a moderate to good diastereoselectivity favouring the *anti* isomer was found. These results appear to be in line with the few reports on aldol-type condensation by lithium enolates of protected glycinates.[3h,3j,4b]

In order to interpret these data it was necessary to get informations on the stereochemistry of enolates 3 and 4. When enolate 4 was generated under "kinetic" conditions[10] (LDA, THF, -78°C), which are the same employed for all entries in table 1, and quenched with either trimethylsilyl chloride (Scheme 1) or *t*-butyldimethylsilyl chloride (Scheme 2), only one of the two possible diastereomeric silyl ketene acetals was formed. The same behaviour was observed by trimethylsilyl chloride quenching of enolate 3.[11] On the contrary, when enolization was carried out in the presence of hexamethylphosphoric triamide (HMPA) ("thermodynamic conditions")[10], quenching with *t*-butyldimethylsilyl chloride gave stereoselectively the other geometric isomer (Scheme 2).[13]

SCHEME 2



a: LDA, THF, -60°C; then *t*-BuMe$_2$SiCl; b: LDA, THF, HMPA, -78°C; then *t*-BuMe$_2$SiCl

NOE experiments on *t*-butyldimethylsilyl ketene acetals **27** and **28** (see experimental part) showed that the "kinetic" product **27** possessed an *E* configuration (thus deriving from the *Z* enolate[14]), whereas the "thermodynamic" product **28** was *Z* . This finding is in agreement with the usual preference for *Z* lithium enolates in kinetically controlled enolization of esters[15] and with the likely higher stability of *E* enolate because of coordination of lithium by the dibenzylamino group.[16]

Since the enolates **3** and **4** used in this work were proved in this way to be *Z*, the observed *anti*-selectivity can be explained by the Zimmermann-Traxler[15] transition states **A** and **B** (Scheme 3). **B**, which leads to the *syn* isomers, should be disfavoured by 1,3-diaxial interaction between OR^1 and R^2. However, being the (Bzl)$_2$N group particularly bulk, also the "gauche" interaction between it and R^2 should be quite important. It has been proposed that such interaction is greater in transition states like **A** than in those like **B**.[15] So, this latter factor may counterbalance the 1,3-diaxial interaction, leading to results highly dependent from substitution, as in the present case. Actually it is well known[15] that lithium *Z* ester enolates show usually only moderate level of diastereoselection in aldol reactions, probably because of this problem. As shown in Table 1, best *anti* selectivities were observed for R^1 = *t*-Bu and when R^2 was bulk (Ph, *cy*-Hex, *t*-Bu). In these case the 1,3-diaxial interaction between OR^1 and R^2 must be particularly severe.

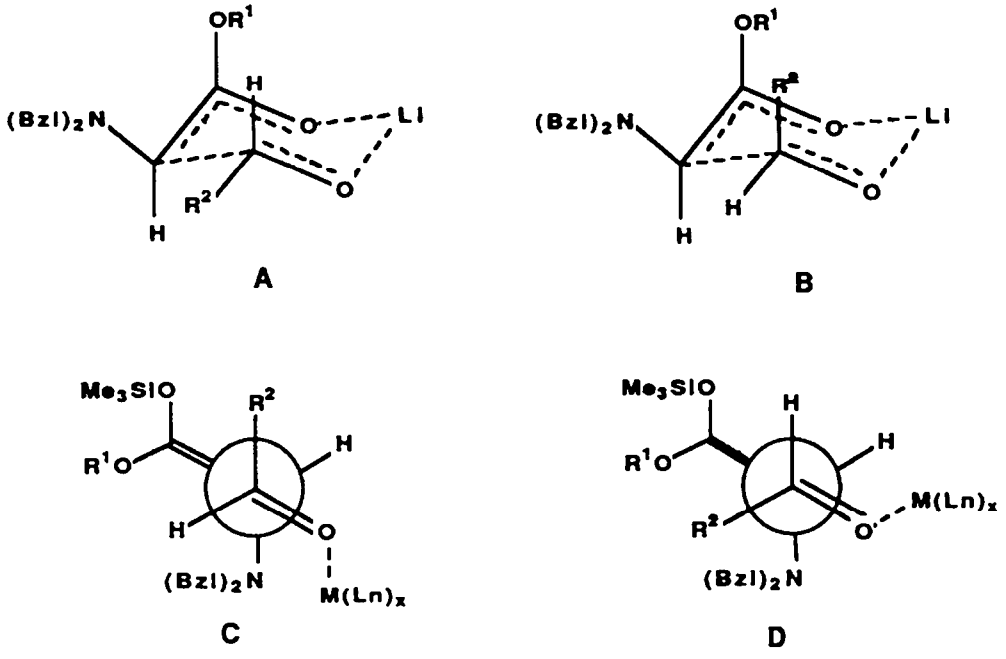
In the attempt to improve the stereoselectivity of this condensation, we examined also other metal enolates. While (tri-*i*-propoxy)-titanium(IV) enolates[17] were completely unreactive, (trichloro)-titanium (IV) enolates, generated from the silyl ketene acetal **5** by treatment with $TiCl_4$,[18] dimerized readily to give dimethyl 2,3-*bis*-(dibenzylamino)-succinates[19] (*vide infra*) and only in the case of reaction with an excess of acetaldehyde, probably because of its high reactivity, the desired adduct could be isolated, albeit in low yields (10-20%) (*syn* : *anti* ratio 85 : 15). The presence of an amino group in the α position evidently facilitates this oxidative dimerization.[20] The chloro-dicyclopentadienyl-zirconium (IV) enolate, obtained by reaction of **3** with zirconocene dichloride,[21] reacted with acetaldehyde but with disappointingly low asymmetric induction (*syn* : *anti* 45 : 55).

Table 1. Aldol-type Condensation of enolates 3 and 4 with aldehydes.

