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Three-Component Biginelli Cyclocondensation Reaction Using *C*-Glycosylated Substrates. Preparation of a Collection of Dihydropyrimidinone Glycoconjugates and the Synthesis of *C*-Glycosylated Monastrol Analogues†

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Received March 25, 2002

The aldehyde−ketoester−urea cyclocondensation reaction has been revisited using *C*-glycosylated reagents with the aim of exploring a potential entry to a library of dihydropyrimidinone glycoconjugates. A collection of 13 mono- and bis-*C*-glycosylated dihydropyrimidinones has been prepared by a parallel synthesis approach using the three-component promoter CuCl/AcOH/BF_3·Et_2O. The sugar residues have been installed at either N1, C4, or C6 in the monoglycosylated derivatives and at both the C4 and C6 in the bisglycosylated products. The mono- and bisglycosylated products at C4 and C6 were obtained as mixtures of diastereoisomers with good to excellent selectivities due to the asymmetric induction by the sugar residue in the formation of the C4 stereocenter of the dihydropyrimidinone ring. Individual stereoisomers were isolated as pure compounds and their structures assigned with the aid of X-ray crystallography and chiroptical properties. As a demonstration of this new concept in the Biginelli reaction, the synthesis of two C4 epimer monastrol analogues bearing the ribofuranosyl moiety at C6 has been described.

Introduction

In the main stream of the current interest in one-pot multicomponent reactions[1] that permit a rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery,[2] the acid-catalyzed condensation of aldehyde, *β*-ketoester, and urea (or thiourea) (Figure 1), known as the Biginelli reaction from the name of its inventor,[3] is receiving increased attention.[4] More than 100 years ago, Biginelli intuitively anticipated the synthetic potential

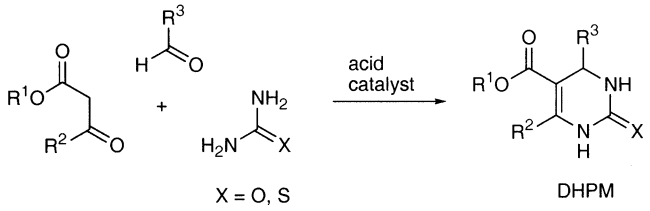

FIGURE 1. Biginelli cyclocondensation reaction leading to the dihydropyrimidine (DHPM) framework.

of multicomponent reactions by combining in a single flask the reactants of two different reactions having one component in common.[5] The result of the three-component reaction was a new product that was correctly characterized as a substituted 3,4-dihydropyrimidin-2(1*H*)-one (DHPM). The synthetic potential of the Biginelli reaction has been recognized and exploited in relatively recent years by the synthesis of numerous DHPMs as well as their sulfur analogues using both solution- and solid-phase reaction techniques.[6] Improved procedures using different types of catalysts[7] and condi-

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† Dedicated to Professor Albert Padwa on the occasion of his 65th birthday.

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(1) Passerini three-component and Ugi four-component condensations are the most popular among many other reactions for their wide scope and synthetic utility. For reviews, see: (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(2) (a) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235. (b) Nuss, J. M.; Renhowe, P. A. *Curr. Opin. Drug Discuss. Dev.* **1999**, *2*, 631. (c) Oliver, S. F.; Abell, C. *Curr. Opin. Chem. Biol.* **1999**, *3*, 299. (d) Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compounds Libraries*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon Press: New York, 1998. (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (f) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144.

(3) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.

(4) For a review, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

(5) Quite fairly, Biginelli stated (ref 3) that his research was inspired by the earlier work of R. Behrend on the urea−ketoester coupling and U. Schiff on the urea−aldehyde coupling.

(6) (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (b) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49. (c) Kappe, C. O.; Falsone, S. F.; Fabian, W. M. F.; Belaj, F. *Heterocycles* **1999**, *51*, 77. (d) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520. (e) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201. (f) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. (g) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819.

10.1021/jo0202076 CCC: $22.00
Published on Web 09/05/2002

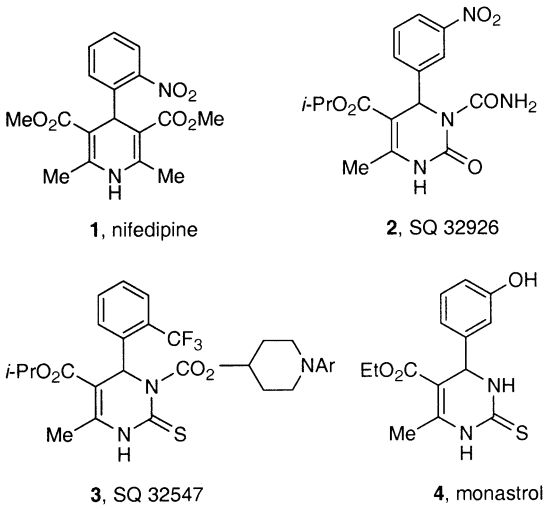

FIGURE 2. Dihydropyridine and dihydropyrimidine derivatives of pharmaceutical relevance.

tions[8] have been reported with the aim of overcoming the main drawbacks of the Biginelli reaction, which are represented by the modest yields and/or some difficulties in product isolation when a large excess of one reagent is employed.

The considerable interest for DHPM-type products stems from their structural similarity to dihydropyridines (Hantzsch products, DHPs),[9] a class of compounds showing remarkable pharmacological properties as calcium channel antagonists, and finding extensive use as therapeutics in the clinical treatment of cardiovascular diseases such as hypertension, cardiac arrhytmias, or angina pectoris.[10] Nifedipine **1**[11] (Figure 2) is a well-known DHP derivative that is marketed as a drug for these types of diseases. DHPMs exhibit similar biological profiles to DHPs[12] as shown, for instance, by the 4-aryl derivatives **2** and **3**. Other biological activities of DHPMs have been also disclosed, including that of α_{1a} adrenergic receptor antagonists as drug candidates for the treatment of benign prostatic hyperplasia.[13] Noteworthy is the recently identified lead compound **4** (monastrol) of a new class of anticancer agents acting as cell division (mitosis) blockers.[14] Hence, it was of some interest to us to explore a route leading to a collection of hitherto scarcely investigated class of dihydropyrimidinones, namely their *C*-glycosyl derivatives.[15] We are aware of only a few reports dealing with the use of rather simple sugar aldehydes (2,3-*O*-isopropylidene-D-glyceraldehyde, 2,4-*O*-ethylidene-D-threose and D-erythrose, 2,5-anhydro-*aldehydo*-D-xylose) in the Biginelli reaction.[16] Aside from the simple expectation that the presence of hydroxy-free sugar residues in the Biginelli products should increase the water solubility and bioavailability, other interesting biological properties may arise from glycosylation considering the extensive and essential role of carbohydrate molecules in the complex machinery of various glycoconjugate biological activity.[17] Glycosylation of heterocycles that are rich in biological activity is a field of increasing interest as shown, for example, by the synthesis of various guanidinoglycosides displaying improved biological properties (anti-influenza and anti-HIV activities) with respect to the nonglycosylated guanidino derivatives.[18] In fact, an attractive aspect of *C*-glycosylated Biginelli products is their resemblance to *C*-nucleosides, i.e., carbon-linked glycoside analogues of N-linked natural products. In addition, the synthesis of these *C*-glycoconjugates[19] is a current topic of research in medicinal chemistry due to the well-established potent activity of various nucleosides as anticancer and antiviral agents.[20]

Despite the fact that the biological activity of 4-aryl-substituted DHPMs is strictly dependent on the absolute configuration at the C4 stereocenter,[6a,13] the Biginelli reaction has been mostly carried out in an achiral version. The separation of enantiomers has been reported using chemical and enzymatic methods or preparative chromatographic techniques with chiral supports.[6a,21] Hence, an additional reason for which we have been spurred to use glycosylated reagents in the Biginelli reaction stems from the desire to achieve some internal asymmetric induction and thus obtain diastereomerically pure DHPMs derivatives.

