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Multicomponent Hantzsch cyclocondensation as a route to highly functionalized 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their *N*-oxides: preparation via a polymer-assisted solution-phase approach

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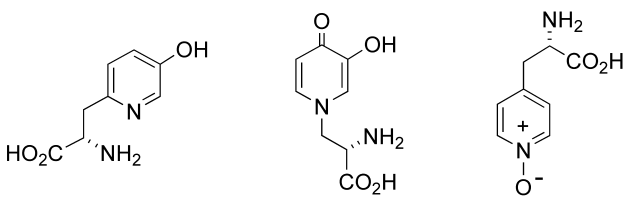
Abstract—An improved and efficient entry to highly functionalized β-(2-pyridyl)- and β-(4-pyridyl)alanines and the corresponding 1,4-dihydro and *N*-oxide derivatives has been developed by one-pot thermal Hantzsch-type cyclocondensation of aldehyde–ketoester–enamine systems in which one of the reagents (aldehyde or ketoester) was carrying the unmasked but protected chiral glycinyl moiety. Thus coupling *N*-Boc-*O*-benzyl aspartate β-aldehyde, acetoacetate and aminocrotonate esters afforded tetrasubstituted β-(4-dihydropyridyl)-alanines (75% yield). One of these products was almost quantitatively transformed into the β-(4-pyridyl)alanine derivative which in turn was oxidized to the corresponding *N*-oxide. Each of these enantiomerically pure (Mosher's amide analysis) heterocyclic α-amino acids was incorporated into a tripeptide by coupling with (*S*)-phenylalanine. In a similar way tetrasubstituted β-(2-dihydropyridyl)alanine, β-(2-pyridyl)alanine and β-(1-oxido-2-pyridyl)alanine were prepared via Hantzsch cyclocondensation reaction using benzaldehyde, aminocrotonate, and acetoacetate carrying the *N*-Boc-*O*-benzyl glycinate moiety. It was shown that the work up of the reaction mixtures derived from the cyclocondensation and oxidation reactions can be carried out by the use of polymer supported reagents and sequestrants thus allowing the isolation of the products in high purity without any chromatography.

1. Introduction

There has been in recent years a growing interest in the development of new non-proteinogenic α-amino acids[1] due to their biological and toxicological properties[2] and their applications in the fields of peptide and combinatorial chemistry as conformationally constrained components, molecular scaffolds, and chiral auxiliaries toward the identification of new leads in peptidic and non-peptidic compounds.[3] Among the variety of non-proteinogenic amino acids, the class of heterocyclic α-amino acids,[4] i.e. heterocycles featuring a side carbon-chain with a chiral glycinyl moiety ($-CH(NH_2)CO_2H$), is of special interest not only for their applications as components of artificial peptides[5] and peptide nucleic acids (PNAs)[6] but also because they display a wide range of their own biological activities.[2] Typically, pyridyl-α-alanines and ring substituted derivatives[4c–e,7] are structural analogues of the natural occurring amino acids histidine, phenylalanine, and tyrosine. Indeed, they have been incorporated as histidine replacements in angiotensin II[8] and as enzyme substrates have been shown to function as antagonists of phenylalanines[9] and inhibitors of histidine decarboxylase.[10] Moreover, as free α-amino acids they have been found to possess anti-inflammatory[11] and anti-tumor-antibiotic activities[12] as shown, for example, by the natural products L-azatyrosine **1**[13] and L-mimosine **2**[14] (Fig. 1). Moreover decapeptides with incorporated homochiral tyrosine analogues such (*S*)-β-(4-pyridyl)alanine *N*-oxide **3** have been shown[15] to act as inhibitors of epidermal growth factor tyrosine kinase whose aberrant levels of activity can result in unregulated cell proliferation associated with cancer.[16] It has been also



L-Azatyrosine, **1** L-Mimosine, **2** **3**

Figure 1. Typical bioactive pyridyl-, dihydropyridyl-, and 1-oxido-pyridyl-α-alanines.

Keywords: Multicomponent reaction; Hantzsch reaction; Heterocyclic α-amino acids; Pyridyl-α-alanines; Unnatural amino acids.

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found[17] that racemic β-(4-pyridyl)alanine *N*-oxide is an antagonist to both phenylalanine and tyrosine in *Escherichia coli* whereas the 2- and 3-pyridyl isomers are less effective inhibitors.

Recently, we have been stimulated to contribute novel chemistry to the interesting field of non-proteinogenic α-amino acids by developing versatile synthetic routes towards highly substituted dihydropyrimidinyl-α-glycines and dihydropyrimidinyl- and pyridyl-α-alanines.[18] In both cases we adopted the technique of one-step heterocyclic amino acid construction through a multicomponent cyclocondensation reaction (MCR), namely the Biginelli[19] aldehyde–ketoester–urea reaction and the Hantzsch-type[20] aldehyde–ketoester–enamine reaction in which one of the reagents (aldehydes **4** and **5** or ketoester **6**) was carrying the masked chiral glycinyl moiety in the form of the configurationally stable *N*-Boc-2,2-dimethyl oxazolidine ring[21] (Fig. 2). One of the advantages of this approach relies on exploiting the potential of MCRs in generating molecular diversity thus opening the route to the preparation of libraries of highly substituted dihydropyrimidinyl- and pyridyl-α-amino acids. Moreover, this approach allows us to overcome the problem of the control of the configuration at the carbon bearing the amino group since this was already in place in the masked glycinyl moiety introduced in one of the reagents taking part in the MCR. However, the oxidative conditions required to unveiling the glycinyl group from the *N*-Boc-2,2-dimethyl oxazolidine ring constituted a limitation in the Hantzsch approach[18] for the isolation of dihydropyridyl α-amino acids because of the concomitant oxidation of the dihydropyridyl ring to the pyridyl ring. Hence aiming at overcoming this drawback and improving the value of the MCR approach by a more rapid entry to the target product, we have investigated the use of reagents such as the aldehyde **7** and the ketoester **8** (Fig. 2) carrying the chiral glycinyl group in a protected instead of a masked form. Another improvement was possible by the use of polymer-supported reagents and sequestrants to make operatively simple and efficient the isolation of the target products on gram scale. These new conditions should allow the application of this methodology to a fully automatized procedure suitable for parallel and/or combinatorial syntheses of highly substituted dihydropyridyl (DHP)-, pyridyl-, and 1-oxido-pyridyl-α-alanines. The access to a variable substitution pattern in the heterocyclic ring of these amino

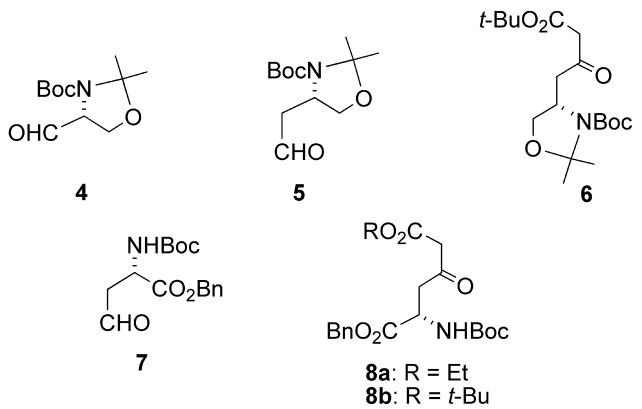


Figure 2. Masked and protected glycinyl moieties embodied in aldehydes and ketoesters employed in Ref. 18 and in this work.

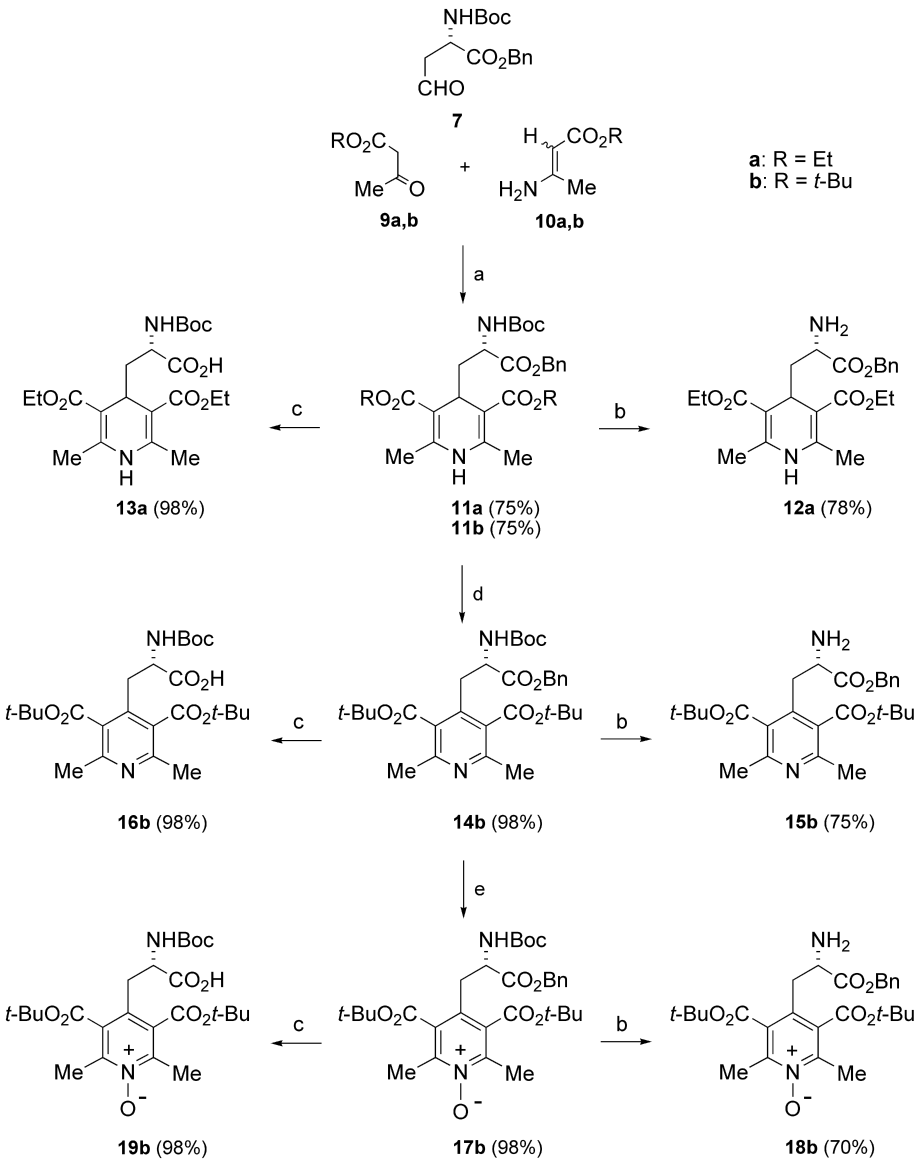
acids is crucial for the discovery of new leads. Our previous[18] and present study constitute the first approach to enantiopure heterocyclic α-amino acid collections through a MCR. A two-step approach which may also be applicable to parallel and/or combinatorial syntheses of diverse families of heterocyclic α-amino acids has been developed by Baldwin and co-workers via cyclocondensation of suitable bifunctional nucleophiles with α-amino acid alkynyl ketones.[4a–c] Hence, we will report herein the results of our improved synthesis of the title α-alanine derivatives of the pyridine family with demonstration of their insertion into oligopeptides.