Entry	R^1	R^2	Product	Yield%[a]	Syn:Anti[b]	Entry	R^1	R^2	Product	Yield%	Syn:Anti[b]
1	Me	Me	**7**	89	57 : 43	6	*t*-Bu	Me	**12**	91	60 : 40
2	Me	Ph	**8**	75	46 : 54	7	*t*-Bu	Ph	**13**	74	18 : 82
3	Me	*n*-Hex	**9**	80	71 : 29	8	*t*-Bu	*n*-Hex	**14**	86	46 : 54
4	Me	*cy*-Hex	**10**	78	21 : 79	9	*t*-Bu	*cy*-Hex	**15**	77	16 : 84
5	Me	*t*-Bu	**11**	65	31 : 69	10	*t*-Bu	*t*-Bu	**16**	56	20 : 80

a: Isolated yields; b: Determined by spectrodensitometry and ^{1}H N.M.R. (see experimental part).

SCHEME 3



Acid catalysed aldol-type condensation of silyl ketene acetals 5 & 6 with aldehydes.

The Lewis acid catalysed aldol-type condensation of esters derived silyl ketene acetals is a well known process.[22] However very little has been reported on the reaction of α-hetero-substituted derivatives.[23] In order to explore this interesting field, we synthesized the α-dibenzylamino-*O*-trimethylsilyl ketene acetals **5** and **6** as above described. Since these derivatives are pretty unstable in the presence of water, the usual hydrolytic work-up must be avoided.

As already discussed above, only one geometric isomer, possessing *E* configuration, was formed under kinetic conditions. The results of condensation of these silyl ketene acetals with aldehydes under the catalysis of various Lewis acids are shown in Table 2.

The yields of these reactions seem to be highly dependent from various factors: a) the order of addition of reagents: as already pointed out above, treatment of **5** or **6** with $TiCl_4$ or $SnCl_4$ lead to rapid formation of the dimeric succinates.[19] So, in order to get acceptable yields, it is necessary to treat **5** or **6** with the aldehyde *pre*-complexed at -78°C with 1 equivalent (relative to the silyl ketene acetal) of Lewis acid; b) stoichiometry and reaction temperature: yields are considerably better if the reaction is carried out at higher temperatures using an excess of aldehyde; c) the nature of R^1: the use of *t*-butyl derivative **6** instead than the methyl analogue **5** minimized the formation of succinates, thus allowing higher yields. When all these conditions were satisfied the isolated yields were in the range of 50-70%.

As regards to asymmetric induction, it is clear from an examination of table 2 that *syn* isomers are always preferred. With the exception of acetaldehyde and benzaldehyde, the stereoselectivities are satisfactory. Although the use of lower reaction temperature allowed the obtainment of very high *syn* : *anti* ratios, the yields were drastically reduced.

TABLE 2: Acid catalysed condensation of silyl ketene acetals 5 and 6 with aldehydes

Entry	R^1	R^2	Product	Lewis acid	Temp.	Yield %[a]	Syn : Anti[b]
1	Me	Me	7	BF_3•Et_2O	-65°C	15	64 : 36
2	Me	Me	7	$SnCl_4$	-65°C	14	55 : 45
3	Me	Me	7	$TiCl_4$	-65°C	17	44 : 56
4	*t*-Bu	Me	12	$TiCl_4$	-65°C	20	85 : 15
5	*t*-Bu	Me	12	$TiCl_4$	R.T.	47 (55)	70 : 30
6	Me	*n*-Hex	9	$TiCl_4$	R.T.	24	54 : 46
7	*t*-Bu	*n*-Hex	14	$TiCl_4$	R.T.	56	85 : 15
8	*t*-Bu	*n*-Hex	14	$TiCl_4$	-20°C	29 (52)	91 : 9
9	*t*-Bu	*n*-Hex	14	$TiCl_4$	-78°C	14 (21)	97 : 3
10	*t*-Bu	*cy*-Hex	15	$TiCl_4$	R.T.	52	84 : 16
11	*t*-Bu	*t*-Bu	16	$TiCl_4$	R.T.	45	91 : 9
12	*t*-Bu	Ph	13	$TiCl_4$	R.T.	66	61 : 39

a) Isolated yields; yields based on unrecovered ester are reported in brackets; b) Determined by standardized spectrodensitometry (see experimental part)

The *syn* selectivity can be explained by the acyclic transition state[15] C (scheme 3). Nonbonding interactions between R^2 and the dibenzylamino group should highly disfavour the alternative transition state D.[12] We also examined the acid catalysed condensation of the *bis*-trimethylsilyl ketene acetal obtained from dibenzylaminoacetic acid by treatment with 2 eq. of LDA, followed by quenching with TMS-Cl.[24] However the reaction of this compound with aldehydes *pre*-complexed with $TiCl_4$ lead to complex, non-analyzable mixtures.

Acylation-reduction of lithium enolates 3 & 4

Although the two methodologies above described could be in some cases useful, they still lack the requisite of generality. On the other hand, based on previous reports on the reduction of α-aminoketones,[25] we anticipated that the reduction of α-dibenzylamino-β-ketoesters 17-26 with hydrides would proceed with high stereoselectivity to give *syn* adducts.

So we treated the lithium enolates 3 and 4 with a series of acyl chlorides to give ketoesters 17-26 in good yields. While in the case of R^1= Me these adducts were isolated by chromatography prior to reduction (yields ranging from 70 to 90%), for R^1= *t*-Bu we found more convenient to carry out the reduction directly on the crude products. When 17-26 were treated with $NaBH_4$ in EtOH or MeOH, no reaction took place, even in the presence of a large excess of reducing agent. Nevertheless, when the the reaction was performed in aqueous EtOH in the presence of NH_4Cl as buffering agent,[25] reduction occurred instantaneously at room temperature. Other buffering agents, like acetic acid or sodium dihydrogen phosphate were found to be efficient as well.