Results and Discussion

Synthesis of Glycosylated Reagents. The aim of this work was to prepare a collection of monoglycosylated and multiple glycosylated DHPM derivatives at N1, C4, and C6 via parallel synthesis employing the Biginelli reaction of suitably *C*-glycosylated reactants. A further

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(9) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

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(13) For a survey on this topic with leading references, see: Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

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(15) For a preliminary report on this subject, see: Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2001**, *42*, 4495.

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(18) For a recent report on the synthesis of new guanidine-sugars and leading references to earlier work on these glycoconjugates, see: Lin, P.; Lee, C. L.; Sim, M. M. *J. Org. Chem.* **2001**, *66*, 8243.

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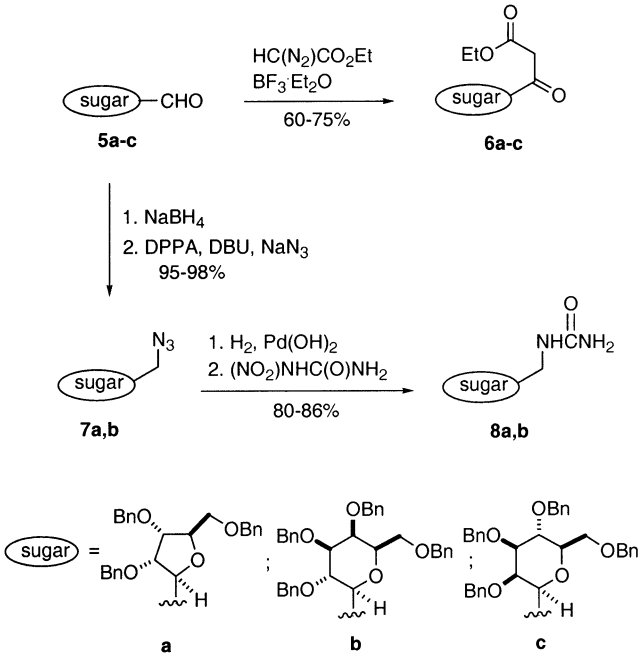
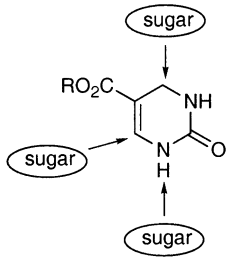
(20) (a) Hunziker, J.; Leumann, C. In *Modern Synthetic Methods 1995*; Ernst, B., Leumann, C., Eds.; VCH: Basel, 1995; p 333. (b) Wilson, L. W.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465. (c) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993. (d) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (e) Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903.

(21) Schnell, B.; Krenn, W.; Faber, K.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4382.

SCHEME 1

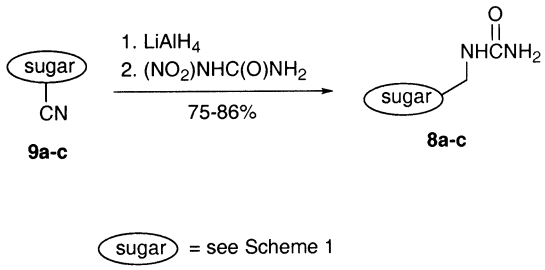


element of diversity was also foreseen by the use of different sugar residues in each substrate. A glycosidic carbon−carbon linkage in the reaction partners was a structural prerequisite to ensure substantial stability toward chemical and enzymatic degradation of the resulting glycosylated DHPM products.



Various anomeric sugar aldehydes (formyl *C*-glycosides) that we needed in this program were accessible in practical quantities starting from sugar lactones through our thiazole-based formylation method.[22] Hence, the *β*-linked *O*-benzyl-protected formyl ribofuranoside[23] **5a**, galactopyranoside[22b] **5b**, and mannopyranoside[22b] **5c** derivatives (Scheme 1) were prepared from the corresponding perbenzylated lactones as described. Moreover, these sugar aldehydes proved to be convenient precursors of the corresponding *C*-glycosyl *β*-ketoesters **6a**−**c** in satisfactory yield (60−75%) via BF_3·Et_2O-promoted coupling with ethyl diazoacetate (Scheme 1) according to a literature procedure.[24] The same aldehydes also turned out to be useful intermediates for the preparation of glycosylmethyl ureas[25] as shown in the case of the ribosyl

SCHEME 2



and galactosyl derivatives **8a** and **8b**. The reaction sequence involved the reduction ($NaBH_4$) of the sugar aldehydes **5a** and **5b** into the corresponding alcohols and transformation of these compounds into the glycosylmethyl azides **7a** and **7b** by the use of diphenylphosphoryl azide (DPPA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and sodium azide. The catalytic hydrogenation of these azides afforded the corresponding amines which upon condensation with nitrourea were transformed into the ureido sugars **8a** and **8b** following a literature procedure.[26] The reduction of the azido to the amino group required some caution such as a short reaction time (20 min) in order to avoid the removal of the *O*-benzyl groups from the sugar moiety. It is noteworthy that all steps in this reaction sequence were high yield reactions, and therefore compounds **8a** and **8b** were isolated in very good overall yields (76−84%).

The above route to glycosylmethyl ureas proved to be not viable in the case of the mannopyranosyl derivative **8c** due to a failure to obtain the corresponding sugar azide **7c**. In fact, treatment of the alcohol derived from the reduction of the aldehyde **5c** with DPPA, DBU, and NaN_3 did not proceed beyond the formation of a glycosylmethyl phosphate. The ureido sugar **8c** as well as the ribofuranosyl and galactopyranosyl derivatives **8a** and **8b** were conveniently prepared starting from the sugar nitriles **9a**−**c** via reduction to amines and condensation with nitrourea (Scheme 2). While this method appears to be quite efficient, its main drawback consists of access to the starting glycosyl cyanides **9a**−**c** since these *β*-linked anomers are obtained as minor isomers by *C*-glycosidation reaction of glycosyl acetates with TMSCN.[27]

Biginelli Reactions. Given the plethora of catalysts and conditions that have been proposed for the execution of the Biginelli reaction,[6−8] the model cyclocondensation of the *O*-tetrabenzylated formyl *C*-galactopyranoside **5b**, ethyl acetoacetate, and urea was studied under different reaction conditions (Table 1). Crucial to this program was finding a suitable acid additive that would be tolerated by the rather sensitive sugar moieties. Entries 1−4 of Table 1 indicated unsatisfactory conditions whereas entries 5−8 showed promising results. A convenient additive (Table 1, entry 9) consisted of a three-component system as a promoter constituted by CuCl/AcOH /BF_3·

(22) (a) Dondoni, A. *Pure Appl. Chem*. **2000**, *72*, 1577. (b) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem*. **1994**, *59*, 6404.

(23) It has to be noted that the *β*-D-configured formyl *C*-ribofuranoside **5a** was erroneously reported (ref 22b) to be the α-isomer. For a revision, see: Dondoni, A.; Formaglio, P.; Marra, A.; Massi, A. *Tetrahedron* **2001**, *57*, 7719.