2. Results and discussion

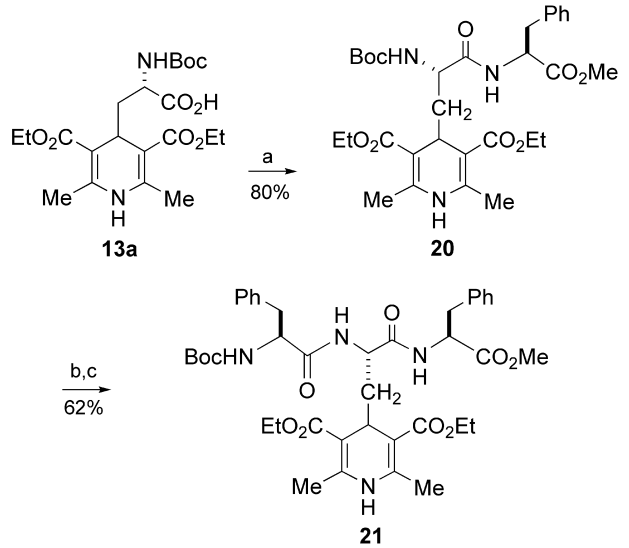
2.1. Synthesis of ring substituted β-(4-dihydropyridyl)-, β-(4-pyridyl)-, and β-(1-oxido-4-pyridyl)alanines

Given the ready access to *N*-Boc-*O*-benzyl aspartate β-aldehyde **7** by different preparative procedures[22] and its sufficient stability as demonstrated by the use in a variety of stereoselective syntheses,[22] we initially considered the Hantzsch MCR3 by coupling this aldehyde with ethyl acetoacetate **9a** and ethyl aminocrotonate **10a** (1:1:1 mixture) in EtOH at 70 °C for 24 h (Scheme 1). From this reaction the β-(4-dihydropyridyl)alanine derivative **11a** was obtained in 75% isolated yield by column chromatography. Quite obviously, the level of enantiomeric purity of this compound depended on the preservation of the stereochemical integrity (*S* configuration) of the aldehyde **7** during the cyclocondensation reaction. Gratifyingly this appeared to be the case since the α-amino ester **11a** by treatment with trifluoroacetic acid (TFA) at 0 °C was converted into its N′-deprotected form **12a** (78%) whose enantiomeric purity established by ^{1}H and ^{19}F NMR analyses of the (*R*)- and (*S*)-Mosher's amides[23] turned out to be greater than 96%. Owing to the orthogonal protection of the ester groups, compound **11a** was also transformed into the *N*′-Boc α-amino acid **13a** (98% yield) by debenzylation via $Pd(OH)_2$ catalyzed hydrogenation. Compounds **12a** and **13a** represent orthogonally protected units suitable for peptide synthesis by chain extension from either the N′- or C-terminus.[24]

Given the potential practical application of β-(4-dihydropyridyl)alanines in the area of artificial peptides, we considered the insertion of **13a** into a tripeptide as a good evidence of its reactivity despite the densely substituted heterocyclic ring. This operation appeared to be also a test of the stability of the dihydropyridine ring under the reaction conditions of peptide formation. Hence coupling of **13a** with L-phenylalanine methyl ester hydrochloride (H-Phe-OMe·HCl), using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop) as coupling reagent and diisopropylethylamine (DIEA) in CH_2Cl_2 (Scheme 2) furnished the dipeptide **20** in 80% isolated yield. Extension from the N′-terminus was next carried out. After Boc removal in **20** by treatment with TFA, the coupling of the resulting free amine with *tert*-butoxycarbonyl-L-phenylalanine (Boc-Phe-OH) using PyBop and DIEA afforded the target tripeptide **21** in 62% overall yield (two steps).



Scheme 1. Reagents and conditions: (a) 4-Å MS, ROH, 70 °C, 24 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (c) H_2, $Pd(OH)_2$, AcOEt–EtOH (2:1), rt, 15 min; (d) 4-Å MS, PCC, CH_2Cl_2, rt, 2 h; (e) MCPBA, CH_2Cl_2, rt, 15 h.



Scheme 2. Reagents and conditions: (a) H-Phe-OMe·HCl, PyBOP, DIEA, CH_2Cl_2, rt, 2 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (c) Boc-Phe-OH, PyBOP, DIEA, CH_2Cl_2, rt, 2 h.

The same MCR3 route was followed in the synthesis of a tetrasubstituted β-(4-pyridyl)alanine and its *N*-oxide. In this case, *tert*-butyl acetoacetate **9b** and *tert*-butyl aminocrotonate **10b** were employed as components in the cyclocondensation with the aldehyde **7** (Scheme 1). In fact it has been shown[18] that the bulky *tert*-butyl in the carboxylate groups at C3 and C5 of the pyridine ring of a β-(4-pyridyl)-alanine inhibits intramolecular condensation reactions to occur during the manipulation of the amino acid functionalities. The effectiveness of the cyclocondensation did not appear to suffer of such a change in the reagents since the one-pot reaction of the ketoester **9b**, enamino ester **10b** and aldehyde **7** (1:1:1 ratio) in *tert*-BuOH at 70 °C after 24 h afforded the corresponding ring substituted β-(4-dihydropyridinyl)alanine **11b** in 75% isolated yield. This compound was almost quantitatively transformed into the β-(4-pyridyl)-alanine **14b** by treatment with pyridinium chlorocromate (PCC) in CH_2Cl_2 and the latter was oxidized to the *N*-oxide **17b** using *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2. The $N^{\prime}$-Boc removal from these compounds by

treatment with TFA furnished the amino free heterocyclic benzyl alaninates **15b** and **18b**, respectively, whereas the debenzylation by $Pd(OH)_2$ catalyzed hydrogenation provided the corresponding *N*′-Boc alanines **16b** and **19b** in very good yields. Compound **16b** was identical by comparison of the optical rotation value ($[\alpha]_D=-25.8$ in MeOH) to the same product reported in our earlier publication[18] and which was prepared using the oxazolidinyl-functionalized aldehyde **5** in the cyclocondensation reaction (Fig. 2). However, the degree of enantiomeric purity higher than 96% was confirmed also in these cases by ^1H and ^{19}F NMR analyses of the (*R*)- and (*S*)-Mosher's amides derived from compounds **15b** and **18b**.

It has been already demonstrated[18] that the two bulky *tert*-butyl ester groups at the pyridine ring of the pyridyl-α-amino acid **16b** do not prevent this compound to be effectively incorporated into a peptide chain as the stepwise coupling of **16b** with two L-phenylalanine units afforded the tripeptide **22** in 74% overall yield (Fig. 3). The same appeared to be true for the *N*-oxide **19b** which was employed to synthesize the tripeptide **23** in 57% overall yield in analogous fashion to **21** and **22**, i.e. by first coupling **19b** with H-Phe-OMe·HCl, then *N*′-Boc removal from the resulting dipeptide and second coupling of the latter with Boc-Phe-OH (see Section 3). Hence the *N*-oxide functional group appeared to be unaffected by the conditions of this peptide synthesis.

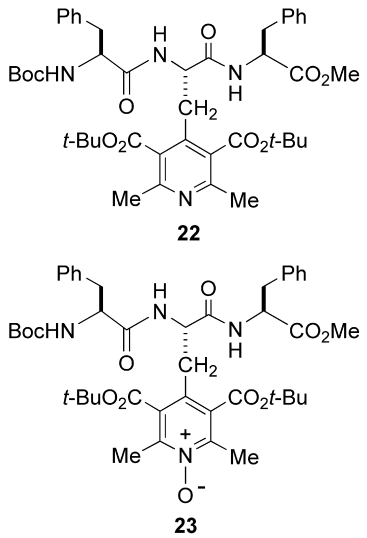
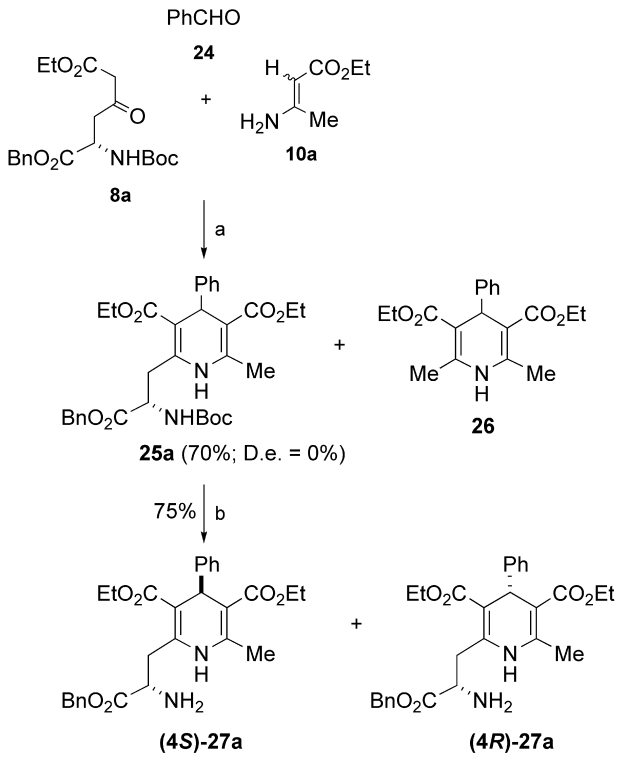


Figure 3. Tripeptides prepared using L-phenylalanine and 4-pyridyl-α-alanine **16b** and its *N*-oxide **19b** (for reagents and conditions, see Section 3).

2.2. Synthesis of ring substituted β-(2-dihydropyridyl)-, β-(2-pyridyl)-, and β-(1-oxido-2-pyridyl)alanines

We next turned our attention to the implementation of the above cyclocondensation–oxidation procedure by considering the synthesis of the 2-regioisomers of the above heterocycle-α-alanines. To this aim the glycinyl substituted ethyl acetoacetate **8a** and *tert*-butyl acetoacetate **8b** (Fig. 2) were prepared in satisfactory yields (ca. 70%) by $BF_3{\cdot}Et_2O$ promoted coupling of the aspartate β-aldehyde **7** with ethyl and *tert*-butyl diazoacetate, respectively, as described[18] for the oxazolidinyl derivative **6** (see Section 3). Then the cyclocondensation between **8a**, benzaldehyde **24** and ethyl aminocrotonate **10a** in 1:1:1 ratio was carried out under the usual conditions (EtOH, 70 °C, 24 h). This reaction afforded the desired ring substituted β-(2-dihydropyridyl)alaninate **25a** (35%) as 1:1 mixture of diastereoisomers having opposite configuration at C4 together with the dihydropyridine **26** (35%, Scheme 3). Evidently, the latter product was formed by cyclocondensation of benzaldehyde **24**, ethyl aminocrotonate **10a** and ethyl acetoacetate **9a**, the latter reagent having been formed by partial hydrolysis of **10a** despite the use of anhydrous EtOH and the presence of molecular sieves. The same reaction carried out in the absence of solvent at 70 °C for 4 h produced the α-amino ester **25a** and the dihydropyridine **26** in 3:1 ratio and 60% overall yield, thus indicating that the hydrolysis of **10a** had not been totally prevented. Hence, since the main objective was to achieve a high conversion of the glycinyl functionalized ketoester **8a** into the target α-amino ester **25a**, the solvent-free cyclocondensation was carried out at 70 °C for 1 h using 2 equiv. of inexpensive benzaldehyde **24** and aminocrotonate **10a**. Under these conditions the target product **25a** was formed in a rewarding 70% yield, as judged by ^1H NMR analysis of the crude reaction mixture, but still contaminated by **26** (3:1 molar ratio). Unfortunately, the separation of the individual diastereoisomers as well as the removal of the dihydropyridine **26** was unsuccessful by the use of column chromatography. Therefore, we proceeded to the removal of the *N*′-Boc from the amino acid functionality by treatment of crude **25a** with TFA at 0 °C. This reaction afforded the amine-free β-(2-dihydropyridyl)alaninate diastereoisomers (4*S*)-**27a** and (4*R*)-**27a** which were individually isolated by chromatography.

The absolute configuration at C4 of the dihydropyridine ring



Scheme 3. Reagents and conditions: (a) 70 °C, 1 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C, 1 h.

of (4*R*)-**27a** was established by the X-ray crystallographic analysis of its (*R*)-Mosher's amide (Fig. 4).[25] Furthermore, ^{1}H and ^{19}F NMR analysis of both Mosher's amides of (4*R*)-**27a** confirmed that the configuration of the glycinyl moiety was preserved during the cyclocondensation reaction.