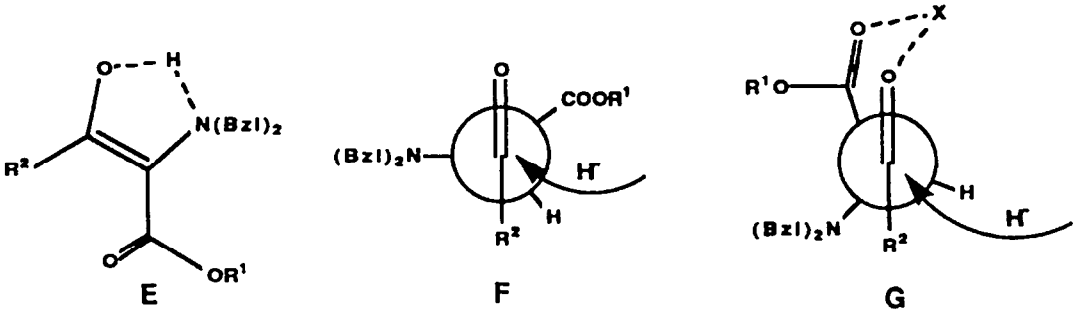
This behaviour can be accounted for by the acidity of the α proton and the presence of a basic, electron-donating atom (that is the aminic nitrogen) which can afford intramolecular stabilization to an enol-type form like E (Scheme 4), unreactive to hydride attack. When the reaction was carried out at pH < 7, protonation of the amino group prevents this stabilization shifting the equilibrium to the ketonic form. The low yields in the reduction of 25 and 26 are probably due to the severe steric requirements of R^1 and R^2 groups. Since under these buffered conditions the reduction is in competition with fast $NaBH_4$ decomposition, a drastic decrease in the rate of reduction can lead to incomplete reaction or even, as in the case of 26, to no reaction at all.

Table 3. $NaBH_4$ REDUCTION OF α-DIBENZYLAMINO-β-KETOESTERS 17-26

Entry	R^1	R^2	Product	Yield%[a]	Syn : Anti[b]	Entry	R^1	R^2	Product	Yield%[c]	Syn:Anti[b]
1	Me	Me	7	81	93 : 7	6	*t*-Bu	Me	12	50	89 : 11
2	Me	Ph	8	70	≥99 : 1	7	*t*-Bu	Ph	13	57	≥99 : 1
3	Me	*n*-Hex	9	75	96 : 4	8	*t*-Bu	*n*-Hex	14	52	89 : 11
4	Me	*cy*-Hex	10	80	95 : 5	9	*t*-Bu	*cy*-Hex	15	35	90 : 10
5	Me	*t*-Bu	11	83	≥99 : 1	10	*t*-Bu	*t*-Bu	16	-[d]	-

a: Isolated yields; b: Determined by spectrodensitometry and ^1H N.M.R. (see experimental); c) Isolated yields from **2** (two steps); d) no reaction occurred.

SCHEME 4



X : see text

As shown in Table 3, the stereoselectivities obtained were gratifying. With R^1=Me, a *syn* : *anti* ratio of at least 13 : 1 was obtained. This high stereoselectivity can be explained both by a Felkin model F (Scheme 4) or with a Cram cyclic model G in which an electrophile **X** [which can be the sodium ion[27] or the ammonium ion (through two hydrogen bonds)[28]] is chelated by the carbonyl and carboxyl oxygens.[29]

Although previous examples of reduction of α-acylamino-β-ketoesters are known[3c,26,30] to show a general preference for the *anti* isomer, we think that the bulkiness of the dibenzylamino group can revert this trend by: a) increasing the discrimination between itself and the $COOR^1$ group in Felkin conformation **F**; b) differentiating to a higher extent the two sides of attack in **G**; c) preventing an alternative Cram cyclic model in which the electrophile is chelated by the carbonyl and the amino group.[25] This coordination may be prevented also by the likely protonation of the amino group under the reaction conditions (pH < 7).[31] It is worth noting that this high asymmetric induction has been achieved without need to use sophisticated reducing agents or low temperature, making this methodology particularly practical.[32]

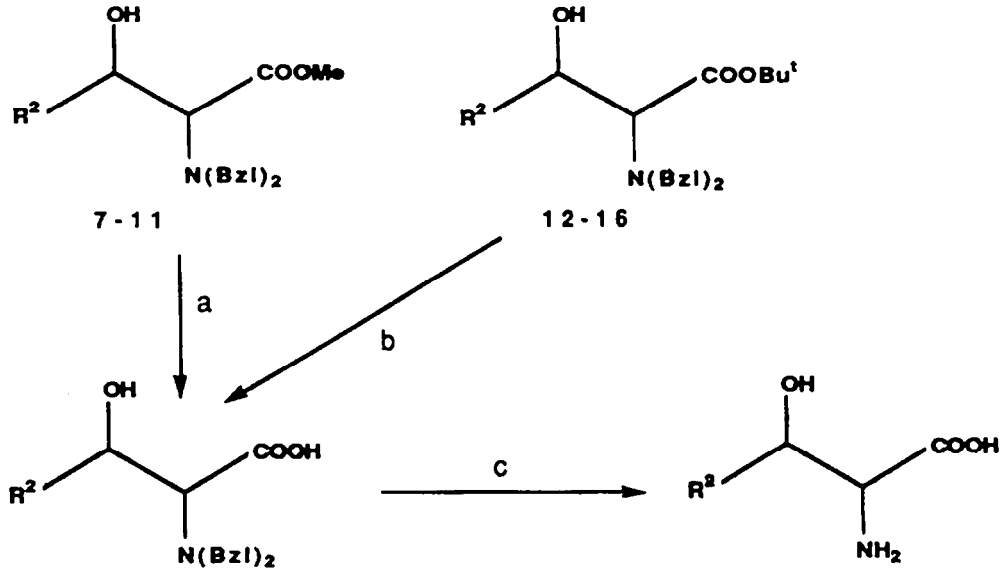
Assignment of relative configuration to α-dibenzylamino-β-hydroxyesters 7-16

Syn diastereoisomers **7a** and **12a** were transformed into d,l-threonine **34a** (*vide infra*). Similarly, **8a** and **13a** were converted into d,l-*threo*-phenylserine **35a**. Comparison with authentic

samples of **34a** and **35a** allowed unequivocal assignment. Hydrolysis of methyl esters **7-11** and *t*-butyl esters **12-16** to the same aminoacids **29-33** allowed the correlation of the two series (Scheme 5).

