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Model Studies toward the Synthesis of Dihydropyrimidinyl and Pyridyl α-Amino Acids via Three-Component Biginelli and Hantzsch Cyclocondensations

Alessandro Dondoni,*[,‡] Alessandro Massi,[‡] Erik Minghini,[‡] Simona Sabbatini,[‡] and Valerio Bertolasi[§]

Dipartimento di Chimica, Università di Ferrara, Via L. Borsari 46, 44100 Ferrara, Italy

adn@dns.unife.it

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A novel and versatile strategy for the synthesis of heterocyclic α-amino acids has been described. The use of components (aldehyde or *β*-ketoester) bearing a masked glycinyl moiety in Biginelli and Hantzsch cyclocondensations allowed access to the 4-dihydropyrimidinyl-α-glycines, 4-dihydropyrimidinyl-α-alanines, 4-pyridyl-α-alanines, and 2-pyridyl-α-alanines classes. Dihydropyrimidinyl-amino acids were obtained as a mixture of diastereoisomers due to the formation of the stereocenter at C4 of the dihydropyrimidinone ring. Individual stereoisomers were isolated as pure compounds and their structures were assigned with the aid of X-ray crystallography and chiroptical properties. The enantiomeric purity of a representative selection of the above amino acids was greater than 96% as verified by derivatization to the corresponding Mosher's amides and subsequent ^{1}H and ^{19}F NMR spectroscopy. Incorporation of the 4-pyridyl-α-alanine derivative into a peptide chain is also described.

Introduction

A growing interest has recently been focused on the synthesis of unnatural α-amino acids; their use in the fields of peptide and combinatorial chemistry as conformational constraints, molecular scaffolds, and chiral auxiliaries is related to the development of new leads in peptidic and nonpeptidic compounds.[1] The class of nonproteinogenic heterocyclic α-amino acids is of particular interest in this context due to their diverse range of chemical and biomedicinal applications not only as components of peptides[2] and peptide nucleic acids (PNAs)[3] but also as free amino acids[4] (e.g. the antitumor−antibiotic agent L-azatyrosine[4a]). A number of methods have been developed for the synthesis of heterocyclic α-amino acids; most of them are based on asymmetric hydrogenation of dehydroamino acid derivatives,[5] and coupling reactions of suitable functionalized heterocycles with chiral glycine[6] or alanine[7] equivalents. More versatile approaches appear where a range of heterocycles can be generated either by cyclocondensations of alkynyl ketone intermediates with bifunctional nucleophiles[8] or by a "ring switching" process.[9] Nevertheless, the potential of a combinatorial approach applicable to a parallel synthesis of analogue families of heterocyclic α-amino acids has not fully exploited so far.[8,10] Furthermore both (D)- and (L)-α-amino acids may have different properties and thus are required in homochiral form. For these reasons we report on the use of substrates **A** (aldehyde[11] or *β*-ketoester) bearing the *N*-Boc-2,2-dimethyl oxazolidine ring as components in Biginelli[12] and Hantzsch[13] cyclocondensations to access two different series of heterocyclic-

‡ Laboratorio di Chimica Organica.

§ Centro di Strutturistica Diffrattometrica. Address correspondence concerning crystallography to this author. Fax: +39 0532 240709. E-mail: m38@unife.it.

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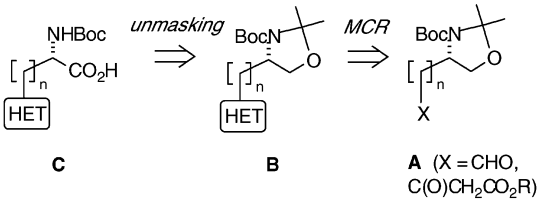


FIGURE 1. Synthetic strategy.

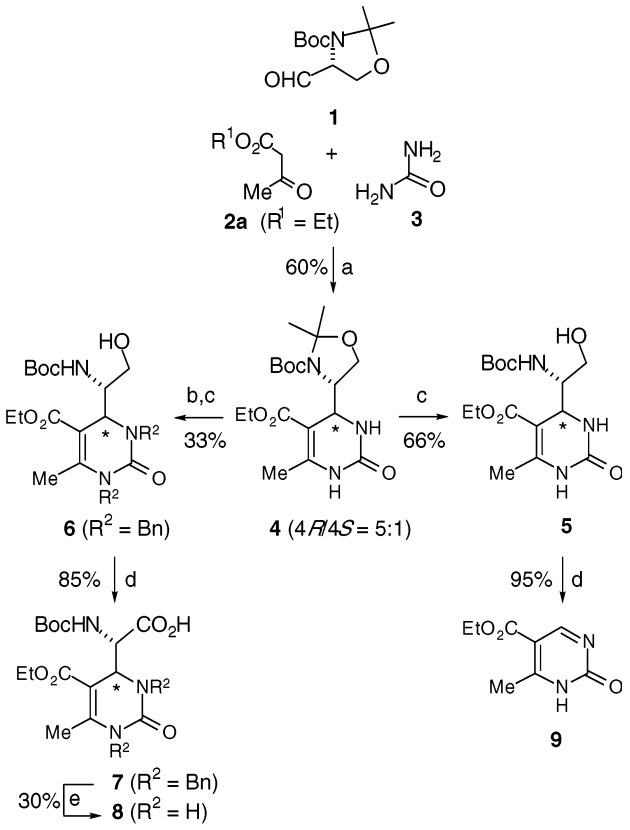
substituted α-amino acids, dihydropyrimidinyl (DHPM)- and pyridyl-α-amino acids (Figure 1). The advantages of this approach rely on exploiting both the potential of multicomponent reactions (MCRs) in generating molecular diversity and the existing configuration at the carbon bearing the amino group in components **A**. It has in fact been demonstrated that the *N*-Boc-2,2-dimethyl oxazolidine ring serves as a convenient masked glycinyl moiety maintaining unaltered the configuration of the stereocenter under a variety of reaction conditions.[14] We have planned to reveal it in the final step of our synthetic strategy to minimize potential racemization of intermediates. Therefore the unmasking protocol, which involves a ring opening-oxidation procedure,[14] should allow the conversion of cyclocondensation products **B** into the corresponding *N*-Boc protected amino acids **C**.

Results and Discussion

To validate this strategy, the synthesis of 4-dihydropyrimidinyl-α-glycine derivatives was chosen as the initial synthetic target for investigation. Thus the thermal, acid-catalyzed Biginelli cyclocondensation[12] of (*R*)-Garner aldehyde[15] **1** with ethyl acetoacetate **2a** and urea **3** was first considered (Scheme 1). Crucial to this step was finding a suitable acid promoter that would be tolerated by the sensitive aldehyde **1** under the harsh reaction conditions. Guided by our previous work on the synthesis of novel classes of DHPM derivatives,[16] we found the use of $Yb(OTf)_3$ to be quite beneficial. In the presence of this Lewis acid the above cyclocondensation (molecular sieves, THF, 70 °C, 14 h) afforded the 4-oxazolidinyl-dihydropyrimidinone **4** in fair yield (60%) as a 5:1 mixture of diastereoisomers due to the formation of the stereocenter at C4 of the DHPM ring.

Removal of the acetonide protective group under standard conditions ($AcOH-H_2O$) transformed **4** into the diastereomeric *N*′-Boc amino alcohols **5**. These C4 epimers

SCHEME 1. Synthesis of 4-DHPM-α-glycines[a]



[a] Reagents and conditions: (a) $Yb(OTf)_3$, 4-Å MS, THF, 70 °C, 14 h; (b) NaH, BnBr, DMF; (c) $AcOH-H_2O$ (5:1), rt; (d) 1 M Jones reagent, 0 °C to rt, 3 h; (e) H_2 (5 atm), $Pd(OH)_2$, AcOH−EtOH (1:1), rt, 7 d.

were separated chromatographically and, since we were unable to obtain crystalline samples suitable for X-ray analysis, their stereochemistry was assigned by using NMR analysis in conjunction with circular dichroism (CD) measurements. First, the enantiomeric excess of both (4*R*)-**5** and (4*S*)-**5** was established to be >96% via derivatization with Mosher's acid and ^1H and ^{19}F NMR analyses of the corresponding esters, thus indicating that the stereochemical integrity of aldehyde **1** has been retained during the cyclocondensation. Second, the (4*R*)-configuration of the major isomer was determined by comparing the CD spectra of each epimeric alcohol **5** with those of various 4-alkyl DHPMs of known absolute configuration.[16a,17a]The CD spectra of (4*R*)-**5** and (4*S*)-**5** appeared as mirror images and exhibited two bands of like sign at ca. 290 and 240 nm (Figure 2). The CD spectrum showing two negative Cotton effects was tentatively assigned to the (4*R*)-epimer in agreement with similar CD data of various 4-alkyl DHPMs.[16a,17a] Although the risk of deducing the absolute stereochemistry by direct comparison of CD spectra has been stressed by

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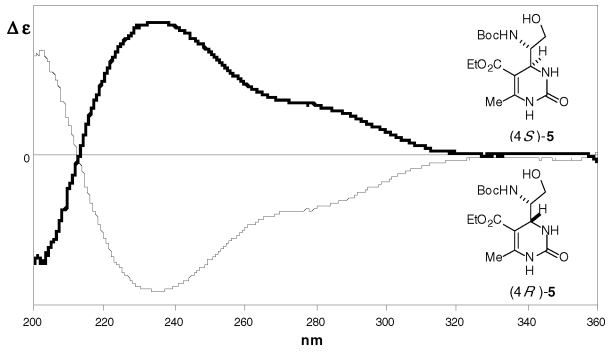


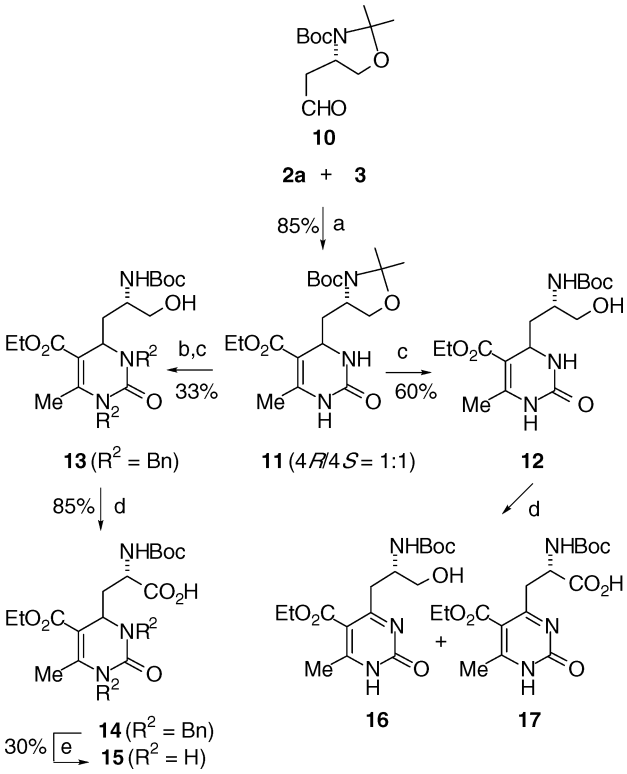
FIGURE 2. Experimental CD spectra of (4*S*)-**5** and (4*R*)-**5**.

several authors,[17b,c] this experimental approach has proved to be reliable so far for the determination of the C4 configuration of various biologically active DHMPs.[16a,17a]

To complete the unmasking of the latent glycinyl moiety, the use of several oxidative systems (TEMPO−BAIB, Jones reagent, and RuO_2−$NaIO_4$) was next considered for the conversion of *N*′-Boc amino alcohols **5** into the corresponding amino acids **8** (Scheme 1).[18] Under different reaction conditions (temperature and reaction time) the use of the above reagents led to the pyrimidinone **9** as a result of the side oxidation of the DHPM ring, which caused the loss of the 4-alkyl chain of **5**.[19] To overcome this difficulty, we envisioned that alkylation of the DHPM ring nitrogens could prevent the above side reaction and thereby selective oxidation of the alcohol to carboxylic acid could be accomplished. Accordingly, cycloadducts **4** were first benzylated under standard conditions (NaH, BnBr) and then subjected to removal of the acetonide group to give the *N*,*N*-dibenzylated DHPMs **6**.[20] The conversion of amino alcohols **6** into the corresponding *N*′-Boc amino acids **7** was then achieved in very good yield (85%) by using 1 M Jones reagent as the optimal oxidant.[21] While the introduction of different alkyl chains into the DHPM scaffold of **4** seems to be feasible by this strategy for increasing molecular diversity, the synthesis of unprotected DHPM-glycines of type **8** was instead investigated. Hydrogenation of derivatives **7** was found to proceed very slowly over 7 days (H_2, $Pd(OH)_2$, rt, 5 atm), affording amino acids **8** in moderate yield (30%).[22]

To diversify the methodology by varying the substitution at the DHPM 4 position, the above chemistry was

SCHEME 2. Synthesis of 4-DHPM-α-alanines[a]



[a] Reagents and conditions: see Scheme 1.

expanded to the use of aldehyde **10**,[23] the one-carbon-higher homologue of Garner aldehyde **1**. This would allow access to the important class of β-heterocyclic substituted α-alanines.[5,6a,8a] Under the previously reported conditions, the Biginelli cyclocondensation of aldehyde **10** with ethyl acetoacetate **2a** and urea **3** (Scheme 2) afforded the cyclocondensation product **11** (85%) as a mixture of two diastereoisomers in a 1:1 ratio. The separation of the isomers was carried out by preparative TLC.