In a second instance, 2-pyridylalanines and their *N*-oxides were targeted using the glycinyl substituted *tert*-butyl acetoacetate **8b** and *tert*-butyl aminocrotonate **10b** as partners of the cyclocondensation with benzaldehyde **24** (Scheme 4). The reasons which led to the use of *tert*-butyl esters in this synthesis were the same of those reported above for the synthesis of 4-pyridylalanines and their *N*-oxides.[18] We were gratified to observe that the reaction of **8b**, **10b**, and **24** in 1:1:1 ratio under the standard conditions (*tert*-BuOH, 70 °C, 24 h) afforded exclusively the ring substituted β-(2-dihydropyridyl)alaninate **25b** in good yield (75%) without the formation of a dihydropyridine side product similar to **26** shown in Scheme 3. Hence, it can be deduced that the enamino ester **10b** unlike the ethyl derivative **10a** is sufficiently stable under the reaction conditions toward the hydrolytic conversion into a keto-ester. Then, conversions of **25b** to the β-(2-pyridyl)alaninate **28b** and the latter to the *N*-oxide **31b** were carried out

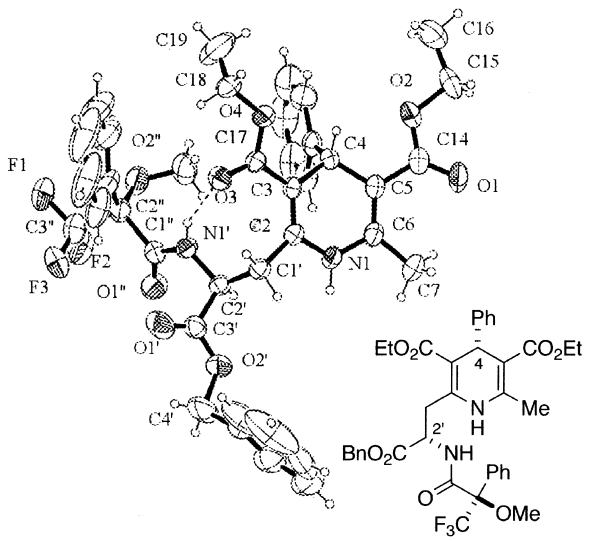
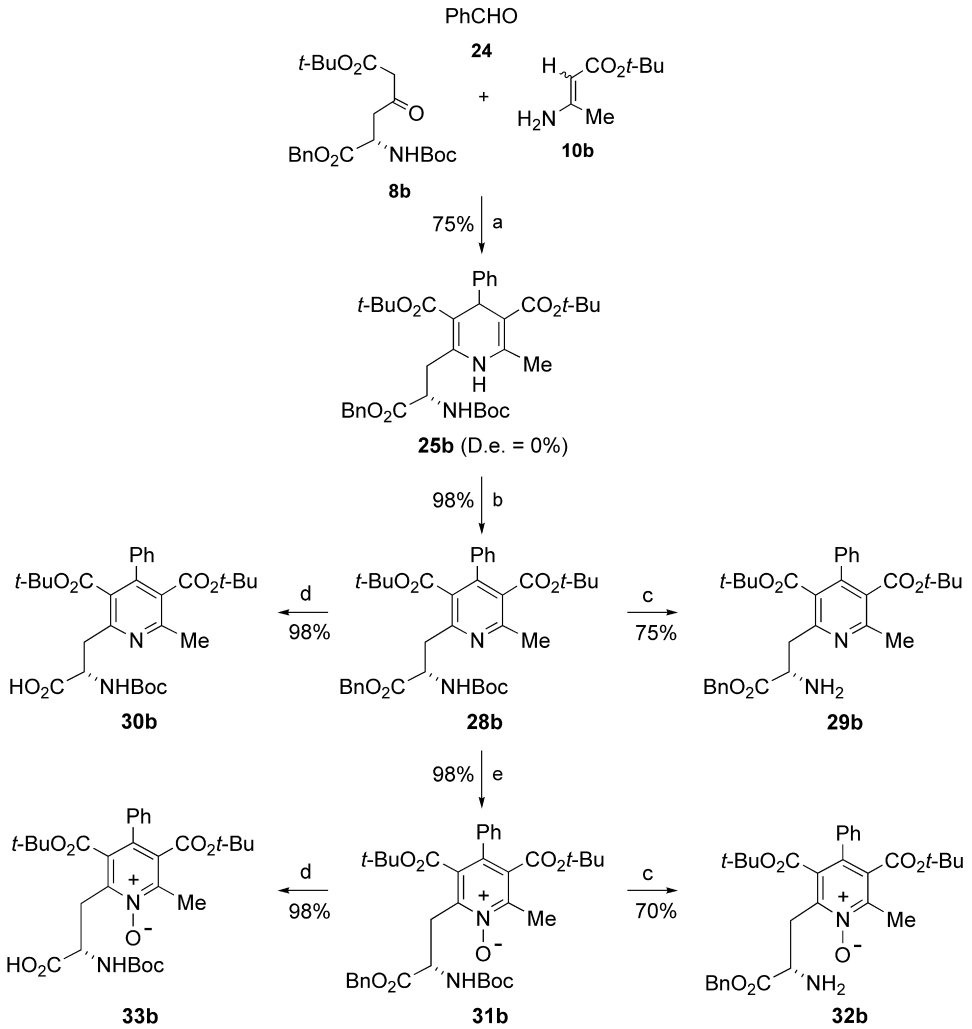


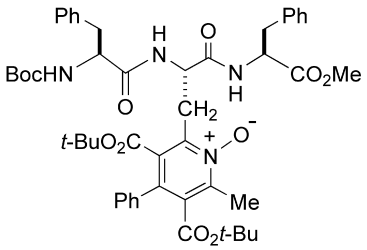
Figure 4. An ORTEP view of the (*R*)-Mosher's amide of (4*R*)-**27a** displaying the thermal ellipsoids at a 30% probability level.



Scheme 4. Reagents and conditions: (a) 4-Å MS, *tert*-BuOH, 70 °C, 24 h; (b) 4-Å MS, PCC, CH_2Cl_2, rt, 2 h; (c) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (d) H_2, $Pd(OH)_2$, AcOEt–EtOH (2:1), rt, 15 min; (e) MCPBA, CH_2Cl_2, rt, 15 h.

by almost quantitative oxidation reactions using PCC and MCPBA, respectively. The selective deprotection of the amino (Boc removal) and carboxyl group (Bn removal) of these compounds furnished the amino alaninates **29b** and **32b** and the *N*′-Boc alanines **30b** and **33b**. The former pair of these products was employed for the demonstration through the Mosher's amides of their enantiomeric purity, which also in this case resulted to be higher than 96% by NMR analysis.

Finally, as proof of the potential of this family of heterocyclic amino acids in peptide synthesis, compound **33b** was incorporated into the tripeptide **34** by sequential reaction with suitably protected L-phenylalanine derivatives as described above (57% overall yield, three steps).



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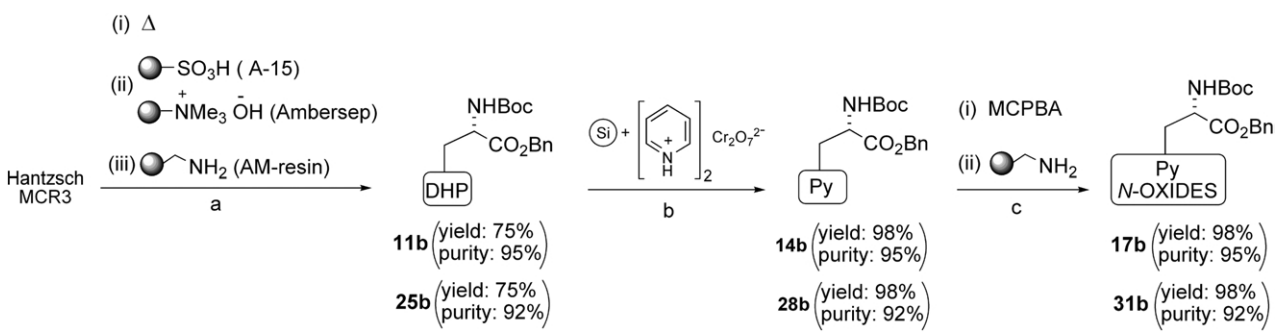
2.3. Polymer-assisted solution-phase synthesis of 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their *N*-oxides

Among the modern criteria considered when establishing the level of efficiency of chemical reactions, such as yield, selectivity, and atom economy, those regarding the reaction processing are equally emphasized in present times.[26] Hence, we envisaged adapting the above synthetic route to techniques that would facilitate easy isolation of the target products. To this aim the use of polymer supported reagents and sequestrants were considered in the whole sequence toward the synthesis of dihydropyridyl-, pyridyl-, and 1-oxido-pyridyl-α-alanines. In fact, the immobilization of reagents on the surface of a polymer bead (or the absorption onto silica gel) simplifies the purification procedure dramatically, reducing it to a simple washing and filtration step. During the last few years polymer-assisted solution-phase (PASP) synthesis has become the prevalent method for the generation and rapid purification of chemical libraries as demonstrated by the increasing number of publications in this area.[27] In many cases, this methodology appears to be superior to the complementary way to con-struct compound collections on polymer beads (solid-phase organic synthesis,[28] SPOS), since the reaction monitoring is easier, reaction optimization is usually faster, and no residue of attachment to the beads remains in final product. This new tendency in combinatorial chemistry is confirmed by the continuous development of highly efficient polymer supported sequestrants, reagents, and catalysts to scavenge excess reactants or side products, and promote reactions in solution.[27]

We have developed a protocol for the isolation of 2- and 4-dihydropyridylalanines **25b** and **11b** avoiding chromatographic separation by the use of suitable supported sequestrants for the work up of the crude reaction mixtures arising from the Hantzsch MCR3. Thus, a mixed resin bed containing the strongly acidic resin Amberlyst 15 (A-15) and the strongly basic resin Ambersep 900 OH was employed to scavenge unreacted enamine and ketoester, respectively (Scheme 5). Then, nucleophilic aminomethylated polystyrene (AM-resin) was added to remove unreacted aldehyde and side products derived from partial condensation reactions such as the enone which is produced by condensation of aldehyde and ketoester (Knoevenagel product). By this purification procedure DHP-α-alanines **11b** and **25b** were obtained in good yield (75%) and high purity (>92%) as judged by ^{1}H NMR analysis. The subsequent conversion into the corresponding pyridyl-α-alanines **14b** and **28b** was performed in almost quantitative yield by using PCC immobilized on silica gel. This reagent which was prepared according to the procedure described by Eynde and co-workers[29] greatly facilitated removal of reduced chromium by-products affording **14b** and **28b** in high purity (>92%). Finally, 1-oxido-pyridyl-α-alanines **17b** and **31b** were prepared following the previously described procedure (MCPBA, CH_2Cl_2, rt, 15 h) but their purification was performed by sequestering excess MCPBA and *m*-chlorobenzoic acid side product with aminomethylated polystyrene resin. At the end of the three-step synthetic sequence, *N*-oxides **17b** and **31b** were obtained in 95 and 92% purity and good overall yield without the need of any chromatographic separation. However, analytical samples of **17b** and **31b** obtained via the polymer-assisted approach were prepared to compare their optical rotation values with those of the same compounds obtained by the conventional solution methodology. The observed identical rotation values confirmed that the resins employed, especially the strongly basic Ambersep 900 OH, did not affect the stereochemical integrity at the α-carbon of the amino acid moiety.



Scheme 5. Reagents and conditions: (a) (i) 4-Å MS, *tert*-BuOH, 70 °C, 24 h; (ii) A-15, Ambersep, CH_2Cl_2, rt, 2 h; (iii) AM-resin, CH_2Cl_2, rt, 2 h. (b) PCC on silica gel, CH_2Cl_2, rt, 24 h. (c) (i) MCPBA, CH_2Cl_2, rt, 15 h; (ii) AM-resin, CH_2Cl_2, rt, 2 h. Purities were determined by ^{1}H NMR analysis.