The relative configuration of compounds with R^2= *n*-Hex, *cy*-Hex, and *t*-Bu could be assigned on the basis of ^1H and ^{13}C n.m.r. analogies. The most caracteristic features for the *t*-butyl esters **12-16** are the following (see Tables 5 and 6): a) the C<u>H</u>-N(Bzl)$_2$ ^1H chemical shift, which is always higher for *anti* compounds (with a difference ranging from 0.04 to 0.23 ppm); b) the difference of chemical shift between the two diastereotopic protons of the N-C<u>H</u>$_2$ group, which is always larger for *syn* isomers (the difference between the two $\Delta\delta$ varies from 0.13 to 0.19 ppm); c) the ^{13}C chemical shift of carboxylic carbons (C-1), which is always higher for *anti* isomers, with a $\Delta\delta$ varying from 2.49 to 3.14 ppm; d) the ^{13}C chemical shift of <u>C</u>H$_2$-N carbon, which is always higher for *anti* isomers ($\Delta\delta$ is in the range 0.44-0.80 ppm); e) the ^{13}C chemical shift of N-CH$_2$-<u>C</u> carbon, which is always higher for *anti* isomers ($\Delta\delta$ from 0.45 to 1.71 ppm). A support for this assignment comes from the t.l.c. on silica gel plates. Using diethyl ether as eluant, the *syn* isomer is always faster running for all the aminoalcohols **7-16**.

SCHEME 5



29: R^2 = Me **30**: R^2= Ph **34**: R^2 = Me
31: R^2 = *n*-Hex **32**: R^2= cy-Hex **35**: R^2 = Ph
33: R^2 = *t*-Bu

a) KOH, EtOH/H_2O; b) CF_3COOH; c) H_2, Pd-C, 95% EtOH

Transformation of α-dibenzylamino-β-hydroxyesters 7-16 into α-amino-β-hydroxyacids (Scheme 5)

The saponification of methyl esters **7a,b-11a,b** with KOH in $MeOH/H_2O$ proceeded uneventfully to give aminoacids **29a,b-33a,b** in good yields (80-90%). On the other hand *t*-butyl esters were hydrolysed by trifluoroacetic acid at 0°C, in lower but still satisfactory yields (60-75%). No epimerization was detected during these hydrolyses by t.l.c. or ^1H n.m.r.

Finally, the removal of the dibenzyl protecting group was realized in excellent yields (90-95%) by hydrogenolysis in refluxing 95% ethanol[33] to give the desired α-amino-β-hydroxyacids.[34]

Conclusion

In conclusion we have demonstrated that dibenzylaminoacetates **1** and **2** are very versatile reagents for the preparation of α-amino-β-hydroxyacids. The acylation-reduction strategy starting from methyl ester **1** is the method of choice for the synthesis of *syn* isomers. Although *t*-butyl ester **2** seems to be less preferable, in view of the slightly lower yields and stereoselectivities in the reduction, as well as lower yields in the hydrolysis step, it can be still very useful in dealing with functionalities sensitive to the basic conditions required for methyl ester hydrolysis. From this point of view, **1** and **2** should be regarded as complementary. The ester enolate aldol-type condensation represents in some cases an useful and simple entry to *anti* α-amino-β-hydroxyacids, although stereoselectivities are not dramatically high. Finally, the acid catalysed condensation of silyl ketene acetal **6** may be employed for the preparation of *syn* α-amino-β-hydroxyacid when the acyl chloride is not easily available, or in reaction with chiral aldehydes.[12]

Application of these methodologies to the diastereoselective synthesis of polyfunctionalised compounds of biological interest, as well as chiral modification on synthons **1** and **2** are being developed in our laboratories.

EXPERIMENTAL

N.m.r. spectra were recorded as $CDCl_3$ solutions on a Varian FT 80 or on a Bruker WP 80 spectrometers using tetramethylsilane as internal standard. NOE experiments were carried out on a Bruker WP 80 instrument, using a flip angle of ca. 90° and an acquisition time of 4.09 s. A saturation time of 8 s. with an r.f. power setting of 58L (low power irradiation) was used to allow the NOE to build up. I.r. spectra were measured with a Perkin-Elmer 257 as $CHCl_3$ solutions. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Spectrodensitometry analyses were performed with a CAMAG TLC-SCANNER using a Hewlett-Packard 3390 A integrator. Samples were deposed on silica gel 60 F_{254} plates (Merck) using an automatic deposer CAMAG Linomat III. Standardization was made performing the analyses of mixture of known composition. 270-400 mesh silica gel (Merck) was used for chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions employing dry solvents were run under a nitrogen atmosphere. The preparation of *t*-butyl dibenzylaminoacetate **2** has already been reported elsewhere.[12]

Methyl dibenzylaminoacetate (1) - A solution of dibenzylaminoacetic acid[35] (10g, 39.2 mmol) in dry MeOH (20 ml) and dry 1,2-dichloroethane (40 ml) was treated with conc. H_2SO_4 (4 ml, 71.8 mmol) and heated at reflux for 26 h. After concentration to small volume under reduced pressure, the residue was diluted with water (10 ml) and treated with 2N NaOH until pH = 10. Extraction with Et_2O and evaporation of the solvent gave a white solid which was recrystallized from 95% EtOH to give pure **1** (9.21 g, 87%). M.p. 41-43°C; Found: C, 75.85; H, 7.20; N, 5.15%; $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%. ^1H n.m.r.: δ 7.20-7.50 (10H, m, aromatics); 3.82 (4H, s, CH_2-Ph); 3.69 (3H, s, OCH_3); 3.32 (2H, s, CH_2-C=O).