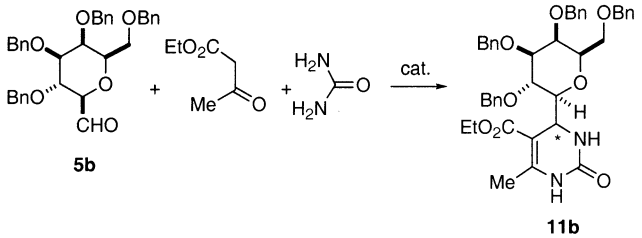
(24) Dhavale, D. D.; Bhujbal, N. N.; Joshi, P.; Desai, S. G. *Carbohydr. Res*. **1994**, *263*, 303.

(25) The attachment of the sugar moiety to the urea through a methylene bridge was designed in order to ensure higher stability with respect to the *N*-glycosyl derivative.

(26) Winkley, M. W. *Carbohydr. Res*. **1973**, *31*, 245.

(27) (a) Togo, H.; Ishigami, S. Fujii, M.; Ikuma, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2931. (b) Igarashi, Y.; Shiozawa, T.; Ichikawa, Y. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 613 and references therein.

TABLE 1. Study of the Model Biginelli Reaction[a]



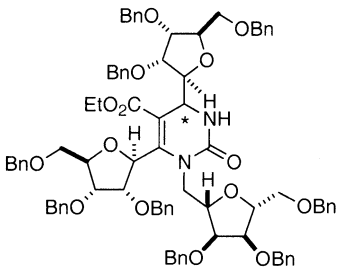
run	additive (equiv)	solvent	*T* (°C)	time (h)	% yield[b] of **11b**
1	aq HCl (cat.)	EtOH	reflux	15	5
2	montmorillonite[c]	THF	reflux	48	5
3	montmorillonite[c]	toluene	100	48	10
4	$InCl_3$ (cat.)	THF	reflux	14	12
5	$InCl_3$(1)	THF	reflux	14	27
6	$Yb(OTf)_3$ (cat.)	THF	reflux	14	32
7	$Yb(OTf)_3$ (1)	THF	reflux	14	60
8	CuCl (cat.) AcOH (cat) BF_3 Et_2O (1.3)	THF	65	14	35
9	CuCl (1) AcOH (0.2) BF_3 Et_2O (1.3)	THF	65	14	48
10	CuCl (1) AcOH (0.2) BF_3 Et_2O (1.3)	THF	65	24	65

[a] All reactions were run with 0.5 mmol of **5b**, 1 equiv of ethyl acetoacetate, and 1.5 equiv of urea in 2 mL of solvent in the presence of 4 Å molecular sieves. [b] Isolated yields of mixtures of diastereoisomers (ca. 5:1 by NMR). [c] Montmorillonite KSF.

Et_2O in *noncatalytic* amount.[28] Optimized conditions were established in THF as a solvent using a reaction temperature and time of 65 °C and 24 h, respectively (Table 1, entry 10). It has to be noted that in all cases the product **11b** consisted of a mixture of diastereoisomers with a marked predominance of one over the other (ca. 5:1).

Due to the satisfactory results of the CuCl/AcOH/BF_3·Et_2O-promoted cyclocondensation of the sugar aldehyde **5b**, the reactions of some of the possible combinations of glycosylated reagents **5**, **6**, **8**, ethyl acetoacetate, aryl aldehydes, and urea were carried out in a parallel manner in order to obtain a collection of mono- and polyglycosylated DHPMs (Table 2). The use of a single glycosylated partner afforded the DHPM glycoconjugate triads **11a**−**c**, **12a**−**c**, and **14a**−**c** in which the heterocyclic ring featured a single sugar residue at C4, C6, and N1, respectively. Compound **13a** represented a type of DHPM derivative that partly resembled compound **3** of Figure 2 since the phenyl ring at C4 was ortho substituted by a trifluoromethyl group. All products **11**−**14** of these Biginelli reactions were obtained as mixtures of diastereoisomers due to the formation of the stereocenter at C4 of the DHPM ring. The overall yields ranged from the excellent value (92%) of **12a** to the modest value (40%) of **14c**. Stereoselectivities varied in a significant range as well since the C4 and C6 glycosylated compounds (*R*)-**11b** and (*S*)-**12b** were obtained with good stereoisomeric excess whereas all the N1-glycosylated derivatives **14a**−**c** were obtained as ca. 1:1 mixtures of diastereoisomers. These stereochemical outcomes are consistent with the main reaction pathway that has been recently identified in the Biginelli reaction.[6a] The proposed mechanism consists of an initial step of condensation between the aldehyde and urea to form an *N*-acyliminium ion intermediate that is trapped by the ketoester to give an open-chain ureide (α-amidoalkylation sequence), which in turn cyclizes to the final product. Since the C4 stereocenter of the DHPM ring is established in the *N*-acyliminium ketoester carbon−carbon bond-forming reaction, it is reasonable that chiral residues in the aldehyde and ketoester exert some internal asymmetric induction while chiral moieties in the urea are inefficient.

Cyclocondensations were also carried out using two glycosylated reaction partners, i.e., the aldehydes and ketoesters (Table 2). Mixtures of bisglycosylated DHPM derivatives **15a**−**c** were obtained in modest chemical yields very likely because of the bulkiness of the two reactants. On the other hand, the level of asymmetric induction was much higher than in the above monoglycosylated products, which indicates that the two sugar components match quite well in the creation of the C4 stereocenter with a preferred configuration. As anticipated by the modest yields of isolated products **15a**−**c**, the cyclocondensation employing three glycosylated reaction partners became problematic due to the considerable steric interactions. Attempts to preparing the DHPM trisglycoconjugate **16a** by cyclocondensation of the ribosyl derivatives **5a**, **6a**, and **8a** has failed so far as this compound was only detected by mass spectroscopy in the crude reaction mixture.

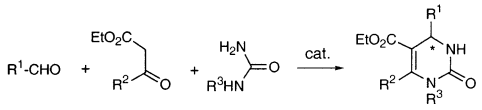


16a

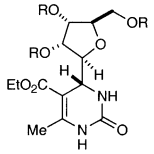
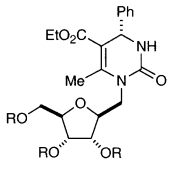
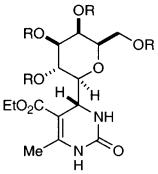
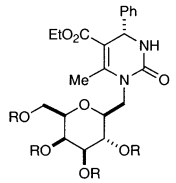
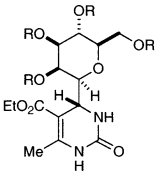
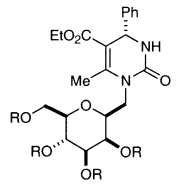
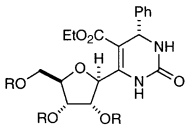
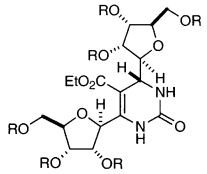
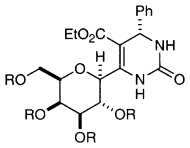
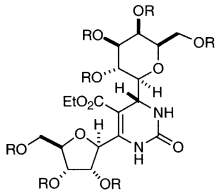
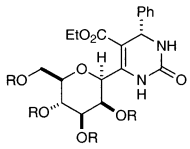
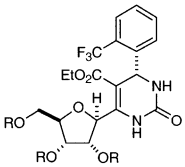
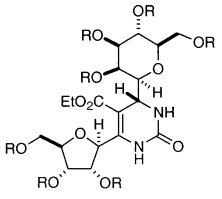
In Table 2 are reported the structures of the major diastereoisomers obtained in the various cyclocondensation reactions that have been examined. In fact, the isomers of each reaction mixture were adequately separated by chromatography and each individual compound was characterized through its NMR and mass spectral data. The absolute configuration at C4 was assigned by a circular dichroism study using the *O*-debenzylated derivatives (see below). The removal of the *O*-benzyl groups from the sugar residues was carried out in almost quantitative manner by hydrogenation over $Pd(OH)_2$. In addition to the structural assignment, the sugar *O*-debenzylated derivatives **11a′**−**15c′** shown in Table 2 and their epimers at C4 are products of considerable importance since they are suitable substrates for biological and pharmacological studies. In closing this section, it is worth pointing out that all of the glycosylated Biginelli products prepared can be viewed as members of new classes of mono- and bis-*C*-nucleosides. The method

(28) The use of catalytic CuCl as described in ref 7f afforded the Biginelli product in much lower yield (ca. 30%). It is likely that the presence of powdered 4-Å molecular sieves, acting as acid sponge, interfered with the action of the heterogeneous promoter.