In conclusion, we described an improved and efficient approach toward the synthesis of 2- and 4-dihydropyridylalanines, 2-and 4-pyridylalanines, and their *N*-oxide derivatives. The strategy employed relies on the use of aldehyde **7** and ketoester **8** carrying the chiral glycinyl moiety in a suitably protected form as components in Hantzsch MCR3. Highly functionalized heterocyclic amino acid derivatives have been obtained by this route and their potential application as units of artificial peptides demonstrated by their insertion into tripeptides. Furthermore, the compatibility of our strategy with a polymer-assisted solution phase synthesis approach has been established by exploiting an orchestrated sequence of polymer supported reagents and sequestrants to produce the title heterocyclic amino acids in high yield and purity without any chromatographic step. While we have not used robotic systems to build a large number of compounds in this study, we believe this route would be entirely adaptable to these high throughput methods.

3. Experimental

3.1. General

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid, or alcoholic solution of ninhydrin. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20±2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Nicolet 510 P FT-IR instrument. ^{1}H (300 MHz), ^{19}F (282 MHz), and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. X-ray diffraction data for compound (4*R*)-**27a** (*R*)-Mosher amide were collected at room temperature, 295 K, on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.7107 Å). The structure was solved by direct methods (SIR97)[30] and refined (SHELXL-97)[31] by full matrix least squares with anisotropic non-H and hydrogen atoms included on calculated positions riding on their carrier atoms, except N–H hydrogens which were refined isotropically. ORTEP[32] view is shown in Figure 4. Aldehyde **7**[22] was synthesized as described. *tert*-Butyl 3-aminocrotonate **10b**[33] was prepared by reaction of the corresponding β-ketoester with ammonium acetate in refluxing *tert*-butyl alcohol. Pyridinium chlorochromate immobilized on silica gel was prepared as described.[29] Pyridines **16b** and **30b** are known compounds.[18]

3.1.1. (2*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-hexanedioic acid 1-benzyl ester 6-ethyl ester (8a). A mixture of aldehyde **7** (615 mg, 2.00 mmol), ethyl diazoacetate (0.25 mL, 2.40 mmol), activated 4-Å powdered molecular sieves (300 mg), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 15 min, and then cooled to 0 °C. To the mixture a solution of $BF_3{\cdot}Et_2O$ (127 μL, 1.00 mmol) in anhydrous CH_2Cl_2 (1 mL) was added drop by drop, controlling the N_2 evolution at a low steady rate. The mixture was stirred at 0 °C for an additional 30 min, diluted with 10% $NaHCO_3$ (10 mL), warmed to room temperature, filtered through a pad of Celite, and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a short column of silica gel with 3:1 cyclohexane–AcOEt to give **8a** (551 mg, 70%) as a yellow syrup. $[\alpha]_D$=+12.0 (*c* 1.6, $CHCl_3$). ^{1}H NMR: δ 7.45–7.30 (m, 5H, Ph), 5.49 (bd, 1H, $J_{2,NH}$= 8.5 Hz, NH), 5.19 (s, 2H, PhCH_2), 4.59 (ddd, 1H, $J_{2,3a}$= 4.5 Hz, $J_{2,3b}$=4.0 Hz, H-2), 4.27–4.12 (m, 2H, CH_2CH$_3$), 3.44 (s, 2H, 2H-5), 3.31 (dd, 1H, $J_{3a,3b}$=18.0 Hz, H-3a), 3.13 (dd, 1H, H-3b), 1.44 (s, 9H, *t*-Bu), 1.28 (t, 3H, *J*= 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 394.7 (M^++H), 416.4 (M^++Na), 432.6 (M^++K). Anal. calcd for $C_{20}H_{27}NO_7$ (393.43): C, 61.06; H, 6.92; N, 3.56. Found: C, 61.05; H, 6.88; N, 3.57.

3.1.2. (2*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-hexanedioic acid 1-benzyl ester 6-*tert*-butyl ester (8b). A mixture of aldehyde **7** (615 mg, 2.00 mmol), *tert*-butyl diazoacetate (0.33 mL, 2.40 mmol), activated 4-Å powdered molecular sieves (300 mg), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 15 min, and then cooled to 0 °C. To the mixture a solution of $BF_3{\cdot}Et_2O$ (127 μL, 1.00 mmol) in anhydrous CH_2Cl_2 (1 mL) was added drop by drop, controlling the N_2 evolution at a low steady rate. The mixture was stirred at 0 °C for an additional 30 min, diluted with 10% $NaHCO_3$ (10 mL), warmed to room temperature, filtered through a pad of Celite, and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a short column of silica gel with 4:1 cyclohexane–AcOEt to give **8b** (590 mg, 70%) as a yellow syrup. $[\alpha]_D$=+9.9 (*c* 1.7, $CHCl_3$). ^{1}H NMR: δ 7.40–7.30 (m, 5H, Ph), 5.49 (bd, 1H, $J_{2,NH}$= 8.5 Hz, NH), 5.19 (s, 2H, PhCH_2), 4.59 (ddd, 1H, $J_{2,3a}$= 4.5 Hz, $J_{2,3b}$=4.0 Hz, H-2), 3.35 (s, 2H, 2H-5), 3.30 (dd, 1H, $J_{3a,3b}$=18.2 Hz, H-3a), 3.12 (dd, 1H, H-3b), 1.48 (s, 9H, *t*-Bu), 1.44 (s, 9H, *t*-Bu). MALDI-TOF MS: 422.8 (M^++H), 444.6 (M^++Na), 460.3 (M^++K). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.70; H, 7.44; N, 3.38.

3.1.3. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (11a). A screw-capped vial, containing a magnetic bar, was charged with aldehyde **7** (615 mg, 2.00 mmol), β-ketoester **9a** (255 μL, 2.00 mmol), aminocrotonate **10a** (258 mg, 2.00 mmol), activated 4-Å powdered molecular sieves (100 mg) and EtOH (3 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (5 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give **11a** (796 mg, 75%) as a yellow

foam. $[\alpha]_D$=+24.1 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3500–3220 (br), 2900, 1750, 1700, 1650. ^1H NMR: δ 7.40–7.20 (m, 5H, Ph), 5.85 (bs, 1H, NH), 5.41 (bd, 1H, $J_{2',NH}$=7.5 Hz, N′H), 5.16 and 5.05 (2d, 2H, *J*=12.5 Hz, PhCH_2), 4.28 (ddd, 1H, $J_{1'a,2'}$=3.5 Hz, $J_{1'b,2'}$=8.5 Hz, H-2′), 4.18 (q, 4H, *J*=7.0 Hz, 2C$H_2$$CH_3$), 4.05 (dd, 1H, $J_{4,1'a}$=6.5 Hz, $J_{4,1'b}$=5.3 Hz, H-4), 2.31 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.90 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.69 (ddd, 1H, H-1′b), 1.42 (s, 9H, *t*-Bu), 1.30 (t, 6H, 2CH_2CH_3). MALDI-TOF MS: 531.6 (M^++H), 553.7 (M^++Na), 569.7 (M^++K). Anal. calcd for $C_{28}H_{38}N_2O_8$ (530.61): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.40; H, 7.28; N, 5.25.

3.1.4. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (11b). A screw-capped vial, containing a magnetic bar, was charged with aldehyde **7** (1.23 g, 4.00 mmol), β-ketoester **9b** (0.66 mL, 4.00 mmol), aminocrotonate **10b** (0.63 g, 4.00 mmol), activated 4-Å powdered molecular sieves (200 mg) and *tert*-BuOH (5 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **11b** (1.76 g, 75%) as a yellow foam. $[\alpha]_D$=+21.4 (*c* 1.0, CH_3OH); IR (Nujol) ν_{max}: 3450–3200 (br), 2900, 1760, 1720, 1650. ^1H NMR (DMSO-d_6, 120 °C): δ 8.21 (bs, 1H, NH), 7.40–7.30 (m, 5H, Ph), 5.92 (bs, 1H, N′H), 5.08 (s, 2H, PhCH_2), 4.05 (dd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.3 Hz, H-2′), 3.89 (dd, 1H, $J_{4,1'a}$=6.1 Hz, $J_{4,1'b}$=5.6 Hz, H-4), 2.19 (s, 6H, 2CH_3), 1.73 (ddd, 1H, $J_{1'a,1'b}$=11.0 Hz, H-1′a), 1.54 (ddd, 1H, H-1′b), 1.46 (s, 18H, 2*t*-Bu), 1.38 (s, 9H, *t*-Bu). MALDI-TOF MS: 587.7 (M^++H), 609.7 (M^++Na), 625.8 (M^++K). Anal. calcd for $C_{32}H_{46}N_2O_8$ (586.72): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.50; H, 7.48; N, 4.75.

3.1.5. (4*R*,2′*S*)- and (4*S*,2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl esters (25a). A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde **24** (407 μL, 4.00 mmol), β-ketoester **8a** (787 mg, 2.00 mmol), aminocrotonate **10a** (517 mg, 4.00 mmol). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 1 h then cooled to room temperature, diluted with AcOEt (10 mL), and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **25a** (830 mg, 70%) as a 1:1 mixture of diastereoisomers contaminated by **26** (155 mg, 0.47 mmol) as judged by ^1H NMR analysis. IR (Nujol) ν_{max}: 3500–3200 (br), 2910, 1710, 1690, 1650, 1640. ^1H NMR (DMSO-d_6, 120 °C) for **25a**: δ 8.33 (bs, 0.5H, NH), 8.23 (bs, 0.5H, NH), 7.40–7.00 (m, 10H, 2Ph), 6.46 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 6.42 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 5.18 and 5.12 (2d, 2H, *J*=13.4 Hz, PhCH_2), 4.95 (s, 1H, H-4), 4.60–4.48 (m, 1H, H-2′), 4.14–4.00 (m, 4H, 2C$H_2$$CH_3$), 3.41 (dd, 0.5H, $J_{1'a,2'}$=5.6 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.28 (dd, 0.5H, $J_{1'a,2'}$=5.4 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′a), 2.97 (dd, 0.5H, $J_{1'b,2'}$=10.5 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′b), 2.76 (dd, 0.5H, $J_{1'b,2'}$=10.0 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′b), 2.28 (s, 1.5H, CH_3), 2.27 (s, 1.5H, CH_3), 1.38 (s, 4.5H, *t*-Bu), 1.36 (s, 4.5H, *t*-Bu), 1.16 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.14 (t, 3H, *J*=7.0 Hz, CH_2CH_3). MALDI-TOF MS: 593.7 (M^++H), 615.4 (M^++Na), 631.6 (M^++K). Anal. calcd for $C_{33}H_{40}N_2O$ (592.68): C, 66.87; H, 6.80; N, 4.73. Found: C, 66.85; H, 6.88; N, 4.72.