(*E*) *N,N'*-Dibenzyl-2-methoxy-2-trimethylsilyloxy-ethenamine (5) - A solution of **1** (2.03 g, 7.54 mmol) in dry THF (18 ml) was added at -60°C to a 0.4M solution of lithium diisopropylamide in THF : *n*-hexane 4 : 1 (21.4 ml, 8.56 mmol). After 10 min. trimethylsilyl chloride (1.4 ml, 11.03 mmol) was added, and the temperature allowed to rise slowly to R.T. After 1 h at R.T., the solvent was evaporated under reduced pressure. The residue was taken up in dry CH_2Cl_2 to give a 0.5M suspension. The solid salts were removed by filtration (through a Millipore™ 10μ filter) or, more conveniently, through decantation, after 1 night at -25°C. The solution obtained in this way can be stored at -25°C and used as such for acid catalysed condensations. A sample was evaporated to dryness and taken up in dry $CDCl_3$ for ^1H n.m.r. analysis: δ 7.33-7.41 (10H, m, aromatics); 4.34 (1H, s, N-C<u>H</u>=C); 3.83 (4H, s, C<u>H</u>$_2$-Ph); 3.52 (3H, s, OC<u>H</u>$_3$); 0.12 (9H, s, C<u>H</u>$_3$-Si).

(*E*) *N,N'*-Dibenzyl-2-*t*-butoxy-2-trimethylsilyloxy-ethenamine (6) - It was prepared with the same procedure used for **5**. ^1H n.m.r.: δ 7.18-7.42 (10H, m, aromatics); 4.55 (1H, s, N-C<u>H</u>=C); 3.80 (4H, s, C<u>H</u>$_2$-Ph); 1.32 (9H, s, C(C<u>H</u>$_3$)$_3$); 0.08 (9H, s, C<u>H</u>$_3$-Si).

(*E*) *N,N'*-Dibenzyl-2-*t*-butoxy-2-(*t*-butyldimethylsilyloxy)-ethenamine (27) - A solution of **2** (300 mg, 0.963 mmol) in dry THF (1 ml) was added at -60°C to a 0.3 M solution of lithium diisopropylamide in THF : *n*-hexane 4.3:1 (3.5 ml, 1.06 mmol). After 10 min. a solution of *t*-butyldimethylsilyl chloride (159 mg, 1.05 mmol) in dry THF (1 ml) was added and the temperature allowed to rise to R.T. After stirring for 2 h and 30 min. at R.T., a pH 7 phosphate buffer solution was added, and the mixture extracted with *n*-pentane. The organic layer was washed thrice with a pH 7 buffer solution, dried (Na_2SO_4) and evaporated to dryness to give **27**. The same isomer was also obtained when HMPA was added to the reaction mixture just after *t*-butyldimethylsilyl chloride.[10] ^1H n.m.r.: δ 7.12-7.40 (10 H, m, aromatics); 4.60 (1 H, s, C<u>H</u>=C); 3.79 (4 H, s, C<u>H</u>$_2$-Ph); 1.30 (9 H, s, OC(C<u>H</u>$_3$)$_3$); 0.88 (9 H, s, (C<u>H</u>$_3$)$_3$C-Si); 0.02 (6 H, s, C<u>H</u>$_3$-Si). Irradiation of C<u>H</u>$_3$-Si signal gave a NOE of 3.4% on C<u>H</u>=C proton.

(*Z*) *N,N'*-Dibenzyl-2-*t*-butoxy-2-(*t*-butyldimethylsilyloxy)-ethenamine (28) - A 0.3 M solution of LDA in THF : *n*-hexane 4.3:1 (3.5 ml, 1.06 mmol) was cooled to -78°C and treated with HMPA (0.909 ml). After 2 min. a solution of **2** (300 mg, 0.963 mmol) in dry THF (1 ml) was added. After 30 min. the solution was treated with *t*-butyldimethylsilyl chloride (159 mg, 1.05 mmol) in THF (1 ml) and the temperature allowed to rise to R.T. After stirring for 3 h, the reaction was worked up as above to give **28**. ^1H n.m.r. ($CDCl_3$): δ 7.13-7.48 (10 H, m, aromatics); 4.63 (1 H, s, C<u>H</u>=C); 3.84 (4 H, s, C<u>H</u>$_2$-Ph); 1.13 (9 H, s, OC(C<u>H</u>$_3$)$_3$); 0.98 (9 H, s, (C<u>H</u>$_3$)$_3$C-Si); 0.19 (6 H, s, C<u>H</u>$_3$-Si). Irradiation of (C<u>H</u>$_3$)$_3$-C-O signal gave a NOE of 12.7% on C<u>H</u>=C proton.

General procedure for lithium enolate aldol-type condensation to give α-dibenzylamino-β-hydroxyesters (7a,b)-(16a,b) - A solution of diisopropylamine (0.84 ml, 6.00 mmol) in THF (14 ml) was treated at 0°C with 1.4N n-BuLi in n-hexane (3.9 ml, 5.50 mmol). After 20 min. the solution was cooled to -60°C, and treated with **1** or **2** (5.00 mmol) in THF (14 ml). After 10 min. the aldehyde (5.50 mmol) was added and the solution was stirred for 30 min. at the same temperature, quenched with saturated aqueous NH_4Cl, extracted with Et_2O, and evaporated to dryness to give a crude product. The diastereomeric ratios were determined by standardized spectrodensitometry (eluant: *n*-hexane : Et_2O; the *syn* isomer is always faster running) or ^1H n.m.r. (by integrating the O-C(C<u>H</u>$_3$)$_3$ signals for **12a,b**-**16a,b**; the COOC<u>H</u>$_3$ signals for **10a,b**-**11a,b**; the C<u>H</u>$_3$-CH-OH signals for **7a,b**; the C<u>H</u>-OH signals for **8a,b**; only in the case of **9a,b** the ratio could not be determined by n.m.r.). Silica gel chromatography of the crude products (eluants: *n*-hexane : Et_2O 8 : 2 for **12a,b**-**16a,b**; CH_2Cl_2 for **7a,b**, **10a,b**, **11a,b**; CH_2Cl_2 : Et_2O 95 : 5 for **9a,b**; CH_2Cl_2 : Et_2O 98 : 2 for **8a,b**) afforded the pure diastereoisomers. All of them gave consistent elemental analyses. Isolated yields are reported in Table 1. ^1H n.m.r. are reported on Tables 4 and 5. ^{13}C n.m.r. of *t*-butyl esters **12a,b**-**16a,b** are reported on Table 6.