TABLE 2. 3,4-Dihydropyrimidin-2(1*H*)-one Glycoconjugates 11−15 Prepared[a]



11-15

R^1, R^2, R^3	Product [b]	Yield %[c]	D.e.%	R^1, R^2,R^3	Product[b]	Yield %[c]	D.e.%
ribosyl , Me, H	 **(*R*)-11a** (R = Bn) **(*R*)-11a'** (R = H)	63	50	Ph, Me, CH_2-ribosyl	 **(*S*)-14a** (R = Bn) **(*S*)-14a'** (R = H)	48	0
galactosyl, Me, H	 **(*R*)-11b** (R = Bn) **(*R*)-11b'** (R = H)	65	70	Ph, Me ,CH_2-galactosyl	 **(*S*)-14b** (R = Bn) **(*S*)-14b'** (R = H)	41	0
mannosyl, Me, H	 **(*R*)-11c** (R = Bn) **(*R*)-11c'** (R = H)	57	50	Ph, Me , CH_2-mannosyl	 **(*S*)-14c** (R = Bn) **(*S*)-14c'** (R = H)	40	0
Ph, ribosyl, H	 **(*S*)-12a** (R = Bn) **(*S*)-12a'** (R = H)	92	50	ribosyl, ribosyl, H	 **(*R*)-15a** (R = Bn) **(*R*)-15a'** (R = H)	42	80
Ph, galactosyl, H	 **(*S*)-12b** (R = Bn) **(*S*)-12b'** (R = H)	75	70	galactosyl, ribosyl, H	 **(*R*)-15b** (R = Bn) **(*R*)-15b'** (R = H)	35	82
Ph, mannosyl, H	 **(*S*)-12c** (R = Bn) **(*S*)-12c'** (R = H)	70	50				
2-(CF_3)-C_6H_4, ribosyl, H	 **(*S*)-13a** (R = Bn) **(*S*)-13a'** (R = H)	82	35	mannosyl, ribosyl, H	 **(*R*)-15c** (R = Bn) **(*R*)-15c'** (R = H)	36	76

[a] All Biginelli reactions were run in THF at 65 °C using the mixture CuCl/AcOH/BF_3·Et_2O as additive (for details see the Experimental Section). [b] Only the major diastereoisomer is shown. [c] Overall yield of the mixture of diastereoisomers.

described herein is, therefore, a new approach to *C*-nucleosides via a one-pot multicomponent cyclocondensation reaction.

Structure Assignments. Structure and absolute configuration assignments of compounds **11**−**15** were performed using mono- and bidimensional ^{1}H and ^{13}C NMR spectroscopic analysis in conjunction with chiroptical data, i.e., Cotton effects (CE), as determined by circular dichroism (CD). The X-ray structure determination of one crystalline compound was also carried out. The β-linkage at the anomeric carbon (C1′) of the sugar moieties was confirmed for all compounds by estimating the $J_{1',2'}$ values or by the aid of NOE measurements, as appropriate. In fact, galactopyranosyl derivatives showed $J_{1',2'}$ values around 9.0 Hz while the ribofuranosyl and mannopyranosyl derivatives displayed probing NOE values between H1′ and H4′ or H1′ and H5′, respectively. These results indicate that the stereochemical integrity at the anomeric carbon of the glycosylated reagents **5**, **6**, and **8** was retained in the course of the three-component cyclocondensation reactions. The assignment of the absolute configuration at the C4 stereocenter was initially based on the comparison of CD spectra with those of DHPMs with known absolute configuration.[29] The observed CD spectra (Figure 3) of the 4-phenyl-6-(β-D-ribofuranosyl) derivative (*S*)-**12a′** (Table 2) and its C4 (*R*)-epimer appeared to be very similar to those reported for other (*S*)- and (*R*)-configured 4-aryl-DHPMs,[29a−c] being of the mirror-image type and exhibiting two bands of opposite sign at 300 and 230 nm. Although the risk of deducing the absolute stereochemistry by direct comparison of CD spectra has been stressed by several authors,[30] this experimental approach has proved to be reliable so far for the determination of the C4 configuration of various biologically active DHMPs.[29b,c] Therefore, the CD spectrum showing a positive long wavelength and a negative short wavelength $\Delta\epsilon$ was attributed to the stereoisomer (*S*)-**12a′** in complete agreement with previously reported assignments.[29a] Very similar CD spectra of the mirror-image type showing the same *minus*−*plus* couplet were also observed for each pair of diastereoisomers of 4-aryl C6-glycosylated DHMPs **12b′**, **12c′**, and **13a′** and N1-glycosylated DHPMs **14a′**−**c′**. Accordingly, the 4*S*-configuration was assigned to those diastereoisomers showing in their CD spectra positive sign of the first (ca. 300 nm) and negative sign of the second band (ca. 230 nm) on the basis of the previously described experimental method.[29a]

The CD spectra of (4*R*)- and (4*S*)-6-methyl-4-(β-D-ribofuranosyl) derivatives **11a′** (Table 2) appeared as mirror images as well but exhibited two bands of like sign at ca. 290 and 240 nm (Figure 4). The CD spectrum showing two negative Cotton effects was tentatively assigned to the (4*R*) diastereoisomer[31] in agreement with

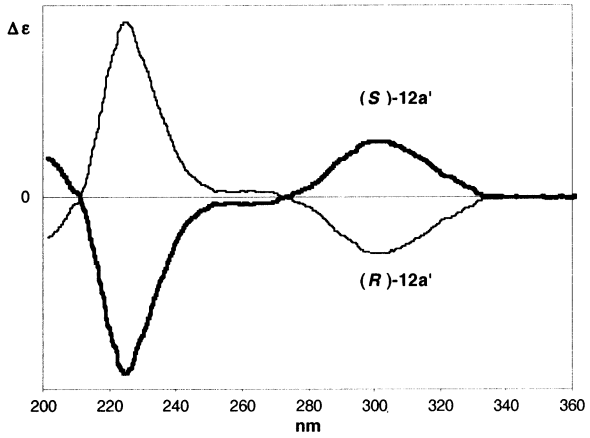


FIGURE 3. Experimental CD spectra of (*S*)-**12a′** and (*R*)-**12a′**.