3.1.6. (4*R*,2′*S*) and (4*S*,2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid di-*tert*-butyl esters (25b). A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde **24** (203 μL, 2.00 mmol), β-ketoester **8b** (843 mg, 2.00 mmol), aminocrotonate **10b** (314 mg, 2.00 mmol), powdered 4 Å molecular sieves (100 mg) and *tert*-BuOH (3 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (5 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **25b** (973 mg, 75%) as a 1:1 mixture of diastereoisomers. IR (Nujol) ν_{max}: 3500–3210 (br), 2920, 1740, 1690, 1660, 1650. ^1H NMR (DMSO-d_6, 120 °C): δ 8.14 (bs, 0.5H, NH), 8.00 (bs, 0.5H, NH), 7.40–7.00 (m, 10H, 2Ph), 6.48 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 6.34 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 5.17 (s, 2H, PhCH_2), 4.90 (s, 0.5H, H-4), 4.88 (s, 0.5H, H-4), 4.60–4.46 (m, 1H, H-2′), 3.34 (dd, 0.5H, $J_{1'a,2'}$=5.6 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.16 (dd, 0.5H, $J_{1'a,2'}$=5.4 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.04 (dd, 0.5H, $J_{1'b,2'}$=10.7 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′b), 2.77 (dd, 0.5H, $J_{1'b,2'}$=10.5 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′b), 2.23 (s, 1.5H, CH_3), 2.22 (s, 1.5H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.37 (s, 9H, *t*-Bu), 1.36 (s, 4.5H, *t*-Bu), 1.35 (s, 4.5H, *t*-Bu). MALDI-TOF MS: 649.9 (M^++H), 671.6 (M^++Na), 687.5 (M^++K). Anal. calcd for $C_{37}H_{48}N_2O_8$ (648.79): C, 68.50; H, 7.46; N, 4.32. Found: C, 68.46; H, 7.44; N, 4.39.

3.2. General procedure for DHP oxidation leading to pyridines 14b and 28b

A mixture of DHP **11b** or **25b** (1.00 mmol), activated 4-Å powdered molecular sieves (200 mg), and anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature for 15 min, and then pyridinium chlorochromate (647 mg, 3.00 mmol) was added. The suspension was stirred for 2 h, and then cyclohexane (15 mL) and Et_2O (30 mL) were added. The mixture was filtered through a pad of silica gel and concentrated. The residue was eluted from a short column of silica gel with the suitable elution system to give the analytical sample of the corresponding pyridine.

3.2.1. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (14b). Column chromatography with 4:1 cyclohexane–AcOEt afforded **14b** (573 mg, 98%) as a white foam. $[\alpha]_D$=−37.0 (*c* 1.2, $CHCl_3$); IR (Nujol) ν_{max}: 3400, 2900, 1740, 1710, 1690. ^1H NMR (DMSO-d_6, 120 °C): δ 7.40–7.20 (m, 5H, Ph), 6.31 (bs, 1H, N′H), 5.10 (s, 2H, PhCH_2), 4.42 (dd, 1H, $J_{1'a,2'}$=7.1 Hz, $J_{1'b,2'}$=9.0 Hz, H-2′), 3.22 (dd, 1H, $J_{1'a,1'b}$=14.2 Hz, H-1′a), 2.89 (dd, 1H, H-1′b), 2.44 (s, 6H, 2CH_3), 1.59 (s, 18H, 2*t*-Bu), 1.31 (s, 9H,

t-Bu). MALDI-TOF MS: 585.7 (M^++H), 607.6 (M^++Na), 623.9 (M^++K). Anal. calcd for $C_{32}H_{44}N_2O_8$ (584.70): C, 65.73; H, 7.58; N, 4.79. Found: C, 65.71; H, 7.56; N, 4.75.

3.2.2. (2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (28b). Column chromatography with 4:1 cyclohexane–AcOEt afforded **28b** (634 mg, 98%) as a white foam. $[\alpha]_D$=+5.6 (*c* 0.7, $CHCl_3$); IR (Nujol) ν_{max}: 3450, 2910, 1760, 1710, 1690. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.45–7.10 (m, 10H, 2Ph), 6.63 (bd, 1H, $J_{2',NH}$=7.3 Hz, N′H), 5.15 and 5.09 (2d, 2H, *J*=12.7 Hz, PhCH_2), 4.75 (ddd, 1H, $J_{1'a,2'}$=6.6 Hz, $J_{1'b,2'}$=7.1 Hz, H-2′), 3.33 (dd, 1H, $J_{1'a,1'b}$=15.1 Hz, H-1′a), 3.19 (dd, 1H, H-1′b), 2.47 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu). MALDI-TOF MS: 647.9 (M^++H), 669.6 (M^++Na), 685.3 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_8$ (646.77): C, 68.71; H, 7.17; N, 4.33. Found: C, 68.66; H, 7.12; N, 4.33.

3.3. General procedure for pyridine oxidation leading to 1-oxido-pyridines 17b and 31b

A mixture of pyridine **14b** or **28b** (1.00 mmol), 3-chloroperoxybenzoic acid (690 mg, 4.00 mmol), and anhydrous CH_2Cl_2 (30 mL) was stirred at room temperature for 15 h, then diluted with 10% $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with the suitable elution system to give the corresponding 1-oxido-pyridine.

3.3.1. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (17b). Column chromatography with 1:1 cyclohexane–AcOEt afforded **17b** (589 mg, 98%) as a white foam. $[\alpha]_D$=−27.1 (*c* 2.1, CH_3OH); IR (Nujol) ν_{max}: 3200, 2900, 1750, 1720, 1690, 1250. ^{1}H NMR (DMSO-d_6, 140 °C): δ 7.40–7.20 (m, 5H, Ph), 6.21 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 5.11 (s, 2H, PhCH_2), 4.45 (ddd, 1H, $J_{1'a,2'}$=7.1 Hz, $J_{1'b,2'}$=9.3 Hz, H-2′), 3.16 (dd, 1H, $J_{1'a,1'b}$=14.4 Hz, H-1′a), 2.87 (dd, 1H, H-1′b), 2.40 (s, 6H, 2CH_3), 1.60 (s, 18H, 2*t*-Bu), 1.33 (s, 9H, *t*-Bu). MALDI-TOF MS: 601.5 (M^++H), 623.7 (M^++Na), 639.8 (M^++K). Anal. calcd for $C_{32}H_{44}N_2O_9$ (600.70): C, 63.98; H, 7.38; N, 4.66. Found: C, 63.90; H, 7.33; N, 4.62.

3.3.2. (2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (31b). Column chromatography with 3.5:1 cyclohexane–AcOEt afforded **31b** (650 mg, 98%) as a white foam. $[\alpha]_D$=+5.8 (*c* 1.2, $CHCl_3$); IR (Nujol) ν_{max}: 3250, 2920, 1780, 1730, 1690, 1260. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.50–7.10 (m, 10H, 2Ph), 6.70 (bd, 1H, $J_{2',NH}$=7.8 Hz, N′H), 5.17 and 5.07 (2d, 2H, *J*=12.7 Hz, PhCH_2), 4.82 (ddd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=8.6 Hz, H-2′), 3.42 (dd, 1H, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.29 (dd, 1H, H-1′b), 2.44 (s, 3H, CH_3), 1.35 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.19 (s, 9H, *t*-Bu). MALDI-TOF MS: 663.6 (M^++H), 685.9 (M^++Na), 701.4 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_9$ (662.77): C, 67.05; H, 7.00; N, 4.23. Found: C, 67.05; H, 7.08; N, 4.17.

3.4. General procedure for Boc deprotection of amino esters 11a, 14b, 17b, 28b and 31b

To a cooled (0 °C), stirred solution of *N*′-Boc amino ester (0.50 mmol) in CH_2Cl_2 (1 mL) was slowly added a solution of TFA–CH_2Cl_2 (1–3 mL). Stirring was continued at 0 °C for an additional 30 min then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding *N*′-deprotected amino ester.

3.4.1. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a). Column chromatography with 4:1 cyclohexane–AcOEt (containing 1% of Et_3N) afforded **12a** (168 mg, 78%) as a white foam. $[\alpha]_D$=+40.8 (*c* 1.3, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1730, 1720. ^{1}H NMR: δ 7.40–7.30 (m, 5H, Ph), 5.92 (bs, 1H, NH), 5.15 and 5.09 (2d, 2H, *J*=12.5 Hz, PhCH_2), 4.25–4.15 (m, 4H, 2CH_2CH_3), 4.10 (dd, 1H, $J_{4,1'a}$=9.0 Hz, $J_{4,1'b}$=4.0 Hz, H-4), 3.48 (bdd, 1H, H-2′), 2.32 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.82 (m, 3H, N′H_2, H-1′a), 1.44 (ddd, 1H, $J_{1'a,1'b}$=13.0 Hz, $J_{1'b,2'}$=9.5 Hz, H-1′b), 1.32 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.30 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 175.2, 167.9, 167.1, 146.1, 145.4, 135.9, 128.5, 128.4, 128.3, 128.2, 103.0, 101.8, 66.4, 60.1, 59.8, 51.7, 41.8, 29.9, 19.9, 194, 14.4, 14.0. MALDI-TOF MS: 431.5 (M^++H), 453.7 (M^++Na), 469.5 (M^++K). Anal. calcd for $C_{23}H_{30}N_2O_6$ (430.49): C, 64.17; H, 7.02; N, 6.51. Found: C, 64.20; H, 7.04; N, 6.56.

3.4.2. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b). Column chromatography with 1:1 cyclohexane–AcOEt afforded **15b** (182 mg, 75%) as a white foam. $[\alpha]_D$=+2.8 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3600–3300 (br), 2900, 1730, 1700, 1690. ^{1}H NMR: δ 7.40–7.26 (m, 5H, Ph), 5.17 (s, 2H, PhCH_2), 3.85 (dd, 1H, $J_{1'a,2'}$=4.5 Hz, $J_{1'b,2'}$=11.0 Hz, H-2′), 3.24 (dd, 1H, $J_{1'a,1'b}$=13.8 Hz, H-1′a), 2.84 (dd, 1H, H-1′b), 2.53 (s, 6H, 2CH_3), 1.57 (s, 18H, 2*t*-Bu), 1.56 (bs, 2H, N′H_2). ^{13}C NMR: δ 174.4, 167.6, 154.6, 154.5, 140.6, 135.4, 128.9, 128.5, 128.4, 128.3, 128.2, 83.3, 66.9, 54.8, 35.4, 28.0, 22.9. MALDI-TOF MS: 485.6 (M^++H), 507.7 (M^++Na), 523.8 (M^++K). Anal. calcd for $C_{27}H_{36}N_2O_6$ (484.58): C, 66.92; H, 7.49; N, 5.78. Found: C, 66.90; H, 7.48; N, 5.75.

3.4.3. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b). Column chromatography with AcOEt afforded **18b** (175 mg, 70%) as a white foam. $[\alpha]_D$=+1.1 (*c* 1.1, CH_3OH); IR (Nujol) ν_{max}: 3700–3200 (br), 2900, 1730, 1710, 1250. ^{1}H NMR: δ 7.40–7.25 (m, 5H, Ph), 5.17 (s, 2H, PhCH_2), 3.84 (dd, 1H, $J_{1'a,2'}$=4.7 Hz, $J_{1'b,2'}$=11.0 Hz, H-2′), 3.16 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 2.79 (dd, 1H, H-1′b), 2.50 (s, 6H, 2CH_3), 1.59 (s, 20H, 2*t*-Bu, N′H_2). ^{13}C NMR: δ 174.3, 165.2, 146.4, 135.3, 132.3, 128.6, 128.5, 128.4, 128.3, 127.3, 84.5, 67.1, 54.8, 35.1, 28.0, 15.8. MALDI-TOF MS: 501.8 (M^++H), 522.7

(M^++Na), 539.3 (M^++K). Anal. calcd for $C_{27}H_{36}N_2O_7$ (500.58): C, 64.78; H, 7.25; N, 5.60. Found: C, 64.80; H, 7.24; N, 5.56.

3.4.4. (2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b). Column chromatography with 1:1 cyclohexane–AcOEt (containing 1% of Et_3N) afforded **29b** (205 mg, 75%) as a white foam. $[\alpha]_D$=−4.2 (*c* 0.7, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3300 (br), 2900, 1730, 1700, 1690. ^{1}H NMR: δ 7.40–7.25 (m, 10H, 2Ph), 5.20 (s, 2H, PhCH_2), 4.14 (bdd, 1H, $J_{1'a,2'}$=4.2 Hz, $J_{1'b,2'}$=7.8 Hz, H-2′), 3.38 (dd, 1H, $J_{1'a,1'b}$=15.0 Hz, H-1′a), 3.22 (dd, 1H, H-1′b), 2.53 (s, 3H, CH_3), 2.05 (bs, 2H, N′H_2), 1.20 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{13}C NMR: δ 174.7, 166.7, 166.5, 154.4, 153.7, 145.4, 136.3, 135.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 82.6, 82.4, 66.8, 53.7, 39.2, 27.5, 27.4, 22.6. MALDI-TOF MS: 547.9 (M^++H), 569.6 (M^++Na), 585.7 (M^++K). Anal. calcd for $C_{32}H_{38}N_2O_6$ (546.65): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.35; H, 7.08; N, 5.17.