TABLE 4: ^{1}H n.m.r. of α-dibenzylamino-β-hydroxyesters (7)-(11)[a]

Compound	R^2	OCH_3 (3H, s)	CH-N (1H, d)	CH_2-Ph (4H, AB syst.)	CH-OH (1H)	Aromatics (10H, bs)	Others
7a	Me	3.82	3.07 (9.6)	3.42, 4.02 (13.3)	3.80-4.20 (m)	7.30	1.08 (3H, d, CH_3-CH, J = 6.0 Hz.)
7b	Me	3.85	3.13 (9.4)	3.44, 3.88 (13.6)	3.70-4.10 (m)	7.32	1.20 (3H, d, CH_3-CH, J = 6.3 Hz.)
8a	Ph	3.66	3.49 (10.0)	3.54, 4.19 (13.2)	5.02 (d, 10.0)	7.33	7.24 (5H, s, aromatics)
8b	Ph	3.90	3.65 (9.4)	3.64, 3.89 (13.8)	5.09 (d, 9.4)	7.35	7.04-7.30 (5H, m, aromatics)
9a	*n*-Hex	3.81	3.13 (9.6)	3.39, 4.02 (13.4)	3.60-4.00 (m)	7.29	0.70-1.50 (13H, m, *n*-Hex)
9b	*n*-Hex	3.80	3.21 (8.9)	3.89, 4.42 (13.3)	3.60-4.00 (m)	7.29	0.70-1.50 (13H, m, *n*-Hex)
10a	*cy*-Hex	3.81	3.35 (10.0)	3.38, 4.03 (13.3)	3.60-4.00 (m)	7.29	1.00-1.80 (11H, m, *cy*-Hex)
10b	*cy*-Hex	3.82	3.37 (10.0)	3.40, 3.88 (13.3)	3.60-4.00 (m)	7.30	1.00-1.80 (11H, m, *cy*-Hex)
11a	*t*-Bu	3.81	3.31 (9.5)	3.27, 4.02 (13.1)	3.75 (d, 9.5)	7.29	0.66 (9H, s, $(CH_3)_3$)
11b	*t*-Bu	3.82	3.10-3.40 (m)	3.54, 4.16 (13.3)	3.60-3.90 (m)	7.29	0.75 (9H, s, $(CH_3)_3$)

a) Spectra taken in $CDCl_3/D_2O$; δ in ppm from TMS; J in Hz. in brackets.

TABLE 5: ^{1}H n.m.r. of α-dibenzylamino-β-hydroxyesters (12)-(16)[a]

Compound	R^2	$OC(CH_3)_3$ (9H, s)	CH-N (1H, d)	CH_2-Ph (4H, AB syst.)	CH-OH (1H)	Aromatics (10H, bs)	Others
12a	Me	1.57	2.92 (9.6)	3.46, 4.03 (13.3)	3.80-4.20 (m)	7.29	1.07 (3H, d, CH_3-CH, J = 5.9 Hz.)
12b	Me	1.60	3.01 (8.7)	3.52, 3.90 (13.3)	3.80-4.20 (m)	7.31	1.16 (3H, d, CH_3-CH, J = 6.3 Hz.)
13a	Ph	1.34	3.29 (10.0)	3.49, 4.15 (13.5)	4.90 (d, 10.0)	7.32	7.12 (5H, s, aromatics)
13b	Ph	1.59	3.48 (9.3)	3.39, 3.92 (13.7)	4.98 (d, 9.3)	7.32	6.90-7.20 (5H, m, aromatics)
14a	*n*-Hex	1.57	2.99 (9.6)	3.45, 4.04 (13.3)	3.70-4.00 (m)	7.29	0.85-1.50 (13H, m, *n*-Hex)
14b	*n*-Hex	1.58	3.09 (8.9)	3.50, 3.90 (13.3)	3.70-4.00 (m)	7.20-7.37 (m)	0.85-1.50 (13H, m, *n*-Hex)
15a	*cy*-Hex	1.57	3.20 (9.9)	3.44, 4.04 (13.3)	3.70 (t, 10.0)	7.28	1.00-1.80 (11H, m, *cy*-Hex)
15b	*cy*-Hex	1.59	3.24 (9.2)	3.48, 3.89 (13.4)	3.40-3;80 (m)	7.29	1.00-1.80 (11H, m, *cy*-Hex)
16a	*t*-Bu	1.59	3.13 (9.7)	3.38, 4.01 (13.1)	3.71 (d, 9.7)	7.30	0.65 (9H, s, $(CH_3)_3$)
16b	*t*-Bu	1.56	3.36 (1.9)	3.61, 4.09 (13.7)	3.56 (d, 1.9)	7.19-7.39 (m)	0.71 (9H, s, $(CH_3)_3$)

a) Spectra taken in $CDCl_3/D_2O$; δ in ppm from TMS; J in Hz. in brackets.