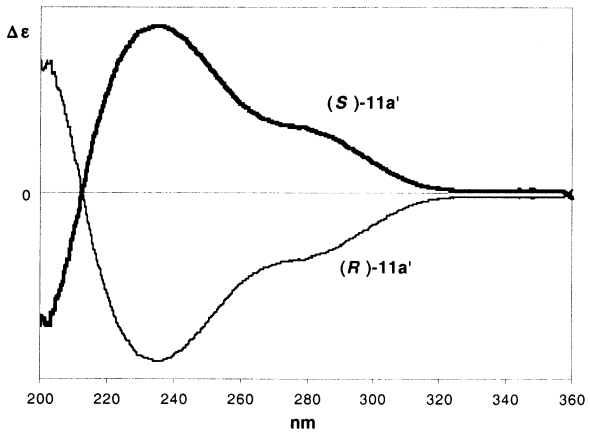


FIGURE 4. Experimental CD spectra of (*S*)-**11a′** and (*R*)-**11a′**.

similar CD data of various 4-alkyl DHPMs.[29d] Since similar shapes were also observed in the CD spectra of the C4 glycosylated compounds **11b′** and **11c′** and the C4 and C6 bis-glycosylated derivatives **15a′**−**c′**, the absolute *R* configuration at C4 was assigned following the same reasoning. These structure assignments were confirmed by the X-ray crystallographic analysis of the C4 glycosylated derivative[32] (*R*)-**17b** whose deprotected derivative (*R*)-**17b′** showed the same shape in the CD spectrum (two bands with negative sign at ca. 290 and 240 nm) observed for all the above C4 glycosylated compounds which were assigned the *R*-configuration.

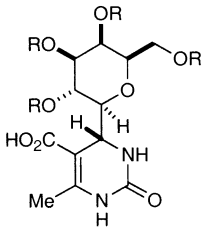
Synthesis of *C*-Glycosylated Monastrol Analogues. Out of a 16320-member collection of small-molecules, monastrol **4** (Figure 2) has been identified as a compound that specifically affects mitosis without targeting tobulin.[14] It has been established that monastrol activity consists of the specific and reversible inhibition of the motility of the mitotic kinesin Eg5, a motor protein known to be required for spindle bipolarity. Due to this biological activity combined with cell permeability, monastrol can be considered as a lead compound for the development of new anticancer drugs. The synthesis of

(29) (a) Krenn, W.; Verdino, P.; Uray, G.; Faber, K.; Kappe, C. O. *Chirality* **1999**, *11*, 659. (b) Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K. ; Kappe, C. O.*Tetrahedron*: *Asymmetry* **2000**, *11*, 1449. (c) Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859. (d) Uray, G.; Verdino, P.; Belaj, F.; Kappe, C. O.; Fabian, W. M. F. *J. Org. Chem.* **2001**, *66*, 6685.

(30) (a) Hansen, A. E.; Bouman, T. D. *Adv. Chem. Phys.* **1980**, *44*, 545. (b) Ripa, L.; Hallberg, A.; Sandström, J. *J. Am. Chem. Soc.* **1997**, *119*, 5701.

(31) It has to be noted that the assignment of the opposite configuration with respect to the ref 29d is due to the different substituent priorities.

(32) Compound (*R*)-**17b** was prepared by selective debenzylation of the corresponding *O*-benzyl ester which was in turn obtained by the standard cyclocondensation reaction using benzyl acetoacetate, urea, and the aldehyde **5b** (see the Experimental Section).

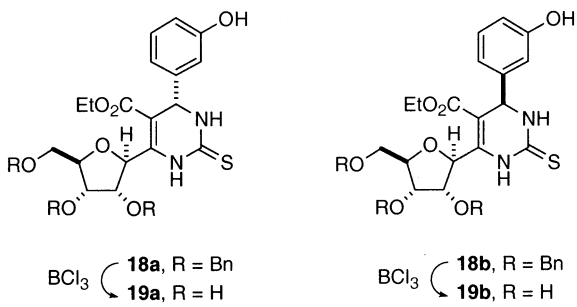


(*R*)-**17b**, R = Bn
(*R*)-**17b'**, R = H

glycosylated monastrol analogues would, therefore, appear to be of great interest.

Wishing to prepare a C6-glycosylated modified monastrol via cyclocondensation of the ribofuranosyl-containing ketoester **6a** with 3-hydroxybenzaldehyde and thiourea (Scheme 3), we found that the three-component CuCl/AcOH/BF_3·Et_2O promoter was not compatible with the latter sulfur-containing reagent since the reaction did not produce appreciable amounts of product. Instead, the use of 0.5 equiv of $Yb(OTf)_3$ proved to be quite beneficial since with this Lewis acid the reaction afforded the C6-glycosylated dihydropyrimidinethione **18** in fair yield (66%) as a mixture of diastereoisomers in a 2:1 ratio.

Attempts to remove the *O*-benzyl groups from the sugar moiety of **18** via Pd-catalyzed hydrogenolysis proved to be unsuccessful due to the inactivation of the catalyst by the thione group. Under these conditions, most of the starting compound **18** was recovered unaltered or decomposed to give desulfurated material. Hence, the two diastereoisomers **18a** and **18b** were separated by chromatography and each individual product was subjected to debenzylation using BCl_3 in methylene dichloride solution at low temperature followed by quenching with a 1:1 mixture of ethanol−methylene dichloride. The yield of this debenzylation procedure was quite fair (75%). The resulting hydroxy-free derivatives **19a** and **19b** were suitable compounds for the absolute configuration assignment at the C4 stereocenter by the CD method as described above for the 4-aryl-6-glycosyldihydropyrimidinones **12a′**−**c′** and **13a′** (see Table 2). As the mirror-image type CD spectra of the major and minor stereoisomer **19a** and **19b** shown in Figure 5 were similar to that of Figure 3 and to those of monastrol enantiomers,[29c] it can be deduced that also in this case the major stereoisomer was that with the (4*S*) configuration.



BCl_3 → **18a**, R = Bn; **19a**, R = H
BCl_3 → **18b**, R = Bn; **19b**, R = H

An alternative synthetic route leading to the glycoconjugates **19a** and **19b** was explored using the known *C*-glycosylated ketoester **20** having *O*-benzoylated hy-

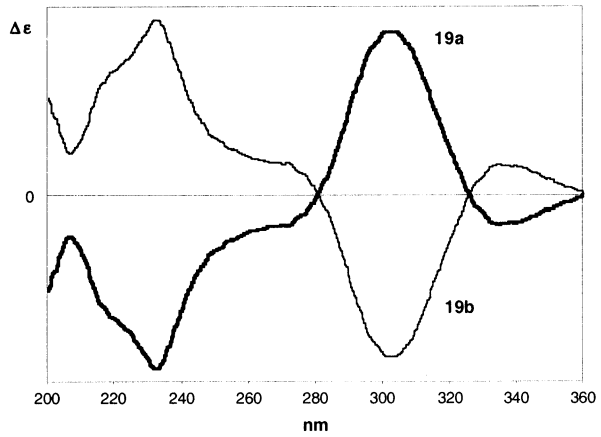
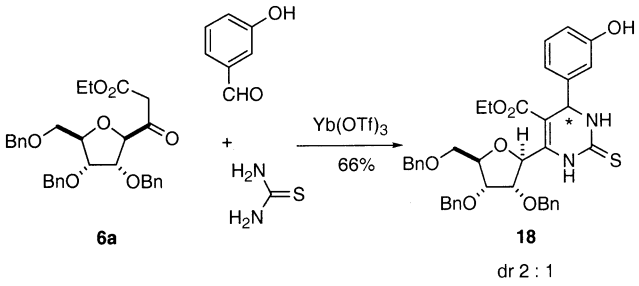
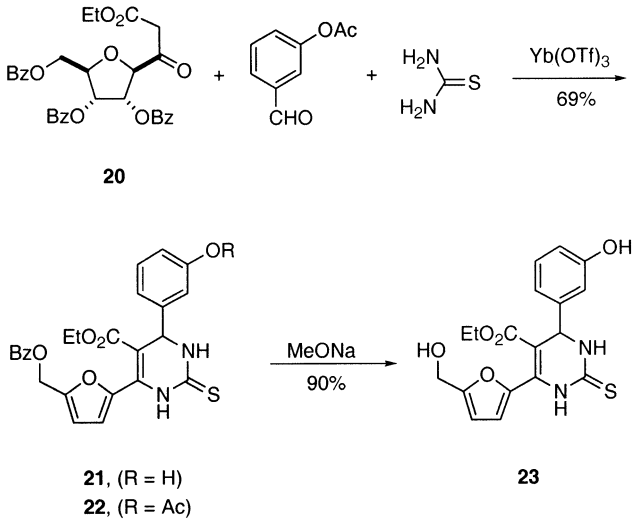