3.4.5. (2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b). Column chromatography with AcOEt (containing 1% of Et_3N) afforded **32b** (197 mg, 70%) as a white foam. $[\alpha]_D$=+21.9 (*c* 0.7, CH_3OH); IR (Nujol) ν_{max}: 3650–3200 (br), 2900, 1730, 1710, 1250. ^{1}H NMR: δ 7.40–7.20 (m, 10H, 2Ph), 5.23 and 5.15 (2d, 2H, *J*=12.0 Hz, PhCH_2), 4.41 (bdd, 1H, $J_{1'a,2'}$=5.7 Hz, $J_{1'b,2'}$= 9.0 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$=13.0 Hz, H-1′a), 3.27 (dd, 1H, H-1′b), 2.54 (s, 3H, CH_3), 1.76 (bs, 2H, N′H_2), 1.20 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{13}C NMR: δ 174.9, 165.4, 146.3, 145.6, 135.6, 132.6, 132.4, 129.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 83.8, 83.5, 66.9, 51.6, 34.5, 27.4, 27.3, 15.6. MALDI-TOF MS: 563.7 (M^++H), 585.4 (M^++Na), 601.6 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_9$ (562.65): C, 68.31; H, 6.81; N, 4.98. Found: C, 68.35; H, 6.88; N, 4.97.

3.4.6. (4*S*,2′*S*)- and (4*R*,2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl esters ((4*S*)-27a and (4*R*)-27a). To a cooled (0 °C), stirred solution of **25a** (0.50 mmol) contaminated by **26** (0.17 mmol) in CH_2Cl_2 (1 mL) was slowly added a solution of TFA–CH_2Cl_2 (1–3 mL). Stirring was continued at 0 °C for 1 h, then the solution was neutralized at 0 °C with Et_3N, concentrated, and eluted from a column of silica gel with 1:1.5 cyclohexane–AcOEt to give the diastereomeric amino esters (4*S*)-**27a** and (4*R*)-**27a** (185 mg, 75%) in 1:1 ratio.

Analytical samples of each diastereoisomer were obtained by preparative TLC (1:2 cyclohexane–AcOEt containing 1% of Et_3N). Eluted first was (4*S*)-**27a**. $[\alpha]_D$=+9.2 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730. ^{1}H NMR: δ 8.61 (s, 1H, NH), 7.40–7.10 (m, 10H, 2Ph), 5.21 and 5.16 (2d, 2H, *J*=12.0 Hz, PhCH_2), 4.98 (s, 1H, H-4), 4.18–4.00 (m, 4H, 2CH_2CH$_3$), 3.88 (dd, 1H, $J_{1'a,2'}$=3.8 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$= 15.2 Hz, H-1′a), 3.03 (dd, 1H, H-1′b), 2.28 (s, 3H, CH_3), 1.73 (bs, 2H, N′H_2), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.21 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 174.1, 167.5, 167.4, 148.0, 144.5, 135.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.0, 104.5, 103.2, 67.3, 59.7, 59.5, 53.4, 39.6, 33.3, 19.3, 14.2, 14.1. MALDI-TOF MS: 493.3 (M^++H), 515.6 (M^++Na), 531.3 (M^++K). Anal. calcd for $C_{28}H_{32}N_2O_6$ (492.56): C, 68.28; H, 6.55; N, 5.69. Found: C, 68.25; H, 6.57; N, 5.62.

Eluted second was (4*R*)-**27a**. $[\alpha]_D$=+15.5 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730. ^{1}H NMR: δ 8.54 (s, 1H, NH), 7.40–7.10 (m, 10H, 2Ph), 5.19 and 5.08 (2d, 2H, *J*=12.0 Hz, PhCH_2), 5.00 (s, 1H, H-4), 4.16–3.98 (m, 4H, 2CH_2CH$_3$), 3.85 (dd, 1H, $J_{1'a,2'}$=3.5, $J_{1'b,2'}$=8.2 Hz, H-2′), 3.67 (dd, 1H, $J_{1'a,1'b}$=15.0 Hz, H-1′a), 2.85 (dd, 1H, H-1′b), 2.31 (s, 3H, CH_3), 1.77 (bs, 2H, N′H_2), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.19 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 174.1, 167.5, 167.4, 147.9, 144.5, 135.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.1, 104.5, 103.2, 67.3, 59.8, 59.6, 53.5, 39.7, 33.2, 19.5, 14.2, 14.1. MALDI-TOF MS: 493.5 (M^++H), 515.6 (M^++Na), 531.3 (M^++K). Anal. calcd for $C_{28}H_{32}N_2O_6$ (492.56): C, 68.28; H, 6.55; N, 5.69. Found: C, 68.22; H, 6.53; N, 5.66.

3.5. General procedure for debenzylation of amino esters 11a, 14b, 17b, 28b and 31b

A vigorously stirred mixture of 20% palladium hydroxide on carbon (50 w/w of substrate), AcOEt (2 mL), and EtOH (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. To this mixture was added a solution of amino benzyl ester (0.30 mmol) in AcOEt (2 mL) previously degassed and saturated with hydrogen as described before. After the solution was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 15 min, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL). The combined filtrates were concentrated to give the corresponding amino acid in almost quantitative yield.

3.5.1. (2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (13a). White foam. $[\alpha]_D$=+28.0 (*c* 1.1, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1650. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.41 (bs, 1H, NH), 5.75 (bd, 1H, $J_{2',NH}$=8.1 Hz, N′H), 4.14 (q, 2H, *J*=7.0 Hz, CH_2CH$_3$), 4.12 (q, 2H, *J*=7.0 Hz, CH_2CH$_3$), 3.94 (dd, 1H, $J_{4,1'a}$=6.6 Hz, $J_{4,1'b}$=5.4 Hz, H-4), 3.92 (dd, 1H, $J_{1'a,2'}$=4.4 Hz, $J_{1'b,2'}$=8.6 Hz, H-2′), 2.24 (s, 6H, 2CH$_3$), 1.71 (ddd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 1.50 (ddd, 1H, H-1′b), 1.41 (s, 9H, *t*-Bu), 1.27 (t, 3H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3). MALDI-TOF MS: 441.8 (M^++H), 463.7 (M^++Na), 479.5 (M^++K). Anal. calcd for $C_{21}H_{32}N_2O_8$ (440.49): C, 57.26; H, 7.32; N, 6.36. Found: C, 57.31; H, 7.34; N, 6.35.

3.5.2. (2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (19b). White foam. $[\alpha]_D$=−11.3 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1250. ^{1}H NMR (DMSO-d_6, 120 °C): δ 5.84 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 4.28 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=10.5 Hz, H-2′), 3.22 (dd, 1H, $J_{1'a,1'b}$=14.4 Hz,

H-1′a), 2.75 (dd, 1H, H-1′b), 2.42 (s, 6H, $2CH_3$), 1.63 (s, 18H, 2*t*-Bu), 1.30 (s, 9H, *t*-Bu). MALDI-TOF MS: 511.4 (M^++H), 533.7 (M^++Na), 549.5 (M^++K). Anal. calcd for $C_{25}H_{38}N_2O_9$ (510.58): C, 58.81; H, 7.50; N, 5.49. Found: C, 58.86; H, 7.46; N, 5.53.

3.5.3. (2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-2′-carboxyethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (33b). White foam. $[\alpha]_D$= −10.3 (*c* 0.8, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1680, 1250. ^{1}H NMR (DMSO-d_6, 120 °C) δ: 7.50–7.40 and 7.30–7.20 (2m, 5H, Ph), 6.17 (bd, 1H, *J*=7.1 Hz, N′H), 4.66 (ddd, 1H, $J_{1'a,2'}$=4.9, $J_{1'b,2'}$= 11.5 Hz, H-2′), 3.45 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.19 (dd, 1H, H-1′b), 2.46 (s, 3H, CH_3), 1.32 (s, 9H, *t*-Bu), 1.22 (s, 18H, 2*t*-Bu). MALDI-TOF MS: 573.5 (M^++H), 595.9 (M^++Na), 611.6 (M^++K). Anal. calcd for $C_{30}H_{40}N_2O_9$ (572.65): C, 62.92; H, 7.04; N, 4.89. Found: C, 62.95; H, 7.08; N, 4.85.

3.5.4. (4*R*,2′*S*)- and (4*S*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl esters (debenzylated 25a). A vigorously stirred mixture of 20% palladium hydroxide on carbon (90 mg), AcOEt (2 mL), and EtOH (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. To this mixture was added a solution of **25a** (0.30 mmol) contaminated by **26** (0.10 mmol) in AcOEt (2 mL) previously degassed and saturated with hydrogen as described before. After the solution was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 15 min, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL). The combined filtrates were concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane–AcOEt (containing 1% of AcOH) to give debenzylated **25a** (148 mg, 98%) as a white foam. IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1650. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.36 (bs, 0.5H, NH), 8.21 (bs, 0.5H, NH), 7.25–7.05 (m, 5H, Ph), 6.24 (bd, 0.5H, $J_{2',NH}$=8.8 Hz, N′H), 6.15 (bd, 0.5H, $J_{2',NH}$=8.8 Hz, N′H), 4.97 (s, 0.5H, H-4), 4.96 (s, 0.5H, H-4), 4.50–4.34 (m, 1H, H-2′), 4.20–4.00 (m, 4H, $2CH_2CH_3$), 3.37 (dd, 0.5H, $J_{1'a,2'}$=5.1 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.22 (dd, 0.5H, $J_{1'a,2'}$=4.9 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′a), 2.99 (dd, 0.5H, $J_{1'b,2'}$=10.7 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′b), 2.74 (dd, 0.5H, $J_{1'b,2'}$=10.8 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′b), 2.28 (s, 1.5H, CH_3), 2.26 (s, 1.5H, CH_3), 1.40 (s, 4.5H, *t*-Bu), 1.37 (s, 4.5H, *t*-Bu), 1.21–1.14 (m, 6H, $2CH_2CH_3$). MALDI-TOF MS: 503.7 (M^++H), 525.8 (M^++Na), 541.3 (M^++K). Anal. Calcd for $C_{26}H_{34}N_2O_8$ (502.56): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.15; H, 6.88; N, 5.52.

3.6. General procedure for Mosher amides formation

To a stirred solution of amino ester (0.10 mmol) in anhydrous CH_2Cl_2 (1 mL) were added either (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (29 mg, 0.12 mmol), 1,3-dicyclohexylcarbodiimide (25 mg, 0.12 mmol), and a catalytic amount of 4-*N*,*N*-(dimethylamino)pyridine. The mixture was stirred for an additional 12 h at room temperature then concentrated. The residue was taken into AcOEt, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC affording the corresponding Mosher amide in almost quantitative yield.

3.6.1. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a (*S*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.81 (d, 1H, $J_{2',NH}$= 7.5 Hz, N′H), 7.70–7.65 and 7.42–7.30 (m, 10H, 2Ph), 5.71 (bs, 1H, NH), 5.16 and 5.10 (2d, 2H, *J*=12.0 Hz, $PhCH_2$), 4.56 (ddd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 4.20–4.05 (m, 4H, $2CH_2CH_3$), 3.95 (dd, 1H, $J_{4,1'a}$=6.5 Hz, $J_{4,1'b}$=5.0 Hz, H-4), 3.56 (q, 3H, *J*=0.7 Hz, OCH_3), 2.20 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.95 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.84 (ddd, 1H, H-1′b), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.18 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.3. Anal. calcd for $C_{33}H_{37}F_3N_2O_8$ (646.65): C, 61.29; H, 5.77; N, 4.33. Found: C, 61.30; H, 5.77; N, 4.33.