The transformation of each epimeric **11** into the corresponding amino alcohol **12** by acetonide removal was then carried out for the stereochemical assignment by CD measurements of the newly created C4 stereocenter as previously described for amino alcohols **5**. Very similar CD spectra of the mirror-image type already reported in Figure 2 were also observed for the pair of epimers (4*S*)-**12** and (4*R*)-**12**. On the basis of the previously described experimental method,[17a] the (4*R*)-configuration was tentatively assigned to that epimer showing in its CD spectrum two positive Cotton effects (ca. 290 and 240 nm). It has to be noted that the assignment of the opposite configuration with respect to alcohols **5** is due to the different substituent priorities. The above structure assignment was then confirmed by the X-ray crystallographic analysis of cycloadduct (4*R*)-**11** (Figure 3),

(18) Conversion to amino acids **8** in two steps involving the formation of the corresponding amino aldehydes as intermediates (Swern oxidation then TEMPO-BAIB) disappointingly gave decomposed products.

(19) The oxidation of DHPM and dihydropyridine (DHP) derivatives is an issue that has been addressed by several authors. Dealkylation (in addition to aromatization) usually occurs when the DHPM and DHP rings bear a secondary alkyl group at the C4 position while dehydrogenation takes place in the presence of a primary alkyl group at the same position. This is a general trend in the oxidation of DHPMs and DHPs and it is explained by a sequence proceeding by a hydride abstraction in the first step. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Slavinskaya, V. A.; Duburs, G.; Sile, D.; Kreile, D.; Khanina, E. L. USSR Patent 632,695, 1978. (c) Eynde, J. J. V.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, *3*, 463. (d) Böcker, R. H.; Guengerich F. P. *J. Med. Chem.* **1986**, *29*, 1596.

(20) Each step occurred in fair yield (benzylation, 65%; hydrolysis, 50%) but after column chromatography it was possible to recover monobenzylated (benzylation step) and dibenzylated (hydrolysis step) derivatives of **4** that were reused in appropriate reactions of Scheme 1.

(21) One-step oxidative cleavage of the oxazolidine ring with the Jones reagent (see ref 14a,b) afforded the corresponding amino acid in lower overall yield.

(22) A different protection strategy based on selective N3 acylation (acetyl and pivaloyl groups) of cycloadducts **4** was also investigated to allow a higher yielding deprotection to **8**. Unfortunately, *N*,*O*-acyl migration occurred during acetonide removal of *N*-acyl cycloadducts affording undesired *O*-acyl derivatives of **5**.

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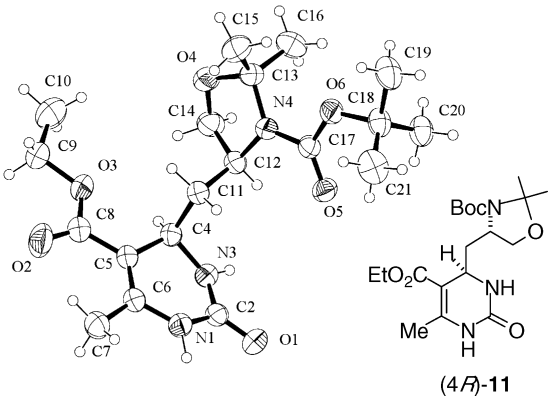


FIGURE 3. An ORTEP view of compound (4*R*)-**11** displaying the thermal ellipsoids at a 40% probability level.

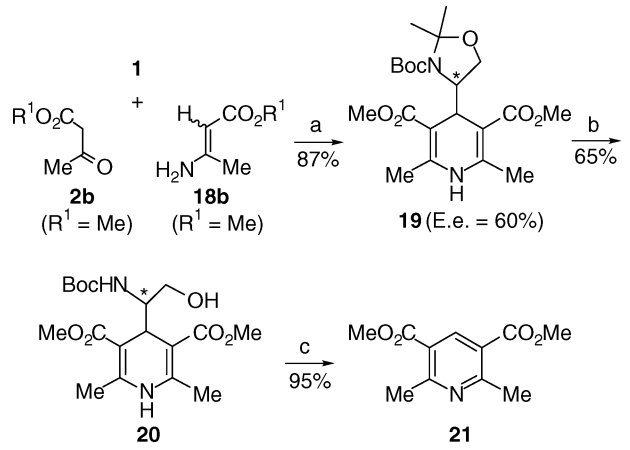
the precursor of alcohol (4*R*)-**12**. As in other known solid-state structures of 4-alkyl-DHPM derivatives,[16a,17a] the DHPM ring of (4*R*)-**11** is in a flattened boat conformation with N1 and C4 as apical atoms and the 4-alkyl substituent in the pseudoaxial position. It is worth pointing out that this evidence gratifyingly supported the assigned absolute configurations at C4 of alcohols **5** as deduced by CD measurements (Figure 2).

Also in this homologous series, direct conversion of **12** into the corresponding amino acids **15** failed due to a competitive oxidation of the DHPM ring affording a complex reaction mixture in which it was possible to identify the pyrimidinyl-amino alcohol **16** and the amino acid **17**.[19] Therefore the same reaction sequence, i.e., alkylation, deacetonization, oxidation, and hydrogenation, employed to transform **4** into **8** (see Scheme 1) was repeated starting from **11** to afford target 4-DHPM-α-alanine derivatives **14** and **15**.

The versatility of the MCR method was further investigated by varying the heterocyclic structure that functionalizes the amino acid moiety. Pyridyl-α-glycines and pyridyl-α-alanines,[4a,5c,6b,7d] which are among the most important series of unnatural amino acids, were the next classes of derivatives to be targeted. It is well-known that three-component Hantzsch cyclocondensation[13] of an aldehyde, a ketoester, and an enamine leads to dihydropyridyl (DHP) cycloadducts which readily undergo oxidation to the corresponding pyridyl derivatives by a number of reagents.[19c,d] In our synthetic strategy we thought that this transformation would take place during the oxidative unmasking of the glycinyl moiety. In an initial study we considered the cyclocondensation of (*R*)-Garner aldehyde **1** with methyl acetoacetate **2b** and methyl aminocrotonate **18b** (Scheme 3).

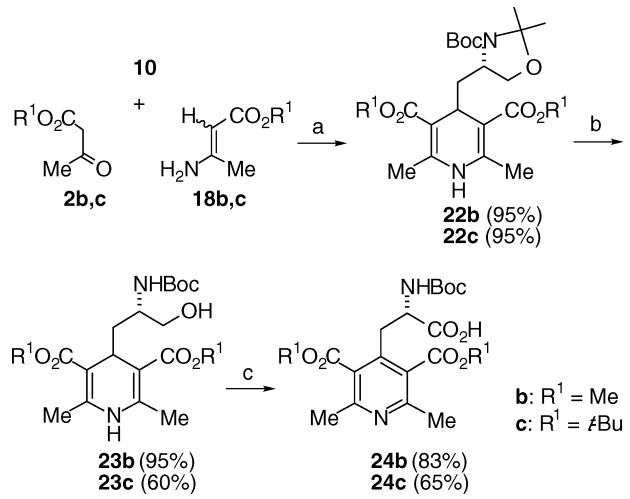
This reaction proceeded smoothly in MeOH at 70 °C (molecular sieves) and gave after 24 h the 4-oxazolidinyl-dihydropyridine **19** in very good yield (87%). Subsequent removal of the acetonide group afforded the amino alcohol **20**, which in turn was converted to the corresponding Mosher's esters for the determination of its enantiomeric purity. We were surprised to find that **20** was a 80:20 mixture of enantiomers, indicating that epimerization of the stereocenter of aldehyde **1** had taken place during the cyclocondensation. Mechanistically this result was intriguing but no further investigation was carried out at this stage since the next oxidative step proved fruitless

SCHEME 3. Abortive Synthesis of 4-Pyridyl-α-glycines[a]



[a] Reagents and conditions: (a) 4-Å MS, R^1OH, 70 °C, 24 h; (b) $AcOH-H_2O$ (5:1), rt, 24 h; (c) 1 M Jones reagent, 0 °C to rt, 3 h.

SCHEME 4. Synthesis of 4-Pyridyl-α-alanines[a]

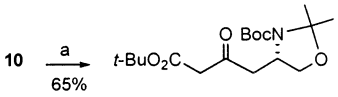


[a] Reagents and conditions: see Scheme 3.

as well. In fact, oxidation of alcohol **20** under different conditions (TEMPO–BAIB, Jones reagent, and RuO_2-NaIO_4) led to the pyridine byproduct **21**.[19] This result definitively precluded the use of our strategy for the synthesis of 4-pyridyl-α-glycine derivatives. In contrast, the approach to the class of 4-pyridyl-α-alanines by the above method turned out to be successful. Optimized Hantzsch cyclocondensation of the nonepimerizable aldehyde **10** with methyl acetoacetate **2b** and methyl aminocrotonate **18b** delivered the DHP-cycloadduct **22b** in almost quantitative yield (Scheme 4). Subsequent removal of the acetonide group followed by simultaneous oxidation (Jones reagent) of the hydroxy group and the DHP ring of amino alcohol intermediate **23b** gave the target 4-pyridyl-α-alanine derivative **24b** in 75% overall yield (3 steps).[21] The same reaction sequence carried out starting from **10**, *tert*-butyl acetoacetate **2c**, and *tert*-butyl aminocrotonate **18c** afforded the corresponding 4-pyridyl-α-alanine derivative **24c** in slightly lower overall yield (Scheme 4).

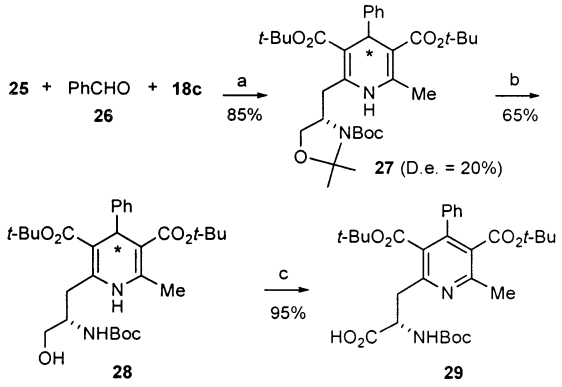
Next, in an attempt to diversify this methodology by installing the amino acid moiety at different heterocyclic

SCHEME 5[a]



[a] Reagents and conditions: (a) HC(N$_2$)CO$_2$*t*-Bu, BF$_3$·Et$_2$O, 4-Å MS, CH$_2$Cl$_2$, 0 °C, 30 min.

SCHEME 6. Synthesis of 2-Pyridyl-α-alanines[a]



[a] Reagents and conditions: (a) 4-Å MS, *t*-BuOH, 70 °C, 24 h; (b) AcOH−H$_2$O (5:1), rt, 24 h; (c) TEMPO−BAIB, rt, 3 h.