FIGURE 5. Experimental CD spectra of **19a** and **19b**.

SCHEME 3



SCHEME 4



droxy groups[33] (Scheme 4). It was hoped that the easily removable ester groups from the sugar residue would provide a high yield protocol. Instead, the $Yb(OTf)_3$-promoted cyclocondensation of **20** with 3-acetoxybenzaldehyde[34] and thiourea afforded a mixture of the C6-substituted furyl dihydropyrimidinethiones **21** and its *O*-acetyl derivative **22** in a 2:1 ratio in 69% overall yield (Scheme 4). The removal of the benzoyl and acetyl protective groups by basic treatment afforded racemic furyl dihydropyrimidinethione **23** as a single product (α_D

(33) Morelli, C. F.; Manferdini, M.; Veronese, A. C. *Tetrahedron* **1999**, *55*, 10803.
(34) The phenolic hydroxy group was protected in order to avoid possible transesterification reactions by the *O*-benzoyl groups.

= 0). These results can be explained by assuming that compound **20** is highly unstable under the Biginelli reaction conditions and undergoes a fast elimination of two molecules of benzoic acid to give a furyl ketoester, which in turn takes part in an achiral cyclocondensation process.

In conclusion, it has been shown that the three-component Biginelli reaction can be applied for the synthesis of different mono- and bis-*C*-glycosylated DHPMs. Given the availability of various glycosylated aldehydes, ketoesters, and ureas, this methodology should permit access to a combinatorial library of glycosylated Biginelli products with a wide range of structural and stereochemical elements of diversity for an extensive exploration of biological properties. It is noteworthy that the Biginelli reactions with glycosylated ketoesters and aldehydes occur with satisfactory asymmetric induction leading to chiral products with a given configuration at the C4 stereocenter of the DHPM ring. This is a remarkable result in view of the strict dependence of the biological properties of this pharmacophore on the configuration at C4. Within the framework of this concept, it appears that it is possible to prepare chiral glycosylated monastrol analogues for an extensive exploration to discover new anticancer drugs.

Experimental Section

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. Flash column chromatography[35] 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) 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. For bisglycosylated DHPMs **15a**−**c** and **15a′**−**c′** *r*, *g*, and *m* refer to *ribo*, *galacto*, and *manno* moieties, respectively; *r4* and *r6* refer to *ribo* moieties linked to the 4 and 6 positions of the heterocycle, respectively. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. CD measurements were carried out using 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 **5a**−**c**,[22b,23] nitriles **9a**−**c**,[27] and β-ketoester **20**[33] were synthesized as described.

Ethyl 3-Oxo-3-(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-propanoate (6a). A mixture of aldehyde **5a** (864 mg, 2.00 mmol), ethyl diazoacetate (0.32 mL, 3.00 mmol), activated 4-Å powdered molecular sieves (600 mg), and anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature for 15 min and then cooled to 0 °C. To the mixture was added drop by drop a solution of BF_3·Et_2O (127 μL, 1.00 mmol) in anhydrous CH_2Cl_2 (2 mL), 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 **6a** (622 mg, 60%) as a white amorphous solid. $[\alpha]_D^{20}$ = +81.0 (*c* 0.6, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.40−7.20 (m, 15 H, 3 Ph), 4.66, 4.62 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.62, 4.54 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.56, 4.52 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.48 (d, 1 H, $J_{1',2'}$ = 5.0 Hz, H-1′), 4.25 (dd, 1 H, $J_{2',3'}$ = 4.8 Hz, H-2′), 4.20 (ddd, 1 H, $J_{3',4'}$ = 5.2 Hz, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 4.8 Hz, H-4′), 4.10 (q, 2 H, J = 7.0 Hz, CH_2CH$_3$), 3.95 (dd, 1 H, H-3′), 3.67 (dd, 1 H, $J_{5'a,5'b}$ = 11.0 Hz, H-5′a), 3.66, 3.61 (2 d, 2 H, J = 14.5 Hz, 2 H-2), 3.59 (dd, 1 H, H-5′b), 1.20 (t, 3 H, CH_3). Anal. Calcd for $C_{31}H_{34}O_7$ (518.60): C, 71.80; H, 6.61. Found: C, 71.82; H, 6.65.

Ethyl 3-Oxo-3-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)propanoate (6b). Aldehyde **5b** (1.10 g, 2.00 mmol) was treated as described for the preparation of **6a**. Column chromatography on silica gel of the residue with 6:1 cyclohexane−AcOEt afforded **6b** (958 mg, 75%) as a syrup. $[\alpha]_D^{20}$ = +22.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.50−7.20 (m, 20 H, 5 Ph), 4.86, 4.58 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.80, 4.59 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.75, 4.69 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.53, 4.49 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.13−4.04 (m, 3 H), 3.99−3.92 (m, 2 H), 3.87−3.76 (m, 2 H), 3.65 (dd, 1 H, $J_{5',6'a}$ = 6.0 Hz, $J_{6'a,6'b}$ = 10.2 Hz, H-6′a), 3.60 (s, 2 H, 2 H-2), 3.59 (dd, 1 H, $J_{5',6'b}$ = 6.8 Hz, H-6′b), 1.17 (t, 3 H, J = 7.0 Hz,CH_3). Anal. Calcd for $C_{39}H_{42}O_8$ (638.75): C, 73.33; H, 6.63. Found: C, 73.28; H, 6.60.

Ethyl 3-Oxo-3-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-mannopyranosyl)propanoate (6c). Aldehyde **5c** (1.10 g, 2.00 mmol) was treated as described for the preparation of **6a**. Column chromatography on silica gel of the residue with 6:1 cyclohexane−AcOEt afforded **6c** (920 mg, 72%) as a syrup. $[\alpha]_D^{20}$ = +11.2 (*c* 1.5, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.50−7.20 (m, 20 H, 5 Ph), 4.83 and 4.70 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.80 and 4.61 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.80 and 4.50 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.62 and 4.54 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.42 (dd, 1 H, $J_{1',2'}$ = 0.8 Hz, $J_{2',3'}$ = 1.0 Hz, H-2′), 4.17 (d, 1 H, H-1′), 4.09 (dq, 2 H, J = 2.0, J = 7.0 Hz, CH_2CH$_3$), 3.88 (dd, 1 H, $J_{3',4'}$ = 8.8 Hz, $J_{4',5'}$ = 9.0 Hz, H-4′), 3.85−3.73 (m, 3 H, H-3′, H-6′a, H-6′b), 3.72 and 3.48 (2 d, 2 H, J = 15.5 Hz, 2 H-2), 3.55 (ddd, 1 H, $J_{5',6'a}$ = 3.0 Hz, $J_{5',6'b}$ = 4.0 Hz, H-5′), 1.18 (t, 3 H, J = 7.0 Hz,CH_3). Anal. Calcd for $C_{39}H_{42}O_8$ (638.75): C, 73.33; H, 6.63. Found: C, 73.31; H, 6.61.