3.6.2. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a (*R*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.89 (bd, 1H, $J_{2',NH}$= 7.2 Hz, N′H), 7.65–7.60 and 7.42–7.20 (m, 10H, 2Ph), 5.78 (s, 1H, NH), 5.11 and 5.06 (2d, 2H, *J*=12.2 Hz, $PhCH_2$), 4.69 (ddd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 4.26–4.09 (m, 4H, $2CH_2CH_3$), 4.07 (dd, 1H, $J_{4,1'a}$=6.2 Hz, $J_{4,1'b}$=5.2 Hz, H-4), 3.50 (q, 3H, *J*=0.7 Hz, OCH_3), 2.31 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.00 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.85 (ddd, 1H, H-1′b), 1.28 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.23 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.5. Anal. calcd for $C_{33}H_{37}F_3N_2O_8$ (646.65): C, 61.29; H, 5.77; N, 4.33. Found: C, 61.27; H, 5.74; N, 4.33.

3.6.3. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b (*S*)-Mosher amide). Elution system: 3.5:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.28 (d, 1H, $J_{2',NH}$= 8.3 Hz, N′H), 7.40–7.00 (m, 10H, 2Ph), 5.21 (s, 2H, $PhCH_2$), 5.06 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=12.9 Hz, H-2′), 3.54 (dd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 3.50 (q, 3H, *J*=0.7 Hz, OCH_3), 2.70 (dd, 1H, H-1′b), 2.40 (s, 6H, $2CH_3$), 1.59 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −69.9. Anal. calcd for $C_{37}H_{43}N_2F_3O_8$ (700.74): C, 63.42; H, 6.19; N, 4.00. Found: C, 63.41; H, 6.16; N, 4.07.

3.6.4. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.23 (d, 1H, $J_{2',NH}$= 7.6 Hz, N′H), 7.60–7.25 (m, 10H, 2Ph), 5.22 and 5.16 (2d, 2H, *J*=12.2 Hz, $PhCH_2$), 5.04 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=12.7 Hz, H-2′), 3.57 (dd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 3.04 (q, 3H, *J*=0.7 Hz, OCH_3), 2.80 (dd, 1H, H-1′b), 2.56 (s, 6H, $2CH_3$), 1.56 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −70.3. Anal. calcd for $C_{37}H_{43}N_2F_3O_8$ (700.74): C, 63.42; H, 6.19; N, 4.00. Found: C, 63.40; H, 6.18; N, 4.05.

3.6.5. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b (*S*)-Mosher amide). Elution system: 1:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.99 (d, 1H, $J_{2',NH}$=8.5 Hz, N′H), 7.40–7.00 (m, 10H, 2Ph), 5.22 (s, 2H, PhCH_2), 5.07 (ddd, 1H, $J_{1'a,2'}$=5.5 Hz, $J_{1'b,2'}$=12.8 Hz, H-2′), 3.58 (q, 3H, J=0.7 Hz, OCH_3), 3.45 (dd, 1H, $J_{1'a,1'b}$=14.2 Hz, H-1′a), 2.57 (dd, 1H, H-1′b), 2.34 (s, 6H, 2CH_3), 1.60 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −69.9. Anal. calcd for $C_{37}H_{43}F_3N_2O_9$ (716.74): C, 62.00; H, 6.05; N, 3.91. Found: C, 61.97; H, 6.02; N, 3.93.

3.6.6. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b (*R*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.23 (d, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.60–7.25 (m, 10H, 2Ph), 5.21 and 5.16 (2d, 2H, J=12.0 Hz, PhCH_2), 5.05 (ddd, 1H, $J_{1'a,2'}$=5.7 Hz, $J_{1'b,2'}$=12.3 Hz, H-2′), 3.47 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.13 (q, 3H, J=0.7 Hz, OCH_3), 2.77 (dd, 1H, H-1′b), 2.54 (s, 6H, 2CH_3), 1.57 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −70.4. Anal. calcd for $C_{37}H_{43}F_3N_2O_9$ (716.74): C, 62.00; H, 6.05; N, 3.91. Found: C, 61.94; H, 6.06; N, 3.95.

3.6.7. (4*R*,2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester ((4*R*)-27a (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.12 (d, 1H, $J_{2',NH}$=6.5 Hz, N′H), 7.50–7.10 (m, 15H, 3Ph), 6.43 (s, 1H, NH), 5.21 and 5.14 (2d, 2H, J=12.0 Hz, PhCH_2), 4.97 (s, 1H, H-4), 4.67 (dd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=6.7 Hz, H-2′), 4.20–3.95 (m, 4H, 2C$H_2$$CH_3$), 3.51 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.26 (q, 3H, J=0.7 Hz, OCH_3), 3.10 (dd, 1H, H-1′b), 2.24 (s, 3H, CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.18 (t, 3H, J=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.3. Anal. calcd for $C_{38}H_{39}F_3N_2O_8$ (708.72): C, 64.40; H, 5.55; N, 3.95. Found: C, 64.48; H, 5.52; N, 3.90.

3.6.8. (4*R*,2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester ((4*R*)-27a (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.30 (d, 1H, $J_{2',NH}$=6.2 Hz, N′H), 7.60–7.10 (m, 15H, 3Ph), 6.30 (s, 1H, NH), 5.20 and 5.10 (2d, 2H, J=12.1 Hz, PhCH_2), 4.99 (s, 1H, H-4), 4.68 (dd, 1H, $J_{1'a,2'}$=7.8 Hz, $J_{1'b,2'}$=6.0 Hz, H-2′), 4.16–3.98 (m, 4H, 2C$H_2$$CH_3$), 3.38 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.23 (dd, 1H, H-1′b), 3.08 (q, 3H, J=0.7 Hz, OCH_3), 2.28 (s, 3H, CH_3), 1.22 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.20 (t, 3H, J=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.1. Anal. calcd for $C_{38}H_{39}F_3N_2O_8$ (708.72): C, 64.40; H, 5.55; N, 3.95. Found: C, 64.45; H, 5.56; N, 3.93.

3.7. Crystallization from pentane afforded small crystals of this compound suitable for X-ray diffraction analysis

3.7.1. (2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.34 (d, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.60–7.20 (m, 15H, 3Ph), 5.22 and 5.17 (2d, 2H, J=11.0 Hz, PhCH_2), 5.16 (ddd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=4.2 Hz, H-2′), 3.56 (q, 3H, J=0.7 Hz, OCH_3), 3.46 (dd, 1H, $J_{1'a,1'b}$=15.7 Hz, H-1′a), 3.34 (dd, 1H, H-1′b), 2.38 (s, 3H, CH_3), 1.23 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{19}F NMR: δ −69.4. Anal. Calcd for $C_{42}H_{45}F_3N_2O_8$ (762.81): C, 66.13; H, 5.95; N, 3.67. Found: C, 66.14; H, 5.96; N, 3.65.

3.7.2. (2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.77 (d, 1H, $J_{2',NH}$=8.2 Hz, N′H), 7.60–7.10 (m, 15H, 3Ph), 5.16 and 5.12 (2d, 2H, J=12.4 Hz, PhCH_2), 5.13 (ddd, 1H, $J_{1'a,2'}$=6.6 Hz, $J_{1'b,2'}$=4.1 Hz, H-2′), 3.57 (dd, 1H, $J_{1'a,1'b}$=16.2 Hz, H-1′a), 3.35 (dd, 1H, H-1′b), 3.29 (q, 3H, J=0.7 Hz, OCH_3), 2.44 (s, 3H, CH_3), 1.19 (s, 9H, *t*-Bu), 1.15 (s, 9H, *t*-Bu). ^{19}F NMR: δ −70.0. Anal. Calcd for $C_{42}H_{45}F_3N_2O_8$ (762.81): C, 66.13; H, 5.95; N, 3.67. Found: C, 66.16; H, 5.93; N, 3.67.

3.7.3. (2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.94 (d, 1H, $J_{2',NH}$=6.8 Hz, N′H), 7.50–7.20 (m, 15H, 3Ph), 5.27 and 5.21 (2d, 2H, J=12.0 Hz, PhCH_2), 5.15 (ddd, 1H, $J_{1'a,2'}$=12.2 Hz, $J_{1'b,2'}$=4.5 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.64 (q, 3H, J=0.7 Hz, OCH_3),3.26 (dd, 1H, H-1′b), 2.08 (s, 3H, CH_3), 1.24 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu). ^{19}F NMR: δ −69.7. Anal. calcd for $C_{42}H_{45}F_3N_2O_9$ (778.81): C, 64.77; H, 5.82; N, 3.60. Found: C, 64.76; H, 5.83; N, 3.65.

3.7.4. (2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 9.27 (d, 1H, $J_{2',NH}$=6.8 Hz, N′H), 7.65–7.25 (m, 15H, 3Ph), 5.21 (2d, 2H, PhCH_2), 5.11 (ddd, 1H, $J_{1'a,2'}$=11.2, $J_{1'b,2'}$=4.8 Hz, H-2′), 3.80 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.44 (dd, 1H, H-1′b), 3.29 (q, 3H, J=0.7 Hz, OCH_3), 2.56 (s, 3H, CH_3), 1.21 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{19}F NMR: δ −70.6. Anal. calcd for $C_{42}H_{45}F_3N_2O_9$ (778.81): C, 64.77; H, 5.82; N, 3.60. Found: C, 64.78; H, 5.84; N, 3.61.

3.7.5. (2′*S*,2″*S*,1″*S*)-4-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (21). To a cooled (0 °C), stirred solution of amino acid **13a** (88 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O

(2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-4-[2′-*tert*-Butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester **20** (96 mg, 80%) as a white foam. $[\alpha]_D$=+26.0 (*c* 0.9, acetone). ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.37 (s, 1H, NH), 7.41 (bd, 1H, $J_{1',NH}$=7.5 Hz, N″H), 7.30–7.10 (m, 5H, Ph), 5.81 (bd, 1H, J=7.0 Hz, N′H), 4.57 (ddd, 1H, $J_{1'',2''a}$=6.0 Hz, $J_{1'',2''b}$=7.5 Hz, H-1″), 4.20–4.05 (m, 4H, 2CH_2CH$_3$), 3.90–3.75 (m, 2H, H-2′, H-4), 3.60 (s, 3H, OCH$_3$), 3.04 (dd, 1H, $J_{2''a,2''b}$=13.8 Hz, H-2″a), 2.94 (dd, 1H, H-2″b), 2.25 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 1.60–1.30 (m, 11H, 2H-1′, *t*-Bu), 1.27 (t, 3H, J=7.0 Hz, CH$_2$CH_3), 1.23 (t, 3H, J=7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 602.5 (M^++H), 624.6 (M^++Na), 640.8 (M^++K). Anal. calcd for $C_{31}H_{43}N_3O_9$ (601.69): C, 61.88; H, 7.20; N, 6.98. Found: C, 61.82; H, 7.26; N, 6.96.