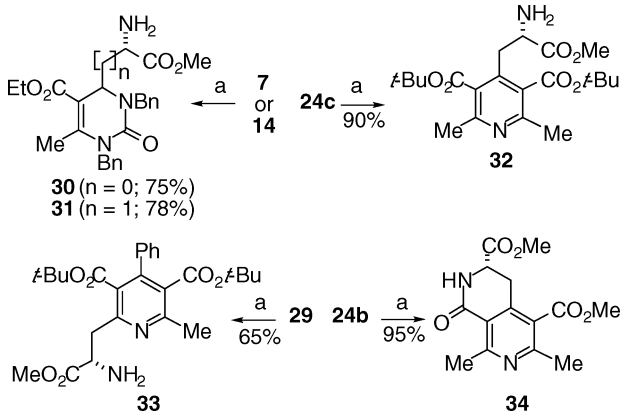
positions, it was decided to expand our strategy to the use of oxazolidinyl-functionalized *β*-ketoesters as components in Hantzsch cyclocondensation. The class of 2-pyridyl-α-alanines was chosen as a representative target for this study due to the pharmacological importance exhibited by some members of this family of heterocyclic α-amino acids (e.g. L-azatyrosine[4a,5c,6b]). To this aim, the hitherto unreported oxazolidinyl *β*-ketoester **25** was first prepared in satisfactory yield (65%) by BF$_3$·Et$_2$O promoted coupling of the corresponding aldehyde **10** with *tert*-butyl diazoacetate according to a literature procedure (Scheme 5). [24]

Hantzsch cyclocondensation of the oxazolidinyl ketoester **25** with benzaldehyde **26** and *tert*-butyl amino crotonate **18c** (molecular sieves, *t*-BuOH, 70 °C, 24 h) gave the DHP-cycloadduct **27** in good yield (85%) as a 1.5:1 mixture of diastereoisomers (Scheme 6). Subsequent acetonide removal led to amino alcohols **28** which in turn were readily oxidized (TEMPO−BAIB)[25] to the target 2-pyridyl-α-alanine derivative **29** in 52% overall yield (3 steps).

Having in hand the set of α-amino acids **7**, **8**, **14**, **15**, **24b**,**c**, and **29** we next determined their enantiomeric purity to verify that stereochemical integrity at α-carbon was retained not only during the cyclocondensation but also in the final oxidation step. Thus, selected amino acids **7**, **14**, **24c**, and **29** were first converted to the corresponding *N*′-deprotected amino esters **30**, **31**, **32**, and **33** (Scheme 7) by treatment with diazomethane followed by Boc deprotection (TFA−CH$_2$Cl$_2$). Subsequent derivatization with Mosher's acid and NMR analysis of the corresponding amides proved the enantiomeric purity of **7**, **14**, **24c**, and **29** to be greater than 96%.

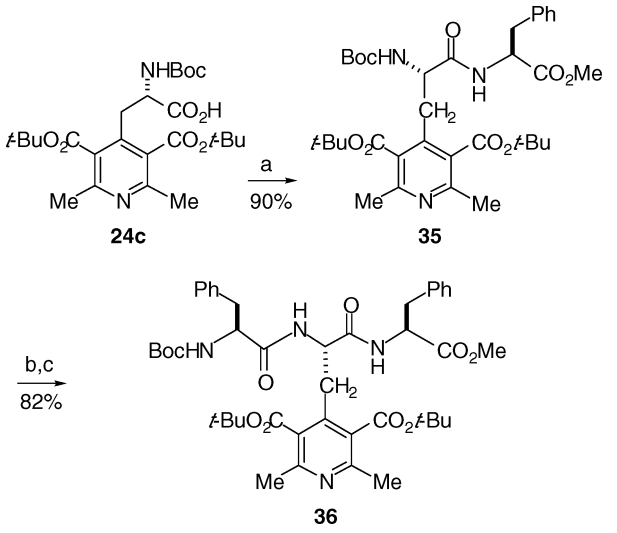
In the case of amino acid **24b** the same esterification−Boc deprotection sequence did not afford the corresponding free amine but gave the lactam **34** (Scheme 7) as a

SCHEME 7[a]



[a] Reagents and conditions: (a) CH$_2$N$_2$, CH$_2$Cl$_2$, 0 °C, 15 min; then TFA−CH$_2$Cl$_2$ (1:4), 0 °C to rt, 1 h.

SCHEME 8[a]



[a] Reagents and conditions: (a) H-Phe-OMe·HCl, PyBOP, DIEA, CH$_2$Cl$_2$, rt, 2 h; (b) TFA−CH$_2$Cl$_2$ (1:4), 0 °C to rt, 1 h; (c) Boc-Phe-OH, PyBOP, DIEA, CH$_2$Cl$_2$, rt, 2 h.

result of an intramolecular condensation of the unprotected amino group in the alanine moiety with a methyl ester function at C3 or C5 of the pyridine ring.

An expanded scope of this work was demonstrating that DHPM- and pyridyl-α-amino acids previously synthesized could be incorporated into a peptide chain. Amino acid **24c** bearing two bulky *tert*-butyl ester groups at the pyridine ring was chosen as a model. Coupling of **24c** with L-phenylalanine methyl ester hydrochloride (H−Phe-OMe·HCl), using PyBop as coupling reagent and DIEA in CH$_2$Cl$_2$, furnished the desired dipeptide **35** in 90% yield (Scheme 8). Extension from the *N*-terminus was next carried out. After Boc removal (TFA−CH$_2$Cl$_2$) in **35** the coupling reaction of the resulting free amine with *tert*-butoxycarbonyl-L-phenylalanine (Boc-Phe-OH), using PyBop and DIEA, afforded the target tripeptide **36** in 82% overall yield (two steps).

(24) Dhavale, D. D.; Bhujbal, N. N.; Joshi, P.; Desai, S. G. *Carbohydr. Res.* **1994**, *263*, 303.

(25) The use of the Jones reagent gave a lower yield (ca. 50%) of *N*′-Boc amino acid **29**.

In summary we described model studies culminating with the synthesis of various heterocyclic amino acid derivatives, i.e., 4-DHPM-α-glycines, 4-DHPM-α-alanines, 4-pyridyl-α-alanines, and 2-pyridyl-α-alanines. The approach that has been employed relies on the use of aldehydes **1** and **10** or *β*-ketoester **25** bearing a masked glycinyl moiety as components in Biginelli and Hantzsch MCRs. This strategy proved not to be viable for the synthesis of 4-pyridyl-α-glycines. Nevertheless, we believe this versatile method, applicable to parallel synthesis, to be of great value for the rapid generation of structurally related compound libraries. Highly functionalized amino acid derivatives have been obtained by this approach in a suitably protected form and thus are capable of incorporation into a peptide chain as demonstrated by the synthesis of tripeptide **36**. Further modifications of DHPM and pyridyl scaffolds by this strategy will be reported in due course.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere with 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. 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}. ^{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 with useof α-cyano-4-hydroxycinnamic acid as the matrix. CD measurements were carried out in a 0.1 cm path length cell with a volume of 350 μL at 20 °C with methanol as solvent. Spectra were recorded between 360 and 200 nm with 1-nm resolution at a scan speed of 10 nm/min and resulted from averaging two scans. The final spectra were baseline-corrected by subtracting the corresponding methanol spectrum obtained under identical conditions. Aldehydes **1**[15] and **10**[23] were synthesized as described. *tert*-Butyl 3-aminocrotonate **18c**[26] was prepared by reaction of the corresponding *β*-ketoester with ammonium acetate in refluxing *tert*-butyl alcohol. Pyridine **21** is a known compound.[19d]

General Procedure for Biginelli Cyclocondensations. A screw-capped vial, containing a magnetic bar, was charged with aldehyde **1** or **10** (2.00 mmol), ethyl acetoacetetate (255 μL, 2.00 mmol), urea (360 mg, 6.00 mmol), $Yb(OTf)_3$ (620 mg, 1.00 mmol), powdered 4-Å molecular sieves (200 mg), and anhydrous THF (5 mL). The mixture was stirred at 70 °C for 14 h then cooled to room temperature, diluted with AcOEt (100 mL), filtered through a pad of Celite, 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 the suitable elution system to give the corresponding dihydropyrimidinones.

(4*R*,4′*S*)- and (4*S*,4′*S*)-4-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyl-oxazolidin-4′-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (4). Column chromatography with 1:2 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **4** (460 mg, 60%) as a 5:1 mixture of (4*R*,4′*S*) and (4*S*,4′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): *δ* 8.59 (br s, 0.16 H, NH), 8.45 (br s, 0.84 H, NH), 6.78 (br s, 0.84 H, NH), 6.65 (br s, 0.16 H, NH), 4.51 (dd, 0.16 H, *J* = 4.5, 5.0 Hz, H-4), 4.40 (dd, 0.84 H, *J* = 4.5, 5.0 Hz, H-4), 4.20−3.80 (m, 5 H, H-1′, 2 H-2′, CH_2CH$_3$), 2.23 (s, 0.48 H, CH_3), 2.20 (s, 2.52 H, CH_3), 1.55 and 1.42 (2 s, 0.96 H, 2 C(CH_3)$_2$), 1.48 and 1.40 (2 s, 5.04 H, 2 C(CH_3)$_2$), 1.46 (s, 1.44 H, *t*-Bu), 1.44 (s, 7.56 H, *t*-Bu), 1.25 (t, 0.48 H, *J* = 7.0 Hz, CH$_2$CH_3), 1.24 (t, 2.52 H, *J* = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 406.4 (M^+ + Na), 422.2 (M^+ + K). Anal. Calcd for $C_{18}H_{29}N_3O_6$ (383.44): C, 56.38; H, 7.62; N, 10.96. Found: C, 56.36; H, 7.68; N, 10.91.

(4*R*,4″*S*)- and (4*S*,4″*S*)-4-(3″-*tert*-Butoxycarbonyl-2″,2″-dimethyl-oxazolidin-4″-ylmethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (11). Column chromatography with 1:2 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **11** (676 mg, 85%) as a 1:1 mixture of (4*R*,4"*S*) and (4*S*,4"*S*) diastereoisomers.

Analytical samples of each diastereoisomer were obtained by preparative TLC (15:1:0.1 CH_2Cl_2−*i*-PrOH−28% NH_4OH). Eluted first was (4*S*)-**11**. $[\alpha]_D$ −174 (*c* 0.4, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): *δ* 8.60 (br s, 1 H, NH), 6.70 (br s, 1 H, NH), 4.22−4.04 (m, 3 H, H-4, CH_2CH$_3$), 3.98−3.88 (m, 2 H, H-4″, H-5″a), 3.73−3.65 (m, 1 H, H-5″b), 2.21 (s, 3 H, CH_3), 1.95−1.80 and 1.70−1.50 (2 m, 2 H, 2 H-1′), 1.42 (s, 9 H, *t*-Bu), 1.21 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{19}H_{31}N_3O_6$ (397.47): C, 57.41; H, 7.86; N, 10.57. Found: C, 57.43; H, 7.82; N, 10.54.

Eluted second was (4*R*)-**11**. $[\alpha]_D$ 103.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): *δ* 8.58 (br s, 1 H, NH), 6.92 (br s, 1 H, NH), 4.24−4.00 (m, 2 H, CH_2CH$_3$), 4.08 (dd, 1 H, $J_{4'',5''a}$ = 8.0, $J_{5''a,5''b}$ = 9.5 Hz, H-5″a), 4.02 (dddd, 1 H, $J_{4'',5''b}$ = 2.8, $J_{1'a,4''}$ = 3.0, $J_{1'b,4''}$ = 4.0 Hz, H-4″), 3.91 (ddd, 1 H, $J_{4,1'a}$ = 1.5 Hz, $J_{4,NH}$ = 6.2 Hz, $J_{4,1'b}$ = 10.5 Hz, H-4), 3.78 (dd, 1 H, H-5″b), 2.21 (s, 3 H, CH_3), 1.96 (ddd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 1.56 (ddd, 1 H, H-1′b), 1.42 (s, 9 H, *t*-Bu), 1.24 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{19}H_{31}N_3O_6$ (397.47): C, 57.41; H, 7.86; N, 10.57. Found: C, 57.49; H, 7.81; N, 10.51.

Crystallization from AcOEt afforded small crystals of (4*R*)-**11** suitable for X-ray diffraction analysis.

The C4 configuration was also determined by converting each epimer **11** into the corresponding alcohol **12** and then performing their CD spectra.

General Procedure for Hantzsch Cyclocondensations Leading to Cycloadducts 19 and 22b,c. A screw-capped vial, containing a magnetic bar, was charged with aldehyde **1** or **10** (4.00 mmol), *β*-ketoester **2** (4.00 mmol), aminocrotonate **18** (4.00 mmol), powdered 4 Å molecular sieves (200 mg), and R^1OH (5 mL; MeOH for **2b**−**18b**, and *t*-BuOH for **2c**−**18c**). 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 90 °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 the suitable elution system to give the corresponding dihydropyridines.

(4′*S*)- and (4′*R*)-4-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyl-oxazolidin-4′-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Dimethyl Esters (19). Column chromatography with 2:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **19** (1.48 g, 87%) as a yellow foam. ^{1}H NMR (DMSO-d_6, 120 °C): *δ* 8.50 (br s, 1 H, NH), 4.32 (d, 1 H, $J_{4,4'}$ = 5.5 Hz, H-4), 3.80−3.68 (m, 3 H, H-4′, 2 H-5′), 3.63 and 3.61 (2 s, 6 H, 2 OCH_3), 2.25 and 2.23 (2 s, 6 H, 2 CH_3), 1.43 (s, 9 H, *t*-Bu), 1.41 and 1.37 (2 s, 6 H, 2 C(CH_3)$_2$). Anal. Calcd for $C_{21}H_{32}N_2O_7$ (424.49): C, 59.42; H, 7.60; N, 6.60. Found: C, 59.41; H, 7.67; N, 6.68.