TABLE 6: ^{13}C NMR OF α-dibenzylamino-β-hydroxyesters (12)-(16)[a]

Compound	R^2	C-1	C-2	C-3	C-4	$\underline{C}Me_3$	$C\underline{Me}_3$	$CH_2\underline{C}H_2Ph$	$\underline{C}CH_2N$	Others
12a	Me	169.46	67.81	63.14	19.11	81.83	28.45	54.83	138.32	129.14, 128.51, 127.43
12b	Me	172.10	67.18 (66.20)	66.20 (67.18)	19.99	82.06	28.64	55.56	138.94	129.08, 128.27, 127.17
13a	Ph	168.53	68.08 (69.66)	69.66 (68.08)	140.35	81.75	28.17	54.77	138.15	129.23, 128.59, 128.01, 127.81, 127.52,
13b	Ph	171.67	66.59	73.03	140.96	82.17	28.62	55.11	138.60	128.89, 128.10, 127.92, 127.81, 126.96
14a	*n*-Hex	169.44	66.22 (66.74)	66.74 (66.22)	33.90	81.77	28.46	54.75	138.28	129.14, 128.51, 127.39, 31.74, 29.29, 25.69, 22.55, 14.06
14b	*n*-Hex	171.95	65.67	69.87	33.10	81.88	28.59	55.55	139.06	129.09, 128.21, 127.12 31.79, 29.30, 24.82, 22.61, 14.11
15a	*cy*-Hex	169.46	63.08	70.25	40.62	81.70	28.46	54.68	138.26	129.18, 128.50, 127.39 30.39, 26.70, 26.44 26.28, 25.87
15b	*cy*-Hex	172.06	62.55	73.87	38.27	81.92	28.64	55.44	139.17	129.23, 128.25, 127.13, 30.92, 26.99, 26.46, 26.31, 24.37
16a	*t*-Bu	169.26	60.83	71.91	34.56	81.71	28.41	54.64	137.85	129.33, 128.50, 127.51, 25.41
16b	*t*-Bu	172.32	59.09	81.75	35.96	82.10	28.37	55.39	139.56	128.96, 128.14, 126.97, 25.91

a) Spectra taken in $CDCl_3$; δ in ppm from TMS.

General procedure for titanium tetrachloride catalysed condensation of silyl ketene acetals (5) and (6) with aldehydes to give α-dibenzylamino-β-hydroxyesters (7a,b)-(16a,b) - A solution of the aldehyde (4 mmol) in dry CH_2Cl_2 (20 ml) was cooled to -78°C and treated with a 1M solution of $TiCl_4$ in CH_2Cl_2 (1 ml, 1 mmol). After 5 min. the flask was removed from the cooling bath, stirred for 1-2 min. at R.T. and finally treated with a 0.5M solution of **5** or **6** in CH_2Cl_2 (2 ml, 1 mmol). After 1 min. the reaction was quenched with 5% NH_4OH, and filtered through a celite pad. The two phases were separated, and the organic layer evaporated to dryness to give a crude product which was analysed and purified as above described. Isolated yields and diastereomeric ratios are reported in table 2.

General procedure for the acylation of (1) and (2) with acyl chlorides to give α-dibenzylamino-β-ketoesters (17)-(26) - A solution of diisopropylamine (0.84 ml, 6.00 mmol) inTHF (14 ml) was treated at 0°C with 1.4N *n*-BuLi in *n*-hexane (3.9 ml, 5.50 mmol). After 20 min. the solution was cooled to -60°C, and treated with **1** or **2** (5.00 mmol) in THF (14 ml). After 10 min. this solution was added dropwise at -60°C to the solution of acyl chloride (5.50 mmol) in dry THF (5 ml). After 5 min. from the end of the addition the reaction was quenched with water, extracted with Et_2O and evaporated to dryness to give the crude products. *t*-Butyl esters **22-26** were used as such for the reduction reaction. On the contrary, methyl esters **17-21** could also be purified by silica gel chromatography (for **17**, **18**, eluant CH_2Cl_2, and **21**, eluant *n*-hexane : AcOEt 9 : 1) or preparative t.l.c. (*n*-hexane : AcOEt 9 : 1)(for **19** and **20**).

17: Y= 78%; ^1H n.m.r.: δ 7.25-7.45 (10H, m, aromatics); 5.20 (1H, s, C$\underline{H}$-N); 3.78 & 3.92 (4H, AB syst., C$\underline{H_2}$-Ph, J 14.5 Hz.); 3.70 (3H, s, C$\underline{H_3}$O); 2.20 (3H, s, C$\underline{H_3}$-C=O). **18**: Y= 82%; ^1H n.m.r.: δ 7.17-7.79 (15H, m, aromatics); 5.10 (1H, s, C$\underline{H}$-N); 4.00 (4H, s, C$\underline{H_2}$-Ph); 3.88 (3H, s, C$\underline{H_3}$O). **19**: Y= 80%; ^1H n.m.r.: δ 7.25-7.40 (10H, m, aromatics); 4.15 (1H, s, C$\underline{H}$-N); 3.83 & 3.94 (4H, AB syst., C$\underline{H_2}$-Ph, J 13.5 Hz.); 3.78 (3H, s, C$\underline{H_3}$O); 2.40-2.65 (2H, m, C$\underline{H_2}$-C=O); 0.79-1.70 (11H, m, $C_5\underline{H_{11}}$). **20**: Y= 83%; ^1H n.m.r.: δ 7.25-7.45 (10H, m, aromatics); 4.29 (1H, s, C$\underline{H}$-N); 3.83 & 3.93 (4H, AB syst., C$\underline{H_2}$-Ph, J 13.5 Hz.); 3.74 (3H, s, C$\underline{H_3}$O); 2.60-2.90 (1H, m, C$\underline{H}$-C=O);

0.80-1.80 (10H, m, $C_5\underline{H}_{10}$). **21**: Y= 87%; ^{1}H n.m.r.: δ 7.30 (10H, bs, aromatics); 4.62 (1H, s, C<u>H</u>-N); 3.86 & 4.11 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.8 Hz.); 3.73 (3H, s, $C\underline{H}_3O$); 1.00 (9H, s, $C(C\underline{H}_3)_3$).

General procedure for reduction of ketoesters (17)-(26) to give α-dibenzylamino-β-hydroxyesters (7a,b)-(16a,b) - A solution of ketoesters 17-26 (1.00 mmol) in 95% EtOH (12.5 ml) was treated with NH_4Cl (1.06 g, 20.1 mmol) and with 3.75 ml of water. To this mixture $NaBH_4$ (0.187 g, 4.96 mmol) was added in three portions every 10 min. 10 minutes after the last addition, the mixture was concentrated nearly to dryness at reduced pressure, taken up with H_2O and CH_2Cl_2, and the pH corrected to 9 with NH_4OH. The phases were separated, and the organic phase evaporated to give the crude products which were analysed and purified as above described. Isolated yields and diastereomeric ratios are reported in Table 3.