To a cooled (0 °C), stirred solution of the above dipeptide **20** (60 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (39 mg, ~78%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (39 mg, ~0.08 mmol), *tert*-butoxycarbonyl-L-phenyl-alanine (32 mg, 0.12 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (73 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (40 μL, 0.23 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give tripeptide **21** (46 mg, 62% from **20**) as a white foam. $[\alpha]_D$=+28.0 (*c* 0.8, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 140 °C): δ 8.37 (s, 1H, NH), 7.40–7.00 (m, 12H, 2Ph, N′H, N‴H), 6.00 (d, 1H, $J_{2'',NH}$=8.5 Hz, N″H), 4.60 (ddd, 1H, $J_{1''',2'''a}$= 6.5 Hz, $J_{1''',2'''b}$=8.0 Hz, H-1‴), 4.30–4.05 (m, 6H, 2CH_2CH$_3$, H-2′, H-2″), 3.90 (dd, 1H, $J_{4,1'a}$=5.6 Hz, $J_{4,1'b}$=6.2 Hz, H-4), 3.60 (s, 3H, OCH$_3$), 3.09 (dd, 1H, $J_{2'',3''a}$=4.5 Hz, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 3.05 (dd, 1H, $J_{2''',2'''a}$=14.0 Hz, H-2‴a), 2.98 (dd, 1H, $J_{2'',3''b}$=6.8 Hz, H-3″b), 2.79 (dd, 1H, H-2‴b), 2.25 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 1.73 (ddd, 1H, $J_{1'a,2'}$=5.8 Hz, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.50 (ddd, 1H, $J_{1'b,2'}$=7.8 Hz, H-1′b), 1.34 (s, 9H, *t*-Bu), 1.26 (t, 3H, J=7.0 Hz, CH$_2$CH_3), 1.23 (t, 3H, J=7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 749.9 (M^++H), 771.3 (M^++Na), 787.9 (M^++K). Anal. calcd for $C_{40}H_{52}N_4O_{10}$ (748.86): C, 64.15; H, 7.00; N, 7.48. Found: C, 64.15; H, 7.02; N, 7.46.

3.7.6. (2′*S*,2″*S*,1″*S*)-4-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (23). To a cooled (0 °C), stirred solution of amino acid **19b** (102 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-4-[2′-*tert*-butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (121 mg, 90%) as a white foam. $[\alpha]_D$=−14.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 7.40–7.10 (m, 5H, Ph), 6.91 (bd, 1H, $J_{1'',NH}$=7.0 Hz, N″H), 5.97 (bd, 1H, $J_{2',NH}$=7.0 Hz, N′H), 4.85 (ddd, 1H, $J_{1'',2''a}$=5.8 Hz, $J_{1'',2''b}$=6.0 Hz, H-1″), 4.52 (bddd, 1H, $J_{1'a,2'}$=4.5 Hz, $J_{1'b,2'}$=13.0 Hz, H-2′), 3.70 (s, 3H, OCH$_3$), 3.26 (dd, 1H, $J_{1'a,1'b}$=14.5 Hz, H-1′a), 3.17 (dd, 1H, $J_{2''a,2''b}$=14.0 Hz, H-2″a), 3.09 (dd, 1H, H-2″b), 2.71 (bdd, 1H, H-1′b), 2.55 (s, 6H, 2CH$_3$), 1.63 (s, 18H, 2*t*-Bu), 1.35 (s, 9H, *t*-Bu). MALDI-TOF MS: 672.5 (M^++H), 694.8 (M^++Na), 710.5 (M^++K). Anal. Calcd for $C_{35}H_{49}N_3O_{10}$ (671.78): C, 62.58; H, 7.35; N, 6.26. Found: C, 62.55; H, 7.36; N, 6.26.

To a cooled (0 °C), stirred solution of the above dipeptide (67 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (40 mg, ~70%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (40 mg, ~0.07 mmol), *tert*-butoxycarbonyl-L-phenyl-alanine (29 mg, 0.11 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (68 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (37 μL, 0.21 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give tripeptide **23** (52 mg, 63% from the corresponding dipeptide) as a white foam. $[\alpha]_D$=−36.8 (*c* 1.0, acetone). ^{1}H NMR (DMSO-d_6, 120 °C) δ: 7.54 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.30–7.10 (m, 11H, 2Ph, N‴H), 6.17 (bd, 1H, $J_{2'',NH}$=7.0 Hz, N″H), 4.64–4.52 (m, 2H, H-2″, H-1‴), 4.18 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=4.5 Hz, H-2′), 3.58 (s, 3H, OCH$_3$), 3.15 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.06 (dd, 1H, $J_{1''',2'''a}$=6.0 Hz, $J_{2'''a,2'''b}$=14.0 Hz, H-2‴a), 2.99 (dd, 1H, $J_{1''',2'''b}$=7.0 Hz, H-2‴b), 2.92 (dd, 1H, $J_{2'',3''a}$=5.0 Hz, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 2.78 (dd, 1H, $J_{2'',3''b}$=2.2 Hz, H-3″b), 2.75 (dd, 1H, H-1′b), 2.40 (2 s, 6H, 2CH$_3$), 1.61

(s, 18H, 2*t*-Bu), 1.32 (s, 9H, *t*-Bu). MALDI-TOF MS: 672.5 (M^++H), 694.8 (M^++Na), 710.5 (M^++K). Anal. calcd for $C_{35}H_{49}N_3O_{10}$ (818.95): C, 64.53; H, 7.14; N, 6.84. Found: C, 64.56; H, 7.12; N, 6.89.

3.7.7. (2′*S*,2″*S*,1″*S*)-2-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (34). To a cooled (0 °C), stirred solution of amino acid **33b** (115 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-2-[2′-*tert*-Butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (132 mg, 90%) as a white foam. $[\alpha]_D$=+14.9 (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 7.50–7.10 (m, 11H, 2Ph, N″H), 6.59 (bd, 1H, N′H), 4.88 (ddd, 1H, $J_{1'',2''a}$=5.8 Hz, $J_{1'',2''b}$=6.5 Hz, $J_{1'',NH}$=7.0 Hz, H-1″), 4.70 (bddd, 1H, H-2′), 3.71 (s, 3H, OCH_3), 3.45–3.30 (m, 2H, 2H-1′), 3.21 (dd, 1H, $J_{2''a,2''b}$=13.5 Hz, H-2″a), 3.11 (dd, 1H, H-2″b), 2.59 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.20 (s, 18H, 2*t*-Bu). MALDI-TOF MS: 734.9 (M^++H), 756.4 (M^++Na), 772.5 (M^++K). Anal. calcd for $C_{40}H_{51}N_3O_{10}$ (733.85): C, 65.47; H, 7.00; N, 5.73. Found: C, 65.43; H, 7.08; N, 5.72.

To a cooled (0 °C), stirred solution of the above dipeptide (73 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (44 mg, ~70%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (44 mg, ~0.07 mmol), *tert*-butoxycarbonyl-L-phenylalanine (29 mg, 0.11 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (68 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (37 μL, 0.21 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1.5:1 cyclohexane–AcOEt to give tripeptide **34** (56 mg, 63% from the corresponding dipeptide) as a white foam. $[\alpha]_D$=−6.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C) δ: 8.28 and 7.62 (2bd, 2H, *J*=7.0 Hz, N′H, N‴H), 7.50–7.10 (m, 15H, 3Ph), 6.17 (bd, 1H, $J_{2'',NH}$=7.0 Hz, N″H), 4.80 (ddd, 1H, $J_{1''',2'''a}$=10.2 Hz, $J_{1''',2'''b}$=4.5 Hz, H-1‴), 4.60 (ddd, 1H, $J_{2'',3''a}$=6.0 Hz, $J_{2'',3''b}$=7.2 Hz, H-2″), 4.17 (ddd, 1H, $J_{1'a,2'}$=5.0 Hz, $J_{1'b,2'}$=8.5 Hz, H-2′), 3.62 (s, 3H, OCH_3), 3.38 (dd, 1H, $J_{2'''a,2'''b}$=13.5 Hz, H-2‴a), 3.19 (dd, 1H, H-2‴b), 3.11 (dd, 1H, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 3.02 (dd, 1H, H-3″b), 2.97 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 2.82 (dd, 1H, H-1′b), 2.48 (s, 3H, CH_3), 1.34 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.21 (s, 9H, *t*-Bu). MALDI-TOF MS: 882.3 (M^++H), 904.2 (M^++Na), 920.0 (M^++K). Anal. calcd for $C_{40}H_{51}N_3O_{10}$ (881.02): C, 66.80; H, 6.86; N, 6.36. Found: C, 66.83; H, 6.88; N, 6.86.

3.8. Polymer-assisted solution-phase synthesis of 11b and 25b

A screw-capped vial, containing a magnetic bar, was charged with aldehyde (0.50 mmol), β-ketoester (0.50 mmol), aminocrotonate **10b** (79 mg, 0.50 mmol), activated 4-Å powdered molecular sieves (50 mg) and *tert*-BuOH (2 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and Amberlyst 15 (400 mg) and Ambersep 900 OH (400 mg) were added. The suspension was shaken for 2 h then the polymers were filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and aminomethylated polystyrene (185 mg, 0.50 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was stirred for an additional 2 h then the polymer was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target DHP-alanine: **11b** (220 mg, 75%; purity: 95%); **25b** (243 mg, 75%; purity: 92%).

Purities were determined by ^{1}H NMR analysis of the reaction mixtures after work up.

3.9. Polymer-assisted solution-phase synthesis of 14b and 28b

A mixture of DHP **11b** or **25b** (0.50 mmol), pyridinium chlorochromate immobilized on silica gel[28] (1.88 g, ~1.50 mmol of a ~0.8 mmol g^{-1} resin) and anhydrous CH_2Cl_2 (7 mL) was stirred at room temperature for 24 h. Then, the immobilized reagent was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target pyridyl-alanine: **14b** (287 mg, 98%; purity: 95%); **28b** (317 mg, 98%; purity: 92%).

Purities were determined by ^{1}H NMR analysis of the reaction mixtures after work up.

3.10. Polymer-assisted solution-phase synthesis of 17b and 31b

A mixture of pyridine **14b** or **28b** (0.50 mmol), 3-chloroperoxybenzoic acid (345 mg, 2.00 mmol), and anhydrous CH_2Cl_2 (12 mL) was stirred at room temperature for 15 h,

then aminomethylated polystyrene (1.11 g, 3.00 mmol of a 2.7 mmol g^{-1} resin) was added in one portion. The suspension was stirred for an additional 2 h then the polymer was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target 1-oxido-pyridyl-alanine: **17b** (294 mg, 98%; purity: 95%); **31b** (325 mg, 98%; purity: 92%).

Purities were determined by ^1H NMR analysis of the reaction mixtures after work up.

3.11. Crystal data for compound ((4*R*)-27a (*R*)-Mosher amide)

$C_{38}H_{39}F_3N_2O_8$; monoclinic, space group $P2_1$, a=9.6979(5), b=10.8821(6), c=17.3140(11) Å, β=91.578(2)°, V=1826.5(2) Å^3, Z=2, Dc=1.289 g cm^{-3}. Intensity data collected with $\theta \leq 27.3°$; 7643 independent reflections measured; 4103 observed [$I(2\sigma(I)$]. Final R index=0.070 (observed reflections). The molecules in the crystal form intramolecular and intermolecular hydrogen bonds: N1′–H…O3 [N1′…O3=2.780(5) Å]; N1–H…O1 (1−x, y−1/2, 1−z) [N1…O1=2.918(6) Å].

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24. Foregoing studies aimed at finding suitable protective groups for the many functionalities displayed by the target class of dihydropyridyl-α-alanines demonstrated that the presence of ethyl ester groups at C3 and C5 positions of the DHP ring was crucial for the elaboration of the amino acid functionality. In fact, the presence of *tert*-butyl ester groups at the same ring positions caused the isolation of a complex reaction mixture during the N′-Boc removal (1:4 TFA–CH_2Cl_2, 0 (C, 1 h). The high reactivity of *tert*-butyl ester groups at C3 and C5 may be attributed to the strong conjugation with the adjacent carbon–carbon double bond of the enaminic system. This speculation is supported by the unreactivity under the above acidic conditions of *tert*-butyl ester groups installed at C3 and C5 of pyridyl and 1-oxido-pyridyl rings. For a discussion about this issue, see: (a) Goerlitzer, K.; Baltrusch, H. *J. Pharmazie* **2000**, *10*, 747–750. (b) Buckler, R. T.; Hartzler, H. E. *J. Med. Chem.* **1975**, *18*, 509–513.
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