(4″*S*)-4-(3″-*tert*-Butoxycarbonyl-2″,2″-dimethyl-oxazolidin-4″-ylmethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Dimethyl Ester (22b). Column chromatography with 2:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **22b** (1.67 g, 95%) as a yellow foam. $[\alpha]_D$ 16.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): *δ* 8.52 (br s, 1 H, NH), 3.91−3.67 (m, 4H, H-4, H-4″, 2 H-5″), 3.66 and 3.64 (2 s, 6 H, 2 OCH_3), 2.22 and 2.21 (2 s, 6 H, 2 CH_3), 1.72 (ddd, 1 H,

(26) Bagley, M. C.; Dale, J. W. Bower, J. *Synlett* **2001**, 1149.

J = 2.0, 12.0, 12.2 Hz, H-1′a), 1.43 and 1.38 (2 s, 6 H, 2 C(CH_3)$_2$), 1.38 (s, 9 H, *t*-Bu), 1.28 (ddd, 1 H, J = 3.5, 12.0, 12.5 Hz, H-1′b). Anal. Calcd for $C_{22}H_{34}N_2O_7$ (438.51): C, 60.26; H, 7.82; N, 6.39. Found: C, 60.20; H, 7.88; N, 6.31.

(4″*S*)-4-(3″-*tert*-Butoxycarbonyl-2″,2″-dimethyl-oxazolidin-4″-ylmethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (22c). Column chromatography with 4:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **22c** (1.99 g, 95%) as a yellow foam. $[\alpha]_D$ −24.3 (*c* 1.5, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.21 (br s, 1 H, NH), 3.92−3.81 (m, 2 H, 2 H-5″), 3.80−3.72 (m, 1 H, H-4″), 3.67 (dd, 1 H, $J_{4,1'a}$ = 4.0, $J_{4,1'b}$ = 9.5 Hz, H-4), 2.20 and 2.18 (2 s, 6 H, 2 CH_3), 1.70−1.50 and 1.40−1.20 (2 m, 2 H, 2 H-1′), 1.45 (s, 18 H, 2 *t*-Bu), 1.38 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{28}H_{46}N_2O_7$ (522.67): C, 64.34; H, 8.87; N, 5.36. Found: C, 64.24; H, 8.81; N, 5.34.

General Procedure for Di-*N*-benzylation of Dihydropyrimidinones 4 and 11. To a cooled (0 °C), stirred solution of cycloadduct **4** or **11** (2.00 mmol) in DMF (10 mL) was added NaH portionwise (192 mg, 4.80 mmol, of a 60% dispersion in oil) and, after 30 min, benzyl bromide (0.71 mL, 6.00 mmol). The mixture was stirred at 70 °C (room temperature for **11**) for 2 h, then treated with EtOH (1 mL), stirred at room temperature for an additional 30 min, diluted with H_2O (15 mL), and extracted with Et_2O (2 × 100 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 di-*N*-benzyl-dihydropyrimidinones.

(4*R*,4′*S*)- and (4*S*,4′*S*)-1,3-Di-*N*-benzyl-4-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyl-oxazolidin-4′-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (Bn-4). Column chromatography with 3:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **Bn-4** (732 mg, 65%) as a 5:1 mixture of (4*R*,4′*S*) and (4*S*,4′*S*) diastereoisomers. MALDI-TOF MS: 586.4 (M^+ + Na), 602.2 (M^+ + K). A mixture of recyclable monobenzylated derivatives (265 mg, 28%) was also isolated.

(4*R*,4″*S*)- and (4*S*,4″*S*)-1,3-Di-*N*-benzyl-4-(3″-*tert*-butoxycarbonyl-2″,2″-dimethyl-oxazolidin-4″-ylmethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (Bn-11). Column chromatography with 4:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) afforded **Bn-11** (692 mg, 60%) as a 1:1 mixture of (4*R*,4″*S*) and (4*S*,4″*S*) diastereoisomers. MALDI-TOF MS: 600.4 (M^+ + Na), 616.8 (M^+ + K). A mixture of recyclable monobenzylated derivatives (341 mg, 35%) was also isolated.

General Procedure for Acetonide Removal in Cycloadducts 4, Bn-4, 11, Bn-11, 19, 22b,c, and 27. A solution of DHPM- or DHP-cycloadduct (1.00 mmol) in acetic acid (7.5 mL) and H_2O (1.5 mL) was stirred at room temperature for 24−48 h then concentrated and eluted from a column of silica gel with the suitable elution system to give the corresponding amino alcohol derivatives.

(4*R*,1′*S*)- and (4*S*,1′*S*)-4-(1′-*tert*-Butoxycarbonylamino-2′-hydroxy-ethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (5). Column chromatography with 11:1:0.1 CH_2Cl_2−MeOH−28% NH_4OH afforded **5** (227 mg, 66%) as a 5:1 mixture of (4*R*,4′*S*) and (4*S*,4′*S*) diastereoisomers. Starting compound **4** (92 mg, 24%) was also isolated. Analytical samples of each epimeric **5** were obtained by preparative TLC (3:1:0.1 AcOEt−acetone−28% NH_4OH). Eluted first was (4*S*)-**5**. $[\alpha]_D$ 41 (*c* 0.2, MeOH). ^{1}H NMR (DMSO-d_6, 130 °C): δ 8.45 (br s, 1 H, NH), 6.50 (br s, 1 H, NH), 5.52 (br d, 1 H, $J_{1',NH}$ = 9.0 Hz, N′H), 4.26 (dd, 1 H, $J_{4,1'}$ = 3.8 Hz, $J_{4,NH}$ = 4.0 Hz, H-4), 4.20−3.90 (m, 3 H, OH, CH_2CH$_3$), 3.64−3.38 (m, 3 H, H-1′, 2 H-2′), 2.16 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{15}H_{25}N_3O_6$ (343.38): C, 52.47; H, 7.34; N, 12.24. Found: C, 52.48; H, 7.38; N, 12.25.

Eluted second was (4*R*)-**5**. $[\alpha]_D$ −53 (*c* 0.4, MeOH). ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.42 (br s, 1 H, NH), 6.38 (br s, 1 H, NH), 5.49 (br d, 1 H, $J_{1',NH}$ = 9.0 Hz, N′H), 4.36 (dd, 1 H, $J_{4,1'}$ = 3.8 Hz, $J_{4,NH}$ = 4.0 Hz, H-4), 4.21 (br t, 1 H, J = 6.0 Hz, OH), 4.13 (q, 2 H, J = 7.0 Hz, CH_2CH$_3$), 3.67 (dddd, 1 H, $J_{1',2'a}$ = 5.0 Hz, $J_{1',2'b}$ = 6.0 Hz, H-1′), 3.50 (dd, 1 H, $J_{2'a,2'b}$ = 11.5 Hz, H-2′a), 3.42 (dd, 1 H, H-2′b), 2.18 (s, 3 H, CH_3), 1.22 (t, 3 H, CH$_2$CH_3). Anal. Calcd for $C_{15}H_{25}N_3O_6$ (343.38): C, 52.47; H, 7.34; N, 12.24. Found: C, 52.41; H, 7.30; N, 12.30.

(4*R*,1′*S*)- and (4*S*,1′*S*)-1,3-Di-*N*-benzyl-4-(1′-*tert*-butoxycarbonylamino-2′-hydroxy-ethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (6). Column chromatography with 1:1 cyclohexane−AcOEt afforded **6** (262 mg, 50%) as a 5:1 mixture of (4*R*,1′*S*) and (4*S*,1′*S*) diastereoisomers.^{1}H NMR (DMSO-d_6, 120 °C): δ 7.40−7.10 (m, 10 H, 2 Ph), 6.08 (br d, 0.84 H, $J_{1',NH}$ = 9.0 Hz, N′H), 5.68 (br d, 0.16 H, $J_{1',NH}$ = 9.0 Hz, N′H), 5.18 and 4.27 (2 d, 2 H, J = 15.5 Hz, PhCH_2), 4.98 and 4.91 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.52 (d, 0.16 H, $J_{4,1'}$ = 6.5 Hz, H-4), 4.48 (d, 0.84 H, $J_{4,1'}$ = 6.8 Hz, H-4), 4.18 (br s, 1 H, OH), 4.12−4.00 (m, 2 H, CH_2CH$_3$), 3.82−3.71 (m, 1 H, H-1′), 3.46−3.38 (m, 2 H, 2 H-2′), 2.26 (s, 0.48 H, CH_3), 2.22 (s, 2.52 H, CH_3), 1.43 (s, 7.56 H, *t*-Bu), 1.39 (s, 1.44 H, *t*-Bu), 1.18 (t, 0.48 H, J = 7.0 Hz, CH$_2$CH_3), 1.17 (t, 2.52 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 524.4 (M^+ + H), 546.8 (M^+ + Na), 562.9 (M^+ + K). Anal. Calcd for $C_{29}H_{37}N_3O_6$ (523.62): C, 66.52; H, 7.12; N, 8.02. Found: C, 66.59; H, 7.18; N, 8.05. Starting compound **Bn-4** (253 mg, 45%) was also isolated.

(4*R*,2′*S*)- and (4*S*,2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-3′-hydroxy-propyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (12). Column chromatography with AcOEt (containing 1% of AcOH) afforded **12** (214 mg, 60%) as a 1:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.56 (br s, 0.5 H, NH), 8.48 (br s, 0.5 H, NH), 6.58 (br s, 0.5 H, NH), 6.50 (br s, 0.5 H, NH), 6.02 (br d, 0.5 H, J = 8.0 Hz, N′H), 5.85 (br d, 0.5 H, J = 8.0 Hz, N′H), 4.30−4.20 (m, 1 H, H-4), 4.19−4.02 (m, 3 H, OH, CH_2CH$_3$), 3.64−3.50 (m, 1 H, H-2′), 3.48−3.32 (m, 2 H, 2 H-3′), 2.01 (s, 1.5 H, CH_3), 2.00 (s, 1.5 H, CH_3), 1.77−1.16 (m, 2 H, 2 H-1′), 1.42 (s, 4.5 H, *t*-Bu), 1.41 (s, 4.5 H, *t*-Bu), 1.22 (t, 1.5 H, J = 7.0 Hz, CH$_2$CH_3), 1.21 (t, 1.5 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 380.3 (M^+ + Na), 396.3 (M^+ + K). Anal. Calcd for $C_{16}H_{27}N_3O_6$ (357.40): C, 53.77; H, 7.61; N, 11.76. Found: C, 53.79; H, 7.65; N, 11.71. Starting compound **11** (139 mg, 35%) was also isolated.

(4*R*,2′*S*)- and (4*S*,2′*S*)-1,3-Di-*N*-benzyl-4-(2′-*tert*-butoxycarbonylamino-3′-hydroxy-propyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (13). Column chromatography with 1:1 cyclohexane−AcOEt afforded **13** (296 mg, 55%) as a 1:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*) diastereoisomers.^{1}H NMR (DMSO-d_6, 120 °C): δ 7.40−7.10 (m, 10 H, 2 Ph), 5.95 (br d, 0.5 H, J = 8.0 Hz, N′H), 5.80 (br d, 0.5 H, J = 8.0 Hz, N′H), 5.16 and 4.22 (2 d, 1 H, J = 15.5 Hz, PhCH), 5.15 and 4.85 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 5.09 and 4.20 (2 d, 1 H, J = 15.0 Hz, PhCH), 4.44−3.20 (m, 1 H, H-4), 4.24−4.16 (m, 1 H, OH), 4.14−3.92 (m, 2 H, CH_2CH$_3$), 3.62−3.50 (m, 0.5 H, H-2′), 3.45−3.20 (m, 2.5 H, H-2′, 2 H-3′), 2.30 (s, 1.5 H, CH_3), 2.28 (s, 1.5 H, CH_3), 1.98−1.68 and 1.65−1.40 (2 m, 2 H, 2 H-1′), 1.42 (s, 4.5 H, *t*-Bu), 1.41 (s, 4.5 H, *t*-Bu), 1.20−1.10 (m, 3 H, CH$_2$CH_3). MALDI-TOF MS: 537.6 (M^+), 560.4 (M^+ + Na), 576.8 (M^+ + K). Anal. Calcd for $C_{30}H_{39}N_3O_6$ (537.65): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.09; H, 7.38; N, 7.87. Starting compound **Bn-11** (202 mg, 35%) was also isolated.