(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)methyl Azide (7a). To a cooled (0 °C), stirred solution of aldehyde **5a** (864 mg, 2.00 mmol) in CH_3OH (10 mL) was added $NaBH_4$ (113 mg, 3.00 mmol). The mixture was stirred at 0 °C for an additional 10 min, diluted with acetone (2 mL), warmed to room temperature, and concentrated. The residue was suspended in CH_2Cl_2 (80 mL), washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated to give (2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)methyl alcohol (851 mg, ∼98%) at least 95% pure by NMR analysis and suitable for the next step (for analytical data see ref 23).

To a stirred solution of the above crude alcohol (851 mg, ∼1.96 mmol), diphenylphosphoryl azide (1.27 mL, 5.88 mmol), and anhydrous DMF (8 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (292 μL, 1.96 mmol). The solution was warmed to 100 °C and stirred for 2 h. Then NaN_3 (382 mg, 5.88 mmol) was added in one portion and the mixture stirred at 100 °C for an additional 2 h. The mixture was cooled to room temperature, diluted with H_2O (10 mL), and extracted with Et_2O (3 × 40 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 7:1 cyclohexane−AcOEt to give **7a** (883 mg, 98%) as a yellow oil. $[\alpha]_D^{20}$ = −65.0 (*c* 1.2, $CHCl_3$) (lit.[36] $[\alpha]_D^{25}$ = −62.8). ^{1}H NMR: δ = 7.45−7.20 (m, 15 H, 3 Ph), 4.61 and 4.48 (2 d, 2

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H, J = 11.0 Hz, PhCH_2), 4.59 (s, 2 H, PhCH_2), 4.58 and 4.52 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.30−4.23 (m, 1 H, H-4′), 4.20 (ddd, 1 H, $J_{1a,\,1'}$ = 4.0, $J_{1b,1'}$ = 5.0 Hz, $J_{1',2'}$ = 6.0 Hz, H-1′), 3.94 (dd, 1 H, $J_{2',3'}$ = 5.0 Hz, $J_{3',4'}$ = 3.5 Hz, H-3′), 3.87 (dd, 1 H, H-2′), 3.58−3.49 (m, 3 H, H-1a, H-5′a, H-5′b), 3.22 (dd, 1 H, $J_{1a,1b}$ = 13.0 Hz, H-1b). Anal. Calcd for $C_{27}H_{29}N_3O_4$ (459.54): C, 70.57; H, 6.36; N, 9.14. Found: C, 70.50; H, 6.31; N, 9.09.

(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)methyl Azide (7b). Aldehyde **5b** (1.10 g, 2.00 mmol) was treated as described for the preparation of **7a**. In the first step, crude (2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)methyl alcohol (1.10 g, ∼99%) was obtained at least 95% pure by NMR analysis and suitable for the next step (for analytical data see ref 37).

To a stirred solution of the above crude alcohol (1.10 g, ∼1.98 mmol), diphenylphosphoryl azide (1.28 mL, 5.94 mmol), and anhydrous DMF (8 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (295 μL, 1.98 mmol). The solution was warmed to 100 °C and stirred for 2 h. Then NaN_3 (386 mg, 5.94 mmol) was added in one portion and the mixture stirred at 100 °C for an additional 12 h. The mixture was cooled to room temperature, diluted with H_2O (10 mL), and extracted with Et_2O (3 × 40 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 12:1 cyclohexane−AcOEt to give **7b** (1.10 g, 96%) as a yellow oil. $[\alpha]_D^{20}$ = −23.1 (*c* 3.1, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.20 (m, 20 H, 4 Ph), 4.99 and 4.67 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.98 and 4.64 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.80 and 4.70 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.53 and 4.45 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.20 (dd, 1 H, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.90 (dd, 1 H, $J_{1',2'}$ = 8.9 Hz, $J_{2',3'}$ = 9.0 Hz, H-2′), 3.66 (dd, 1 H, H-3′), 3.65−3.58 (m, 3 H, H-5′, H-6′a, H-6′b), 3.53−3.45 (m, 2 H, H-1a, H-1′), 3.39 (dd, 1 H, $J_{1a,1b}$ = 13.0 Hz, $J_{1b,1'}$ = 6.5 Hz, H-1b). Anal. Calcd for $C_{35}H_{37}N_3O_5$ (579.69): C, 72.52; H, 6.43; N, 7.25. Found: C, 72.60; H, 6.48; N, 7.32.

(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)methylurea (8a). Route A. A vigorously stirred mixture of **7a** (689 mg, 1.50 mmol), 20% palladium hydroxide on carbon (345 mg), and AcOEt (8 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 20 min under a slightly positive pressure of hydrogen (balloon), filtered through a plug of cotton, and concentrated to give (2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)methylamine (643 mg, ∼99%) at least 95% pure by NMR analysis and suitable for the next step. ^{1}H NMR δ = 7.45−7.20 (m, 15 H, 3 Ph), 4.65 and 4.52 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.63 and 4.58 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.58 and 4.52 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.24 (ddd, 1 H, $J_{3',4'}$ = 5.5 Hz, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 4.0 Hz, H-4′), 4.07 (ddd, 1 H, $J_{1a,1'}$ = 3.0 Hz, $J_{1b,1'}$ = 5.5 Hz, $J_{1',2'}$ = 6.5 Hz, H-1′), 3.96 (dd, 1 H, $J_{2',3'}$ = 5.0 Hz, H-3′), 3.80 (dd, 1 H, H-2′), 3.58 (dd, 1 H, $J_{5'a,5'b}$ = 10.5 Hz, H-5′a), 3.53 (dd, 1 H, H-5′b), 2.97 (dd, 1 H, $J_{1a,1b}$ = 13.5 Hz, H-1a), 2.71 (dd, 1 H, H-1b).

To a stirred solution of the above crude amine (643 mg, ∼1.48 mmol) in absolute EtOH was added nitrourea (187 mg, 1.78 mmol) in one portion. The mixture was stirred under reflux for 1.5 h, cooled to room temperature, and concentrated. The residue was eluted from a column of silica gel with 20:1 AcOEt−MeOH to give **8a** (566 mg, 80%) as a white solid: mp 89−90 °C (cyclohexane−AcOEt). $[\alpha]_D^{20}$ = 18.0 (*c* 1.0, EtOH) (lit.[26] $[\alpha]_D^{26}$ = 18.7 (*c* 1.0, EtOH)). ^{1}H NMR: δ = 7.50−7.20 (m, 15 H, 3 Ph), 5.05 (bs, 1 H, NH), 4.66 and 4.35 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.62 and 4.57 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.49 and 4.45 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.24−4.10 (m, 2 H, H-1′, H-4′), 3.99 (dd, 1 H, J = 5.0, J = 6.0 Hz, H-2′ or H-3′), 3.90 (dd, 1 H, J = 3.5, 5.0 Hz, H-2′ or H-3′), 3.80 (dd, 1 H, $J_{4',5'a}$ = 3.0 Hz, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.59 (dd, 1 H, $J_{4',5'b}$ = 2.5 Hz, H-5′b), 3.57−3.36 (m, 3 H, H-1a, NH_2), 3.19 (dd, 1 H, $J_{1a,1b}$ = 14.5 Hz, $J_{1b,1'}$ = 3.0 Hz, H-1b). Anal. Calcd for $C_{28}H_{32}N_2O_5$ (476.56): C, 70.57; H, 6.77; N, 5.88. Found: C, 70.50; H, 6.71; N, 5.87.