General procedure for the hydrolysis of methyl esters (7a,b)-(11a,b) to give α-dibenzylamino-β-hydroxyacids (29a,b)-(33a,b) - A suspension of **7a,b-11a,b** (1 mmol) in 0.5N KOH in MeOH : H_2O 7 : 3 (12 ml, 6 mmol) was stirred at room temperature for the time required for reaction completion (from 5h to 2 days). The resulting solution was neutralized with 0.3M KH_2PO_4 (20 ml, 6 mmol), evaporated to dryness, and taken up with AcOEt and brine. Separation of the phases and evaporation of the solvent gave crude products which were purified by silica gel chromatography eluted with AcOEt or AcOEt : *n*-hexane. All compounds were oils and gave satisfactory elemental analyses. ^{1}H n.m.r. spectra were taken in $CDCl_3$/ D_2O.

29a: Y= 90%; ^{1}H n.m.r.: δ 7.31 (10H, s, aromatics); 3.90-4.10 (1H, m, C<u>H</u>-OH); 3.64 & 4.06 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.2 Hz.); 3.15 (1H, d, C<u>H</u>-N, J 9.1 Hz.); 1.19 (3H, d, $C\underline{H}_3$, J 6.5 Hz.). **29b**: Y= 89%; ^{1}H n.m.r.: δ 7.33 (10H, s, aromatics); 4.10-4.30 (1H, m, C<u>H</u>-OH); 4.03 (4H, s, $C\underline{H}_2$-Ph); 3.39 (1H, d, C<u>H</u>-N, J 5.3 Hz.); 1.34 (3H, d, $C\underline{H}_3$, J 6.4 Hz.). **30a**: Y= 91%; ^{1}H n.m.r.: δ 7.31 (10H, s, aromatics); 7.18 (5H, s, aromatics); 5.05 (1H, d, C<u>H</u>-OH, J 9.0 Hz.); 3.66 & 4.04 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.3 Hz.); 3.51 (1H, d, C<u>H</u>-N, J 9.0 Hz.). **30b**: Y= 93%; ^{1}H n.m.r.: δ 7.27 (10H, s, aromatics); 7.15 (5H, s, aromatics); 5.21 (1H, d, C<u>H</u>-OH, J 8.0 Hz.); 3.86 (4H, S, $C\underline{H}_2$-Ph); 3.79 (1H, d, C<u>H</u>-N, J 8.0 Hz.). **31a**: Y= 88%; ^{1}H n.m.r.: δ 7.29 (10H, s, aromatics); 4.00-4.20 (1H, m, C<u>H</u>-OH); 3.59 & 4.03 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.0 Hz.); 3.15 (1H, d, C<u>H</u>-N, J 9.3 Hz.); 0.75-1.20 (13H, m, $C_6\underline{H}_{13}$). **31b**: Y= 85%; ^{1}H n.m.r.: δ 7.36 (10H, s, aromatics); 3.32-4.45 (6H, m, C<u>H</u>-OH, $C\underline{H}_2$-Ph, C<u>H</u>-N); 0.85-1.58 (13H, m, $C_6\underline{H}_{13}$). **32a**: Y= 82%; ^{1}H n.m.r.: δ 7.29 (10H, s, aromatics); 4.00-4.20 (1H, m, C<u>H</u>-OH); 3.55 & 4.04 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.4 Hz.); 3.37 (1H, d, C<u>H</u>-N, J 9.7 Hz.); 1.00-1.58 (11H, m, $C_6\underline{H}_{11}$). **32b**: Y= 83%; ^{1}H n.m.r.: δ 7.38 (10H, s, aromatics); 3.99-4.69 (6H, m, C<u>H</u>-OH, $C\underline{H}_2$-Ph, C<u>H</u>-N); 0.90-1.55 (11H, m, $C_6\underline{H}_{11}$). **33a**: Y= 78%; ^{1}H n.m.r.: δ 7.31(10H, s, aromatics); 3.80 (1H, d, C<u>H</u>-OH, J 9.6 Hz.); 3.41 & 4.04 (4H, AB syst., $C\underline{H}_2$-Ph, J 13.3 Hz.); 3.34 (1H, d, C<u>H</u>-N, J 9.6 Hz.); 0.69 (9H, s, $C(C\underline{H}_3)_3$). **33b**: Y= 79%; ^{1}H n.m.r.: δ 7.38(10H, s, aromatics); 3.64-4.62 (6H, m, C<u>H</u>-OH, $C\underline{H}_2$-Ph, C<u>H</u>-N); 0.84 (9H, s, $C(C\underline{H}_3)_3$).

General procedure for the hydrolysis of *t*-butyl esters (12a,b)-(16a,b) to give α-dibenzylamino-β-hydroxyacids (29a,b)-(33a,b) - **12a,b-16a,b** (1.00 mmol) were dissolved at 0°C in trifluoroacetic acid (10 ml) and stirred at the same temperature for the required time (from 30 min. to 8h). After evaporation of the solvent under reduced pressure, the crude products were chromatographed on silica gel (AcOEt or *n*-hexane : AcOEt). Yields: **29a** : 58%; **29b**: 61%; **30a**: 76%; **30b**: 64%; **31a**: 67%; **31b**: 69%; **32a**: 62%; **32b**: 65%; **33a**: 67%; **33b**: 71%.

(d,l) Threonine (34a) - A solution of **29a** (100 mg, 0.334 mmol) in 95% ethanol (10 ml) was hydrogenated over 10% palladium on carbon (30 mg) for 5h at reflux. After filtration of the catalyst, the solution was evaporated to dryness to give pure **34a** as a white solid (36 mg, 90%), pure at t.l.c. and ^{1}H n.m.r., and identical to an authentic sample.

(d,l) *threo* Phenylserine (35a) - It was prepared with the same procedure utilised for **34a**: Y= 94%. This compound was identical at t.l.c. and ^{1}H n.m.r. with an authentic sample.

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