(1′*S*)- and (1′*R*)-4-(1′-*tert*-Butoxycarbonylamino-2′-hydroxy-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Dimethyl Esters (20). Column chromatography with 1:1 cyclohexane−AcOEt afforded **20** (250 mg, 65%) as a white foam. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.58 (br s, 1 H, NH), 5.10 (br d, 1 H, $J_{1',NH}$ = 8.0 Hz, N′H), 3.95 (d, 1 H, $J_{4,1'}$ = 6.5 Hz, H-4), 3.74 (br t, 1 H, J = 5.0 Hz, OH), 3.65 and 3.64 (2 s, 6 H, 2 OCH_3), 3.40−3.20 (m, 3 H, H-1′, 2 H-2′), 2.21 (s, 6 H, 2 CH_3), 1.38 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{18}H_{28}N_2O_7$ (384.42): C, 56.24; H, 7.34; N, 7.29. Found: C, 56.30; H, 7.31; N, 7.21.

(2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-3′-hydroxy-propyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Dimethyl Ester (23b). Column chromatography with 1:3 cyclohexane−AcOEt afforded **23b** (379 mg, 95%) as a white foam. $[\alpha]_D$ −8.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ 5.74 (br s, 1 H, NH), 5.04 (br d, 1 H, $J_{2',NH}$ = 5.5 Hz, N′H), 3.90 (br t, 1 H, *J* = 6.0 Hz, H-4), 3.75 and 3.74 (2 s, 6 H, 2 OCH_3), 3.70−3.50 (m, 3 H, H-2′, 2 H-3′), 3.25 (br s, 1 H, OH), 2.30 (s, 6 H, 2 CH_3), 1.65−1.40 (m, 2 H, 2 H-1′), 1.42 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{19}H_{30}N_2O_7$ (398.45): C, 57.27; H, 7.59; N, 7.03. Found: C, 57.35; H, 7.51; N, 7.08.

(2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-3′-hydroxy-propyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (23c). Column chromatography with 2:1 cyclohexane−AcOEt afforded **23c** (290 mg, 60%) as a white foam. $[\alpha]_D$ −14.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.18 (br s, 1 H, NH), 5.38 (br s, 1 H, N′H), 3.85 (br s, 1 H, OH), 3.77 (br t, 1 H, *J* = 6.5 Hz, H-4), 3.44−3.34 (m, 3 H, H-2′, 2 H-3′), 2.20 and 2.18 (2 s, 6 H, 2 CH_3), 1.50−1.38 and 1.35−1.18 (2 m, 2 H, 2 H-1′), 1.45 and 1.44 (2 s, 18 H, 2 *t*-Bu), 1.38 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{25}H_{42}N_2O_7$ (482.61): C, 62.22; H, 8.77; N, 5.80. Found: C, 62.28; H, 8.71; N, 5.83.

(4*R*,2′*S*)- and (4*S*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-3′-hydroxy-propyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Esters (28). Column chromatography with 1.5:1 cyclohexane−AcOEt afforded **28** (354 mg, 65%) as 1.5:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C) selected data: δ 7.85 (br s, 0.4 H, NH), 7.80 (br s, 0.6 H, NH), 7.40−7.00 (m, 5 H, Ph), 5.82 (br d, 0.6 H, $J_{2',NH}$ = 8.0 Hz, N′H), 5.62 (br d, 0.4 H, $J_{2',NH}$ = 8.0 Hz, N′H), 4.91 (s, 0.6 H, H-4), 4.89 (s, 0.4 H, H-4), 2.21 (s, 1.8 H, CH_3), 2.20 (s, 1.2 H, CH_3). MALDI-TOF MS: 546.0 (M^+ + H), 569,8 (M^+ + Na), 585.7 (M^+ + K). Anal. Calcd for $C_{30}H_{44}N_2O_7$ (544.68): C, 66.15; H, 8.14; N, 5.14. Found: C, 66.19; H, 8.12; N, 5.10.

General Procedure for Mosher Esters Formation. To a stirred solution of amino alcohol (4*R*)-**5** or **20** (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 ester in almost quantitative yield.

(4*R*,1′*S*,2″*R*)-4-[1′-*tert*-Butoxycarbonylamino-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionyloxy)-ethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*R*)-5 (*R*)-Mosher Ester). Elution system: 9:1:0.1 CH_2Cl_2−MeOH−28% NH_4OH. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.70 (br s, 1 H, NH), 7.60−7.40 (m, 5 H, Ph), 7.05 (br s, 1 H, NH), 6.07 (br d, 1 H, $J_{1',NH}$ = 10.0 Hz, N′H), 4.48 (dd, 1 H, $J_{1',2'a}$ = 4.0 Hz, $J_{2'a,2'b}$ = 11.5 Hz, H-2′a), 4.29 (dd, 1 H, $J_{1',2'b}$ = 8.5 Hz, H-2′b), 4.26 (dd, 1 H, $J_{4,1'}$ = 3.8 Hz, $J_{4,NH}$ = 4.0 Hz, H-4), 4.20−4.04 (m, 2 H, CH_2CH$_3$), 3.98 (dddd, 1 H, H-1′), 3.49 (q, 3 H, *J* = 0.7 Hz, OCH_3), 2.20 (s, 3 H, CH_3), 1.22 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). ^{19}F NMR (DMSO-d_6, 120 °C): δ −71.7. Anal. Calcd for $C_{25}H_{32}F_3N_3O_8$ (559.53): C, 53.66; H, 5.76; N, 7.51. Found: C, 53.60; H, 5.71; N, 7.58.

(4*R*,1′*S*,2″*S*)-4-[1′-*tert*-Butoxycarbonylamino-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionyloxy)-ethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*R*)-5 (*S*)-Mosher Ester). Elution system: 9:1:0.1 CH_2Cl_2−MeOH−28% NH_4OH. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.55 (br s, 1 H, NH), 7.60−7.40 (m, 5 H, Ph), 6.80 (br s, 1 H, NH), 6.05 (br d, 1 H, $J_{1',NH}$ = 8.0 Hz, N′H), 4.37 (dd, 1 H, $J_{1',2'a}$ = 8.0 Hz, $J_{2'a,2'b}$ = 11.0 Hz, H-2′a), 4.32 (dd, 1 H, $J_{1',2'b}$ = 6.0 Hz, H-2′b), 4.27 (dd, 1 H, $J_{4,1'}$ = 3.8 Hz, $J_{4,NH}$ = 4.0 Hz, H-4), 4.18−4.02 (m, 2 H, CH_2CH$_3$), 3.97 (dddd, 1 H, H-1′), 3.51 (q, 3 H, *J* = 0.7 Hz, OCH_3), 2.20 (s, 3 H, CH_3), 1.20 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). ^{19}F NMR (DMSO-d_6, 120 °C): δ −71.6. Anal. Calcd for $C_{25}H_{32}F_3N_3O_8$ (559.53): C, 53.66; H, 5.76; N, 7.51. Found: C, 53.68; H, 5.75; N, 7.52.

(1′*S*,2″*R*)- and (1′*R*,2″*R*)-4-[1′-*tert*-Butoxycarbonylamino-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionyloxy)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Dimethyl Esters (20 (*R*)-Mosher Esters). Preparative TLC (5:1 *i*-Pr$_2$O−AcOEt) gave **20 (*R*)-Mosher ester** as a 4:1 mixture of (1′*S*,2″*R*) and (1*R*′,2″*R*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.65 (br s, 1 H, NH), 7.60−7.40 (m, 5 H, Ph), 5.56 (br d, 0.8 H, $J_{1',NH}$ = 8.0 Hz, N′H), 5.52 (br d, 0.2 H, $J_{1',NH}$ = 8.0 Hz, N′H), 4.30 (dd, 1 H, $J_{1',2'a}$ = 4.2 Hz, $J_{2'a,2'b}$ = 11.0 Hz, H-2′a), 4.14 (dd, 1 H, $J_{1',2'b}$ = 8.5 Hz, H-2′b), 3.99 (br d, 1 H, $J_{4,1'}$ = 6.5 Hz, H-4), 3.70−3.58 (m, 1 H, H-1′), 3.64 (s, 4.8 H, 2 CO_2CH_3), 3.63 (s, 1.2 H, 2 CO_2CH_3), 3.50 (q, 2.4 H, *J* = 0.7 Hz, OCH_3), 3.47 (q, 0.6 H, *J* = 0.7 Hz, OCH_3), 2.22 (s, 6 H, 2 CH_3), 1.30 (s, 9 H, *t*-Bu). ^{19}F NMR (DMSO-d_6, 120 °C): δ −71.8 (major diastereoisomer), −71.7 (minor diastereoisomer). Anal. Calcd for $C_{28}H_{35}F_3N_2O_9$ (600.58): C, 56.00; H, 5.87; N, 4.66. Found: C, 56.10; H, 5.81; N, 4.63.

General Procedure for Oxidation with Jones Reagent of *N*′-Boc Amino Alcohols 5, 6, 12, 13, 20, and 23b,c. To a cooled (0 °C), stirred solution of *N*′-Boc amino alcohol (1.00 mmol) in acetone (10 mL) was added freshly prepared 1 M Jones reagent (3.00 mL, 3.00 mmol). The mixture was allowed to warm to room temperature in 30 min, stirred at room temperature for an additional 3 h, and then diluted with *i*-PrOH (1 mL). The suspension was neutralized with saturated aqueous $NaHCO_3$, diluted with AcOEt (100 mL), and washed with brine (2 × 15 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding oxidized derivative.

(4*R*,1′*S*)- and (4*S*,1′*S*)-1,3-Di-*N*-benzyl-4-(*tert*-butoxycarbonylamino-carboxy-methyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (7). Column chromatography with AcOEt (containing 1% of AcOH) afforded **7** (457 mg, 85%) as a 5:1 mixture of (4*R*,1′*S*) and (4*S*,1′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.40−7.10 (m, 10 H, 2 Ph), 6.25 (br d, 0.84 H, $J_{1',NH}$ = 9.0 Hz, N′H), 5.85 (br d, 0.16 H, $J_{1',NH}$ = 9.0 Hz, N′H), 5.18 and 4.24 (2 d, 2 H, *J* = 16.0 Hz, PhCH_2), 5.00 and 4.87 (2 d, 0.32 H, *J* = 16.5 Hz, PhCH_2), 4.98 and 4.88 (2 d, 1.68 H, *J* = 16.5 Hz, PhCH_2), 4.82 (d, 0.84 H, $J_{4,1'}$ = 6.0 Hz, H-4), 4.76 (d, 0.16 H, $J_{4,1'}$ = 5.5 Hz, H-4), 4.41 (dd, 0.16 H, H-1′), 4.34 (dd, 0.84 H, H-1′), 4.14−3.96 (m, 2 H, CH_2CH$_3$), 2.26 (s, 0.48 H, CH_3), 2.24 (s, 2.52 H, CH_3), 1.41 (s, 7.56 H, *t*-Bu), 1.40 (s, 1.44 H, *t*-Bu), 1.18 (t, 0.48 H, *J* = 7.0 Hz, CH$_2$CH_3), 1.17 (t, 2.52 H, *J* = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 538.8 (M^+ + H), 560.9 (M^+ + Na), 576.8 (M^+ + K). Anal. Calcd for $C_{29}H_{35}N_3O_7$ (537.60): C, 64.79; H, 6.56; N, 7.82. Found: C, 64.71; H, 6.53; N, 7.88.

6-Methyl-2-oxo-1,2-dihydro-pyrimidine-5-carboxylic Acid Ethyl Ester (9). Column chromatography with 11:1:0.1 CH_2Cl_2−MeOH−28% NH_4OH afforded **9** (173 mg, 95%) slightly contaminated by uncharacterized byproducts. ^{1}H NMR (DMSO-d_6 + D_2O): δ 8.65 (s, 1 H, H-4), 4.24 (q, 3 H, *J* = 7.0 Hz, CH_2CH$_3$), 2.58 (s, 3 H, CH_3), 1.22 (t, 3 H, CH$_2$CH_3). MALDI-TOF MS: 183.8 (M^+ + H), 205.7 (M^+ + Na), 221.4 (M^+ + K).

(4*R*,2′*S*)- and (4*S*,2′*S*)-1,3-Di-*N*-benzyl-4-(2′-*tert*-butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14). Column chromatography with AcOEt (containing 1% of AcOH) afforded **14** (469 mg, 85%) as a 1:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.40−7.10 (m, 10 H, 2 Ph), 6.48 (br d, 0.5 H, *J* = 8.0 Hz, N′H), 6.34 (br d, 0.5 H, *J* = 8.0 Hz, N′H), 5.18 and 4.28 (2 d, 1 H, *J* = 15.0 Hz, PhC*H*), 5.16 and 4.88 (2 d, 1 H, *J* = 16.0 Hz, PhC*H*), 5.12 and 4.18 (2 d, 1 H, *J* = 15.0 Hz, PhC*H*), 5.06 and 4.84 (2 d, 1 H, *J* = 16.0 Hz, PhC*H*), 4.52−4.40 (m, 1 H, H-4), 4.14−3.92 (m, 2.5 H, H-2′, CH_2CH$_3$), 3.91−3.80 (m, 0.5

H, H-2′), 2.36 (s, 1.5 H, CH_3), 2.35 (s, 1.5 H, CH_3), 2.20−1.76 (m, 2 H, 2 H-1′), 1.42 (s, 4.5 H, *t*-Bu), 1.41 (s, 4.5 H, *t*-Bu), 1.20−1.08 (m, 3 H, CH_2CH_3). MALDI-TOF MS: 552.3 (M^+ + H), 574.9 (M^+ + Na), 590.9 (M^+ + K). Anal. Calcd for $C_{30}H_{37}N_3O_7$ (551.63): C, 65.32; H, 6.76; N, 7.62. Found: C, 65.31; H, 6.72; N, 7.58.

(2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-3′-hydroxy-propyl)-6-methyl-2-oxo-1,2-dihydro-pyrimidine-5-carboxylic Acid Ethyl Ester (16) and (2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (17). Column chromatography with 9:1 AcOEt−MeOH (containing 1% of AcOH) afforded first **16** (107 mg, 30%) contaminated by uncharacterized byproducts. ^{1}H NMR (DMSO-d_6, 120 °C) selected data: δ 7.38 (br s, 1 H, NH), 5.78 (br d, 1 H, J = 8.0 Hz, N′H), 4.40−4.00 (m, 3 H, H-2′, CH_2CH_3), 3.28 (dd, 1 H, $J_{1'a,2'}$ = 6.5 Hz, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 3.04 (dd, 1 H, $J_{1'b,2'}$ = 7.0 Hz, H-1′b), 2.30 (s, 3 H, CH_3), 1.42 (s, 9 H, *t*-Bu), 1.22 (t, 3 H, J = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 356.5 (M^+ + H), 378.3 (M^+ + Na), 394.3 (M^+ + K).

Eluted second was **17** (55 mg, 15%) contaminated by uncharacterized byproducts. ^{1}H NMR selected data: δ 5.62 (br d, 1 H, J = 8.0 Hz, N′H), 4.42 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 3.44 (dd, 1 H, $J_{1'a,2'}$ = 6.0 Hz, $J_{1'a,1'b}$ = 16.0 Hz, H-1′a), 3.34 (dd, 1 H, $J_{1'b,2'}$ = 5.0 Hz, H-1′b), 2.40 (s, 3 H, CH_3), 1.42 (s, 9 H, *t*-Bu), 1.22 (t, 3 H, CH_2CH_3). MALDI-TOF MS: 370.5 (M^+ + H), 392.3 (M^+ + Na), 408.3 (M^+ + K).

(2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Dimethyl Ester (24b). Column chromatography with AcOEt (containing 1% of AcOH) afforded **24b** (341 mg, 83%) as a white foam. $[\alpha]_D$ −21.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ 6.20 (br s, 1 H, N′H), 4.17 (ddd, 1 H, $J_{1'a,2'}$ = 5.0 Hz, $J_{2',NH}$ = 9.0 Hz, $J_{1'b,2'}$ = 9.5 Hz, H-2′), 3.92 (s, 6 H, 2 OCH_3), 3.20 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 2.94 (dd, 1 H, H-1′b), 2.42 (2 s, 6 H, 2 CH_3), 1.30 (s, 9 H, *t*-Bu). MALDI-TOF MS: 411.0 (M^+ + H), 449.0 (M^+ + K). Anal. Calcd for $C_{19}H_{26}N_2O_8$ (410.42): C, 55.60; H, 6.39; N, 6.83. Found: C, 55.70; H, 6.31; N, 6.80.

(2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (24c). Column chromatography with AcOEt (containing 1% of AcOH) afforded **24c** (321 mg, 65%) as a white foam. $[\alpha]_D$ −25.8 (*c* 0.9, MeOH). ^{1}H NMR (DMSO-d_6, 120 °C): δ 5.82 (br d, 1 H, $J_{2',NH}$ = 6.5 Hz, N′H), 4.28 (ddd, 1 H, $J_{1'a,2'}$ = 6.0 Hz, $J_{1'b,2'}$ = 11.0 Hz, H-2′), 3.29 (dd, 1 H, $J_{1'a,1'b}$ = 14.5 Hz, H-1′a), 2.78 (dd, 1 H, H-1′b), 2.26 (s, 6 H, 2 CH_3), 1.62 (s, 18 H, 2 *t*-Bu), 1.30 (s, 9 H, *t*-Bu). MALDI-TOF MS: 495.7 (M^+ + H), 517.4 (M^+ + Na), 533.9 (M^+ + K). Anal. Calcd for $C_{25}H_{38}N_2O_8$ (494.58): C, 60.71; H, 7.74; N, 5.66. Found: C, 60.75; H, 7.71; N, 5.68.

(4*R*,1′*S*)- and (4*S*,1′*S*)-4-(*tert*-Butoxycarbonylamino-carboxy-methyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (8). A vigorously stirred mixture of 20% palladium hydroxide on carbon (80 mg), AcOH (4 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 **7** (161 mg, 0.30 mmol) in EtOH (2 mL) previously degassed and saturated with hydrogen as described before. After the solution was stirred under a positive pressure of hydrogen (5 atm) at room temperature for 7 days, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL), H_2O (0.5 mL), and DMF (2 mL). The combined filtrates were concentrated and eluted from a column of silica gel with 9:1 AcOEt−MeOH (containing 1% of AcOH) to give **8** (32 mg, 30%) as a 5:1 mixture of (4*R*,1′*S*) and (4*S*,1′*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C) selected data for (4*R*)-isomer: δ 8.41 (br s, 1 H, NH), 6.38 (br s, 1 H, NH), 5.50 (br d, 1 H, $J_{1',NH}$ = 9.0 Hz, N′H), 4.38 (dd, 1 H, $J_{4,1'}$ = 3.8 Hz, $J_{4,NH}$ = 4.0 Hz, H-4), 4.16−3.90 (m, 3 H, H-1′, CH_2CH_3), 2.20 (s, 3 H, CH_3), 1.18 (t, 3 H, J = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 358.7 (M^+ + H), 380.4 (M^+ + Na), 396.2 (M^+ + K). Anal. Calcd for $C_{15}H_{23}N_3O_7$ (357.36): C, 50.41; H, 6.49; N, 11.76. Found: C, 50.49; H, 6.51; N, 11.70. The fully hydrogenated hexahydro-pyrimidine derivative of **8** was also isolated (∼15%).

(4*R*,2′*S*)- and (4*S*,2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (15). Treatment of **14** (165 mg, 0.30 mmol) as described for the preparation of **8** gave **15** (33 mg, 30%) as a 1:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*)-diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.55 (br s, 0.5 H, NH), 8.50 (br s, 0.5 H, NH), 6.55 (br s, 0.5 H, N′H), 6.48 (br s, 0.5 H, NH), 6.00 (br d, 0.5 H, $J_{2',NH}$ = 8.0 Hz, N′H), 5.82 (br d, 0.5 H, $J_{2',NH}$ = 8.0 Hz, N′H), 4.30−4.20 (m, 1 H, H-4), 4.15−3.80 (m, 3 H, H-2′, CH_2CH_3), 2.30 (s, 1.5 H, CH_3), 2.28 (s, 1.5 H, CH_3), 2.20−1.75 (m, 2 H, 2 H-1′), 1.20−1.08 (m, 3 H, CH_2CH_3). MALDI-TOF MS: 372.7 (M^+ + H), 394.8 (M^+ + Na), 410.8 (M^+ + K). Anal. Calcd for $C_{16}H_{25}N_3O_7$ (371.39): C, 51.74; H, 6.78; N, 11.31. Found: C, 51.68; H, 6.72; N, 11.34. The fully hydrogenated hexahydro-pyrimidine derivative of **15** was also isolated (∼15%).

(4*S*)-4-(3′-*tert*-Butoxycarbonyl-2-oxo-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (25). A mixture of aldehyde **10** (486 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, then cooled to 0 °C. To the mixture a solution of BF_3·Et_20 (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 6:1 cyclohexane−AcOEt to give **25** (465 mg, 65%) as a yellow amorphous solid; $[\alpha]_D$ +26.3 (*c* 0.8, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ 4.17 (dddd, 1 H, $J_{4,5a}$ = 6.0 Hz, $J_{4,5b}$ = 2.0 Hz, $J_{4,1'a}$ = 3.3 Hz, $J_{4,1'b}$ = 9.5 Hz, H-4), 4.00 (dd, 1 H, $J_{5a,5b}$ = 9.0 Hz, H-5a), 3.65 (dd, 1 H, H-5b), 3.44 (s, 2 H, 2 H-3′), 3.03 (dd, 1 H, $J_{1'a,1'b}$ = 17.0 Hz, H-1′a), 2.77 (dd, 1 H, H-1′b), 1.44 (s, 9 H, *t*-Bu), 1.43 (s, 9 H, *t*-Bu), 1.42 and 1.41 (2 s, 6 H, 2 $C(CH_3)_2$). MALDI-TOF MS: 358.6 (M^+ + H), 380.5 (M^+ + Na), 397.2 (M^+ + K). Anal. Calcd for $C_{18}H_{31}NO_6$ (357.44): C, 60.48; H, 8.74; N, 3.92. Found: C, 60.51; H, 8.72; N, 3.95.

(4*R*,4″*S*)- and (4*S*,4″*S*)-2-(3″-*tert*-Butoxycarbonyl-2″,2″-dimethyl-oxazolidin-4″-ylmethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Esters (27). A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde **26** (102 μL, 1.00 mmol), β-ketoester **25** (357 mg, 1.00 mmol), *tert*-butyl 3-aminocrotonate **18c** (158 mg, 1.00 mmol,), powdered 4-Å molecular sieves (50 mg), and *t*-BuOH (1 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 7:1 cyclohexane−AcOEt to give **27** (497 mg, 85%) as a 1.5:1 mixture of (4*R*,4″*S*) and (4*S*,4″*S*) diastereoisomers. ^{1}H NMR (DMSO-d_6, 120 °C) selected data: δ 7.70 (br s, 0.6 H, NH), 7.68 (br s, 0.4 H, NH), 7.45−7.05 (m, 5 H, Ph), 4.91 (s, 0.4 H, H-4), 4.88 (s, 0.6 H, H-4), 2.24 (s, 1.8 H, CH_3), 2.23 (s, 1.2 H, CH_3). MALDI-TOF MS: 586.0 (M^+ + H), 607.1 (M^+ + Na), 623.8 (M^+ + K). Anal. Calcd for $C_{33}H_{48}N_2O_7$ (584.74): C, 67.78; H, 8.27; N, 4.79. Found: C, 67.75; H, 8.29; N, 4.80.

(2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (29). A mixture of **28** (136 mg, 0.25 mmol), BAIB ([bis(acetoxy)-iodo]benzene, 338 mg, 1.05 mmol), TEMPO (2,2,6,6-tetramethyl-piperidinyloxyl, 11 mg, 0.07 mmol), and 1:1 CH_3CN-H_2O (2 mL) was stirred for 3 h at room temperature, then filtered through a pad of Celite and concentrated.

The residue was suspended with AcOEt (10 mL) and washed with brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 7:3 cyclohexane−AcOEt to give **29 (**135 mg, 95%) as a white foam. $[\alpha]_D$ +77.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ 7.41−7.20 (m, 5 H, Ph), 5.97 (br d, 1 H, $J_{2',NH}$ = 8.0 Hz, N′H), 4.58 (ddd, 1 H, $J_{1'a,2'}$ = 2.0 Hz, $J_{1'b,2'}$ = 9.0 Hz, H-2′), 3.45 (dd, 1 H, $J_{1'a,1'b}$ = 16.0 Hz, H-1′a), 3.30 (dd, 1 H, H-1′b), 2.61 (s, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu), 1.20 and 1.19 (2 s, 18 H, 2 *t*-Bu). MALDI-TOF MS: 557.8 (M^+ + H), 579.5 (M^+ + Na), 595.3 (M^+ + K). Anal. Calcd for $C_{30}H_{40}N_2O_8$ (556.65): C, 64.73; H, 7.24; N, 5.03. Found: C, 64.70; H, 7.26; N, 5.08.

General Procedure for Methyl Ester Derivatization and Boc Deprotection of Amino Acids 7, 14, 24b,c, and 29. A solution of *N*′-Boc amino acid (0.50 mmol) in 1:1 CH_2Cl_2−MeOH (8 mL) was treated with ethereal diazomethane at 0 °C for 5 min and then concentrated to give the corresponding methyl ester, at least 95% pure by NMR analysis, suitable for the next step.

To a cooled (0 °C), stirred solution of the above *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 *N*′-deprotected amino esters **30**, **31**, **32**, **33**, and byproduct **34**.

(4*R*,1′*S*)- and (4*S*,1′*S*)-4-(Amino-methoxycarbonyl-methyl)-1,3-di-*N*-benzyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (30). Column chromatography with AcOEt afforded **30** (169 mg, 75%) as a 5:1 mixture of (4*R*,1′*S*) and (4*S*,1′*S*) diastereoisomers. ^{1}H NMR: δ 7.40−7.10 (m, 10 H, 2 Ph), 5.36 and 3.99 (2 d, 1.68 H, *J* = 15.5 Hz, PhCH_2), 5.23 and 3.99 (2 d, 0.32 H, *J* = 15.5 Hz, PhCH_2), 5.19 and 4.87 (2 d, 0.32 H, *J* = 16.5 Hz, PhCH_2), 5.15 and 4.93 (2 d, 1.68 H, *J* = 16.5 Hz, PhCH_2), 4.80 (d, 0.84 H, $J_{4,1'}$ = 4.5 Hz, H-4), 4.73 (d, 0.16 H, $J_{4,1'}$ = 4.5 Hz, H-4), 4.20−4.08 (m, 2 H, CH_2CH$_3$), 3.73 (s, 3 H, CO_2CH_3), 3.62 (d, 0.84 H, H-1′), 3.57 (d, 0.16 H, H-1′), 2.45 (s, 2.52 H, CH_3), 2.43 (s, 0.48 H, CH_3), 1.20 (t, 2.52 H, *J* = 7.0 Hz, CH_2CH_3), 1.19 (t, 0.48 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 452.5 (M^+ + H), 474.4 (M^+ + Na), 490.5 (M^+ + K). Anal. Calcd for $C_{25}H_{29}N_3O_5$ (451.51): C, 66.50; H, 6.47; N, 9.31. Found: C, 66.58; H, 6.41; N, 9.34.

(4*R*,2′*S*)- and (4*S*,2′*S*)-4-(2′-Amino-2′-methoxycarbonyl-ethyl)-1,3-di-*N*-benzyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (31). Column chromatography with AcOEt afforded **31** (182 mg, 78%) as a 1:1 mixture of (4*R*,2′*S*) and (4*S*,2′*S*) diastereoisomers.

Analytical samples of each diastereoisomer were obtained by preparative TLC (AcOEt). Eluted first was (4*S*)-**31**. $[\alpha]_D$ 5.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR: δ 7.40−7.10 (m, 10 H, 2 Ph), 5.33 and 4.81 (2 d, 2 H, *J* = 16.5 Hz, PhCH_2), 5.27 and 4.36 (2 d, 2 H, *J* = 15.0 Hz, PhCH_2), 4.69 (dd, 1 H, $J_{4,1'b}$ = 5.5 Hz, $J_{4,1'a}$ = 9.0 Hz, H-4), 4.18−4.02 (m, 2 H, CH_2CH$_3$), 3.70 (s, 3 H, CO_2CH_3), 3.50 (dd, 1 H, $J_{1'a,2'}$ = 4.5 Hz, $J_{1'b,2'}$ = 9.5 Hz, H-2′), 2.60 (s, 3 H, CH_3), 2.10 (ddd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 1.66 (ddd, 1 H, H-1′b), 1.20 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 176.4, 165.5, 154.1, 150.5, 138.3, 137.7, 128.7, 128.6, 128.5, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 104.7, 60.1, 52.1, 51.2, 51.1, 49.2, 46.8, 38.5, 16.3, 14.2. MALDI-TOF MS: 466.7 (M^+ + H), 488.4 (M^+ + Na), 504.6 (M^+ + K). Anal. Calcd for $C_{26}H_{31}N_3O_5$ (465.54): C, 67.08; H, 6.71; N, 9.03. Found: C, 67.10; H, 6.71; N, 9.04.

Eluted second was (4*R*)-**31**. $[\alpha]_D$ 25.9 (*c* 0.6, $CHCl_3$). ^{1}H NMR: δ 7.40−7.10 (m, 10 H, 2 Ph), 5.34 and 4.84 (2 d, 2 H, *J* = 16.5 Hz, PhCH_2), 5.16 and 4.20 (2 d, 2 H, *J* = 15.0 Hz, PhCH_2), 4.50 (dd, 1 H, $J_{4,1'b}$ = 5.0 Hz, $J_{4,1'a}$ = 9.2 Hz, H-4), 4.20−4.08 (m, 2 H, CH_2CH$_3$), 3.70 (s, 3 H, CO_2CH_3), 3.43 (dd, 1 H, $J_{1'a,2'}$ = 4.5 Hz, $J_{1'b,2'}$ = 9.5 Hz, H-2′), 2.41 (s, 3 H, CH_3), 2.08 (ddd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 1.73 (ddd, 1 H, H-1′b), 1.20 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 175.2, 166.1, 154.3, 150.8, 138.2, 137.1, 128.7, 128.6, 128.5, 128.4, 127.8, 127.7, 127.5, 127.2, 126.7, 126.5, 104.1, 60.4, 52.2, 51.0, 50.9, 50.2, 46.9, 38.9, 16.7, 14.2. MALDI-TOF MS: 466.8 (M^+ + H), 488.5 (M^+ + Na), 504.3 (M^+ + K). Anal. Calcd for $C_{26}H_{31}N_3O_5$ (465.54): C, 67.08; H, 6.71; N, 9.03. Found: C, 67.12; H, 6.79; N, 9.08.

(2′*S*)-4-(2′-Amino-2′-methoxycarbonyl-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (32). Column chromatography with 1:1 cyclohexane−AcOEt afforded **32** (184 mg, 90%) as a white foam. $[\alpha]_D$ −3.1 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ 3.82 (dd, 1 H, $J_{1'a,2'}$ = 4.5 Hz, $J_{1'b,2'}$ = 11.0 Hz, H-2′), 3.74 (s, 3 H, OCH_3), 3.25 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 2.83 (dd, 1 H, H-1′b), 2.56 (s, 6 H, 2 CH_3), 1.62 (s, 18 H, 2 *t*-Bu).^{13}C NMR: δ 175.0, 167.7, 154.6, 140.8, 128.9, 83.3, 54.9, 52.1, 35.4, 28.0, 23.0. MALDI-TOF MS: 409.3 (M^+ + H), 431.5 (M^+ + Na), 447.8 (M^+ + K). Anal. Calcd for $C_{21}H_{32}N_2O_6$ (408.49): C, 61.75; H, 7.90; N, 6.86. Found: C, 61.70; H, 7.99; N, 6.81.

(2′*S*)-2-(2′-Amino-2′-methoxycarbonyl-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (33). Column chromatography with 1:4 cyclohexane−AcOEt afforded **33** (153 mg, 65%) as a white foam. $[\alpha]_D$ +11.7 (*c* 0.9, CH_3OH). ^{1}H NMR: δ 7.40−7.20 (m, 5 H, Ph), 4.06 (dd, 1 H, $J_{1'a,2'}$ = 4.2 Hz, $J_{1'b,2'}$ = 8.2 Hz, H-2′), 3.74 (s, 3 H, OCH_3), 3.33 (dd, 1 H, $J_{1'a,1'b}$ = 15.0 Hz, H-1′a), 3.13 (dd, 1 H, H-1′b), 2.59 (s, 3 H, CH_3), 1,82 (br s, 2 H, N′H_2), 1.20 and 1.19 (2 s, 18 H, 2 *t*-Bu). ^{13}C NMR: δ 175.6, 166.7, 166.5, 154.4, 153.8, 145.3, 136.3, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 82.6, 82.3, 53.7, 52.0, 39.7, 27.5, 22.7. MALDI-TOF MS: 471.7 (M^+ + H), 493.3 (M^+ + Na), 509.6 (M^+ + K). Anal. Calcd for $C_{26}H_{34}N_2O_6$ (470.56): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.32; H, 7.29; N, 5.92.

(3*S*)-6,8-Dimethyl-1-oxo-1,2,3,4-tetrahydro-[2,7]naphthyridine-3,5-dicarboxylic Acid Dimethyl Ester (34). Column chromatography with 1:2 cyclohexane−AcOEt afforded **34** (139 mg, 95%) as a white foam. $[\alpha]_D$ −129.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 6.43 (br s, 1 H, NH), 4.31 (ddd, 1 H, $J_{3,NH}$ = 2.5 Hz, $J_{3,4a}$ = 5.0 Hz, $J_{3,4b}$ = 10.5 Hz, H-3), 4.00 (s, 3 H, OCH_3), 3.82 (s, 3H, OCH_3), 3.29 (dd, 1 H, $J_{4a,4b}$ = 16.0 Hz, H-4a), 3.11 (dd, 1 H, H-4b), 2.92 and 2.60 (2 s, 6 H, 2 CH_3).^{13}C NMR: δ 170.0, 167.9, 163.8, 161.4, 157.8, 144.4, 124.9, 120.2, 53.1, 52.6, 51.8, 29.9, 25.2, 23.7. MALDI-TOF MS: 293.3 (M^+ + H), 315.4 (M^+ + Na), 331.6 (M^+ + K). Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.29): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.58; H, 5.51; N, 9.50.

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.

(4*R*,1′*S*,2″*R*)-1,3-Di-*N*-benzyl-4-[methoxycarbonyl-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-methyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*R*)-30 (*R*)-Mosher Amide). Elution system: 2:1 cyclohexane−AcOEt. ^{1}H NMR: δ 8.00 (d, 1 H, $J_{1',NH}$ = 9.0 Hz, N′H), 7.60−7.10 (m, 15 H, 3 Ph), 5.42 and 4.04 (2 d, 2 H, *J* = 15.5 Hz, PhCH_2), 5.39 and 4.54 (2 d, 2 H, *J* = 16.5 Hz, PhCH_2), 5.00 (d, 1 H, $J_{4,1'}$ = 2.5 Hz, H-4), 4.97 (dd, 1 H, H-1′), 4.22−4.06 (m, 2 H, CH_2CH$_3$), 3.78 (s, 3 H, CO_2CH_3), 3.38 (q, 3 H, *J* = 0.7 Hz, OCH_3), 2.35 (s, 3 H, CH_3), 1.22 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.1. Anal.

Calcd for $C_{35}H_{36}F_3N_3O_7$ (667.67): C, 62.96; H, 5.43; N, 6.29. Found: C, 63.00; H, 5.41; N, 6.20.

(4*R*,1′*S*,2″*S*)-1,3-Di-*N*-benzyl-4-[methoxycarbonyl-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-methyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*R*)-30 (*S*)-Mosher Amide). Elution system: 2:1 cyclohexane−AcOEt. ^{1}H NMR: δ 7.70−7.00 (m, 16 H, 3 Ph, N′H), 5.37 and 4.92 (2 d, 2 H, J = 15.5 Hz, PhCH_2), 5.28 and 4.98 (2 d, 2 H, J = 16.5 Hz, PhCH_2), 5.00 (dd, 1 H, $J_{4,1'}$ = 3.0 Hz, $J_{1',NH}$ = 9.0 Hz, H-1′), 4.82 (d, 1 H, H-4), 4.24−4.00 (m, 2 H, CH_2CH$_3$), 3.76 (s, 3 H, CO_2CH_3), 3.69 (q, 3 H, J = 0.7 Hz, OCH_3), 2.15 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). ^{19}F NMR: δ −68.8. Anal. Calcd for $C_{35}H_{36}F_3N_3O_7$ (667.67): C, 62.96; H, 5.43; N, 6.29. Found: C, 63.10; H, 5.44; N, 6.28.

(4*S*,2′*S*,2″*R*)-1,3-Di-*N*-benzyl-4-[2′-methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*S*)-31 (*R*)-Mosher Amide). Elution system: AcOEt. ^{1}H NMR: δ 7.80−7.10 (m, 16 H, 3 Ph, NH), 5.38 and 4.78 (2 d, 2 H, J = 16.5 Hz, PhCH_2), 5.26 and 4.14 (2 d, 2 H, J = 15.0 Hz, PhCH_2), 4.84−4.74 (m, 1 H, H-2′), 4.45 (dd, 1 H, $J_{4,1'a}$ = 6.5 Hz, $J_{4,1'b}$ = 7.0 Hz, H-4), 4.20−4.00 (m, 2 H, CH_2CH$_3$), 3.59 (s, 3 H, CO_2CH_3), 3.30 (q, 3 H, J = 0.7 Hz, OCH_3), 2.41 (s, 3 H, CH_3), 2.24 (ddd, 1 H, $J_{1'a,2'}$ = 5.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 2.08 (ddd, 1 H, $J_{1'b,2'}$ = 8.0 Hz, H-1′b), 1.21 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). ^{19}F NMR: δ −69.4. Anal. Calcd for $C_{36}H_{38}F_3N_3O_7$ (681.70): C, 63.43; H, 5.62; F, 8.36; N, 6.16. Found: C, 63.41; H, 5.66; F, 8.38; N, 6.11.

(4*S*,2′*S*,2″*S*)-1,3-Di-*N*-benzyl-4-[2′-methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((4*S*)-31 (*S*)-Mosher Amide). Elution system: AcOEt. ^{1}H NMR: δ 7.80−7.00 (m, 16 H, 3 Ph, NH), 5.34 and 4.72 (2 d, 2 H, J = 16.5 Hz, PhCH_2), 5.14 and 3.97 (2 d, 2 H, J = 15.0 Hz, PhCH_2), 4.79 (ddd, 1 H, $J_{1'a,2'}$ = 5.0 Hz, $J_{1'b,2'}$ = 7.0 Hz, $J_{2',NH}$ = 9.5 Hz, H-2′), 4.20 (dd, 1 H, $J_{4,1'a}$ = 6.5 Hz, $J_{4,1'b}$ = 7.0 Hz, H-4), 4.10−3.95 (m, 2 H, CH_2CH$_3$), 3.56 (s, 3 H, CO_2CH_3), 3.52 (q, 3 H, J = 0.7 Hz, OCH_3), 2.38 (s, 3 H, CH_3), 2.13 (ddd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 2.05 (ddd, 1 H, H-1′b), 1.12 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). ^{19}F NMR: δ −69.2. Anal. Calcd for $C_{36}H_{38}F_3N_3O_7$ (681.70): C, 63.43; H, 5.62; F, 8.36; N, 6.16. Found: C, 63.46; H, 5.61; F, 8.38; N, 6.18.

(2′*S*,2″*R*)-4-[2′-Methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (32 (*R*)-Mosher Amide). Elution system: 3:1 cyclohexane−AcOEt. $[\alpha]_D$ −37.5 (*c* 0.8, CHCl$_3$). ^{1}H NMR: δ 8.21 (br d, 1 H, $J_{2',NH}$ = 8.0 Hz, N′H), 7.60−7.50 and 7.42−7.36 (2 m, 5 H, Ph), 4.97 (ddd, 1 H, $J_{1'a,2'}$ = 5.5 Hz, $J_{1'b,2'}$ = 12.5 Hz, H-2′), 3.75 (s, 3 H, CO_2CH_3), 3.57 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 3.05 (q, 3 H, J = 0.7 Hz, OCH_3), 2.80 (dd, 1 H, H-1′b), 2.57 (s, 6 H, 2 CH_3), 1.60 (s, 18 H, 2 *t*-Bu). ^{19}F NMR: δ −70.2. Anal. Calcd for $C_{31}H_{39}F_3N_2O_8$ (624.65): C, 59.61; H, 6.29; N, 4.48. Found: C, 59.69; H, 6.21; N, 4.43.

(2′*S*,2″*S*)-4-[2′-Methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (32 (*S*)-Mosher Amide). Elution system: 3:1 cyclohexane−AcOEt. $[\alpha]_D$ −28.2 (*c* 1.7, CHCl$_3$). ^{1}H NMR: δ 8.32 (br d, 1 H, $J_{2',NH}$ = 8.0 Hz, N′H), 7.30−7.22 and 7.16−7.04 (2 m, 5 H, Ph), 5.00 (ddd, 1 H, $J_{1'a,2'}$ = 5.5 Hz, $J_{1'b,2'}$ = 13.0 Hz, H-2′), 3.80 (s, 3 H, CO_2CH_3), 3.57 (q, 3 H, J = 0.7 Hz, OCH_3), 3.54 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 2.72 (dd, 1 H, H-1′b), 2.41 (s, 6 H, 2 CH_3), 1.62 (s, 18 H, 2 *t*-Bu). ^{19}F NMR: δ −70.0. Anal. Calcd for $C_{31}H_{39}F_3N_2O_8$ (624.65): C, 59.61; H, 6.29; N, 4.48. Found: C, 59.65; H, 6.29; N, 4.41.

(2′*S*,2″*R*)-2-[2′-Methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (33 (*R*)-Mosher Amide). Elution system: 2:1 cyclohexane−AcOEt. $[\alpha]_D$ +2.9 (*c* 1.1, CH$_3$OH). ^{1}H NMR: δ 8.75 (br d, 1 H, $J_{2',NH}$ = 8.0 Hz, N′H), 7.70−7.60 and 7.50−7.20 (2 m, 10 H, 2 Ph), 5.08 (ddd, 1 H, $J_{1'a,2'}$ = 6.5 Hz, $J_{1'b,2'}$ = 5.2 Hz, H-2′), 3.74 (s, 3 H, CO_2CH_3), 3.53 (dd, 1 H, $J_{1'a,1'b}$ = 15.5 Hz, H-1′a), 3.38 (dd, 1 H, H-1′b), 3.36 (q, 3 H, J = 0.7 Hz, OCH_3), 2.55 (s, 3 H, CH_3), 1.21 and 1.20 (2 s, 18 H, 2 *t*-Bu). ^{19}F NMR: δ −69.9. Anal. Calcd for $C_{36}H_{41}F_3N_2O_8$ (686.71): C, 62.96; H, 6.02; N, 4.08. Found: C, 62.98; H, 6.03; N, 4.05.

(2′*S*,2″*S*)-2-[2′-Methoxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (33 (*S*)-Mosher Amide). Elution system: 2:1 cyclohexane−AcOEt. $[\alpha]_D$ +21.9 (*c* 0.7, CHCl$_3$). ^{1}H NMR: δ 8.35 (br d, 1 H, $J_{2',NH}$ = 8.0 Hz, N′H), 7.40−7.20 (m, 10 H, 2 Ph), 5.07 (ddd, 1 H, $J_{1'a,2'}$ = 7.0 Hz, $J_{1'b,2'}$ = 4.5 Hz, H-2′), 3.75 (s, 3 H, CO_2CH_3), 3.60 (q, 3 H, J = 0.7 Hz, OCH_3), 3.39 (dd, 1 H, $J_{1'a,1'b}$ = 15.5 Hz, H-1′a), 3.32 (dd, 1 H, H-1′b), 2.43 (s, 3 H, CH_3), 1.21 and 1.18 (2 s, 18 H, 2 *t*-Bu). ^{19}F NMR: δ −69.0. Anal. Calcd for $C_{36}H_{41}F_3N_2O_8$ (686.71): C, 62.96; H, 6.02; N, 4.08. Found: C, 62.97; H, 6.04; N, 4.08.

(2′*S*,1″*S*)-4-[2′-*tert*-Butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (Boc-Pal-Phe-OMe) (35). To a cooled (0 °C), stirred solution of amino acid **24c** (49 mg, 0.10 mmol), L-phenylalanine methyl ester hydrochloride (32 mg, 0.15 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (62 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (52 μL, 0.30 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 dipeptide **35** (59 mg, 90%) as 1:1 mixture of conformers. $[\alpha]_D$ −23.5 (*c* 0.8, CHCl$_3$). ^{1}H NMR (DMSO-d_6, 140 °C): δ 8.16 (s, 1 H, N″H), 7.40−7.10 (m, 5 H, Ph), 5.85 (br d, 1 H, J = 8.0 Hz, N′H), 4.66 (dd, 0.5 H, $J_{1'',2''a}$ = 6.5 Hz, $J_{1'',2''b}$ = 7.2 Hz, H-1″), 4.63 (dd, 0.5 H, $J_{1'',2''a}$ = 6.5 Hz, $J_{1'',2''b}$ = 7.2 Hz, H-1″), 4.33 (ddd, 1 H, $J_{1'a,2'}$ = 5.5 Hz, $J_{1'b,2'}$ = 11.0 Hz, H-2′), 3.60 (s, 3 H, OCH_3), 3.21 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 3.12 (dd, 1 H, $J_{2''a,2''b}$ = 13.8 Hz, H-2″a), 3.04 (dd, 1 H, H-2″b), 2.69 (dd, 1 H, H-1′b), 2.45 (s, 6 H, 2 CH_3), 1.60 (s, 18 H, 2 *t*-Bu), 1.30 (s, 3 H, *t*-Bu). MALDI-TOF MS: 656.4 (M^+ + H), 679.0 (M^+ + Na), 695.4 (M^+ + K). Anal. Calcd for $C_{35}H_{49}N_3O_9$ (655.78): C, 64.10; H, 7.53; N, 6.41. Found: C, 64.15; H, 7.55; N, 6.48.

(2′*S*,2″*S*,1‴*S*)-4-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1‴-methoxycarbonyl-2‴-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic Acid Di-*tert*-butyl Ester (Boc-Phe-Pal-Phe-OMe) (36). To a cooled (0 °C), stirred solution of dipeptide **35** (66 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 free amine (47 mg, ∼85%), at least 95% by pure by NMR analysis, suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (47 mg, ∼0.09 mmol), *tert*-butoxycarbonyl-L-phenylalanine (36 mg, 0.14 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (84 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (46 μL, 0.27 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 2:1 cyclohexane−AcOEt to give tripeptide **36** (66 mg, 82% from **35**). $[\alpha]_D$ −32.1 (*c* 1.9, $CHCl_3$). ^1H NMR (DMSO-d_6, 120 °C): δ 7.60 (br d, 1 H, $J_{2',N''H}$ = 8.0 Hz, N″H), 7.40−7.00 (m, 10 H, 2 Ph), 6.08 (br d, 1 H, $J_{2'',NH}$ = 8.0 Hz, N*H*Boc), 4.64−4.52 (m, 2 H, H-2″, H-1‴), 4.14 (ddd, 1 H, $J_{1'a,2'}$ = 5.5 Hz, $J_{1'b,2'}$ = 8.5 Hz, H-2′), 3.59 (s, 3 H, OCH_3), 3.24 (dd, 1 H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 3.06 (dd, 1 H, $J_{1''',2'''a}$ = 6.5, $J_{2'''a,2'''b}$ = 14.0 Hz, H-2‴a), 2.99 (dd, 1 H, $J_{1''',2'''b}$ = 7.0 Hz, H-2‴b), 2.86 (dd, 1 H, $J_{2'',3''a} \approx$ 0.5 Hz, $J_{3''a,3''b}$ = 13.5 Hz, H-3″a), 2.82 (dd, 1 H, $J_{2'',3''b}$ = 4.0 Hz, H-3″b), 2.72 (dd, 1 H, H-1′b), 2.50 (2 s, 6 H, 2 CH_3), 1.60 (s, 18 H, 2 *t*-Bu), 1.30 (s, 9 H, *t*-Bu). MALDI-TOF MS: 803.4 (M^+ + H), 825.4 (M^+ + Na), 841.6 (M^+ + K). Anal. Calcd for $C_{44}H_{58}N_4O_{10}$ (802.95): C, 65.82; H, 7.28; N, 6.98. Found: C, 65.89; H, 7.21; N, 6.92.

Crystal data for compound (4*R*)-11: $C_{19}H_{31}N_3O_6$, M_r = 397.47, colorless crystal (0.12 × 0.17 × 0.31 mm^3), orthorhombic, space group $P2_12_12_1$ (no. 19) with a = 5.8209(2) Å, b = 15.1688(4) Å, c = 24.5767(9) Å, V = 2170.0(1) $Å^3$, Z = 4, D_c = 1.217 g cm^{-3}, 7282 reflections measured, 4361 indipendent, R_{int} = 0.041, (3.6 < θ < 27.5°, T = 295 K, Mo Kα radiation, λ = 0.71073 Å) on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SIR97)[27] and refined on F^2 (SHELXL-97).[28] Refinement converged at a final *w*R2 value of 0.1047 (all reflections), R1 = 0.0409 (for 3671 reflections with $I > 2\sigma(I)$), S = 1.045. All non-H atoms were refined anisotropically; the N−H hydrogen atoms were refined isotropically; all other hydrogens were included on calculated positions, riding on their carrier atoms. A final difference Fourier map showed no residual density outside −0.17 and 0.16 $Å^{-3}$. An ORTEP[29] view of the molecule is shown in Figure 3.

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Supporting Information Available: CIF file for compound (4*R*)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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