Route B. To a stirred mixture of $LiAlH_4$ (304 mg, 8.00 mmol) and anhydrous THF (10 mL) was added a solution of sugar nitrile **9a** (858 mg, 2.00 mmol) in anhydrous THF (2 mL). The mixture was stirred under reflux for 30 min, cooled to room temperature, and diluted with 28% NH_4OH (1 mL). The mixture was stirred at room temperature for an additional 30 min, filtered through a pad of Celite, and concentrated to give crude (2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)methylamine (857 mg, ∼99%) at least 95% pure by NMR analysis and suitable for the next step.

To a stirred solution of the above crude amine (857, ∼1.98 mmol) in absolute EtOH was added nitrourea (252 mg, 2.40 mmol) in one portion. The mixture was stirred under reflux for 1.5 h, cooled to room temperature, and concentrated. The residue was eluted from a column of silica gel with 20:1 AcOEt/MeOH to give **8a** (755 mg, 80%).

(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)methylurea (8b). Route A. Azide **7b** (870 mg, 1.50 mmol) was treated as described for the preparation of **8a**. In the first step, crude (2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)methylamine (821 mg, ∼99%) was obtained at least 95% pure by NMR analysis and suitable for the next step. ^{1}H NMR: δ = 7.50−7.20 (m, 20 H, 4 Ph), 4.95 and 4.63 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.94 and 4.65 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.78 and 4.70 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.48 and 4.43 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.00 (dd, 1 H, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.75 (dd, 1 H, $J_{1',2'}$ = 8.9 Hz, $J_{2',3'}$ = 9.0 Hz, H-2′), 3.64 (dd, 1 H, H-3′), 3.63−3.48 (m, 3 H, H-5′, H-6′a, H-6′b), 3.26 (bddd, 1 H, H-1′), 3.04 (bdd, 1 H, H-1a), 2.77 (bdd, 1 H, H-1b).

Treatment of the above crude amine (821 mg, ∼1.49 mmol) as described for the preparation of **8a** afforded **8b** (762 mg, 86%) as a white amorphous solid. $[\alpha]_D^{20}$ = 8.0 (*c* 0.4, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.20 (m, 20 H, 4 Ph), 4.97 and 4.59 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.93 and 4.68 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.87 (bs, 1 H, NH), 4.80 and 4.72 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.47 (s, 2 H, PhCH_2), 4.34 (bs, 2 H, NH_2), 3.98 (dd, 1 H, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = ∼ 0.5 Hz, H-4′), 3.80 (dd, 1 H, $J_{1',2'}$ = 8.9 Hz, $J_{2',3'}$ = 9.0 Hz, H-2′), 3.63 (dd, 1 H, H-3′), 3.59−3.40 (m, 5 H, 2 H-1, H-5′, 2 H-6′), 3.41−3.30 (m, 1 H, H-1′). Anal. Calcd for $C_{36}H_{40}N_2O_6$ (596.71): C, 72.46; H, 6.76; N, 4.69. Found: C, 72.53; H, 6.80; N, 4.73.

Route B. Treatment of sugar nitrile **9b** (1.10 g, 2.00 mmol) as described for the preparation of **8a** afforded **8b** (1.02 g, 86%).

(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)methylurea (8c). Sugar nitrile **9c** (1.10 g, 2.00 mmol) was treated as described for the preparation of **8a** (route B). In the first step, crude (2′,3′,4′,6′-tetra-*O*-benzyl-β-D-mannopyranosyl)methylamine (1.09 g, ∼99%) was obtained at least 95% pure by NMR analysis and suitable for the next step. ^{1}H NMR: δ = 7.50−7.10 (m, 20 H, 4 Ph), 5.20 and 4.72 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.91 and 4.57 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.82 and 4.76 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.65 and 4.57 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 3.94 (dd, 1 H, $J_{3',4'}$ = 8.9 Hz, $J_{4',5'}$ = 9.0 Hz, H-4′), 3.87 (dd, 1 H, $J_{1',2'}$ = ∼0.5 Hz, $J_{2',3'}$ = 2.8 Hz, H-2′), 3.78 (dd, 1 H, $J_{5',6'a}$ = 2.0 Hz, $J_{6'a,6'b}$ = 10.5 Hz, H-6′a), 3.72 (dd, 1 H, $J_{5',6'b}$ = 5.0 Hz, H-6′b), 3.65 (dd, 1 H, H-3′), 3.49 (ddd, 1 H, H-5′), 3.25 (ddd, 1 H, $J_{1a,1'}$ = 7.0 Hz, $J_{1b,1'}$ = 5.5 Hz, H-1′), 3.01 (dd, 1 H, $J_{1a,1b}$ = 13.0 Hz, H-1a), 2.64 (dd, 1 H, H-1b).

Treatment of the above crude amine (1.09 g, ∼1.98 mmol) as described for the preparation of **8a** afforded **8c** (1.00 g, 85%) as a white foam. $[\alpha]_D^{20}$ = 4.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.10 (m, 20 H, 4 Ph), 4.99 and 4.55 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.95 (bs, 1 H, NH), 4.91 and 4.65 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.80 and 4.74 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.55 and 4.48 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.32 (bs, 2 H, NH_2), 3.93 (dd, 1 H, $J_{3',4'}$ = 8.9 Hz, $J_{4',5'}$ = 9.0 Hz, H-4′), 3.82 (dd, 1 H, $J_{1',2'}$ = ∼0.5 Hz, $J_{2',3'}$ = 2.8 Hz, H-2′), 3.70 (dd, 1 H,

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$J_{5',6'a}$ = 3.0 Hz, $J_{6'a,6'b}$ = 10.5 Hz, H-6′a), 3.65 (dd, 1 H, $J_{5',6'b}$ = 3.5 Hz, H-6′b), 3.59 (dd, 1 H, H-3′), 3.40 (ddd, 1 H, H-5′), 3.34−3.24 (m, 2 H, 2 H-1). Anal. Calcd for $C_{36}H_{40}N_2O_6$ (596.71): C, 72.46; H, 6.76; N, 4.69. Found: C, 72.51; H, 6.79; N, 4.71.

General Procedure for the Synthesis of C4-, C6-, and Bisglycosylated DHPMs 11a−c, 12a−c, 13a, and 15a−c. A mixture of aldehyde (1.00 mmol), β-ketoester (1.00 mmol), urea (1.50 mmol), BF_3·OEt_2 (165 μL, 1.30 mmol), CuCl (99 mg, 1.00 mmol), glacial acetic acid (11 μL, 0.20 mmol), powdered 4-Å molecular sieves (300 mg), and anhydrous THF (5 mL) was stirred at 65 °C for 24 h. The mixture was cooled to room temperature, quenched with Et_3N, filtered through a pad of Celite, and concentrated. The residue was suspended in EtOAc (100 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 the suitable elution system to give the corresponding dihydropyrimidinones.

(4*R*)- and (4*S*)-4-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (11a). Column chromatography with 1.5:1 cyclohexane−AcOEt afforded first (*S*)-**11a** (93 mg, 16%) as a white foam. $[\alpha]_D^{20}$ = 41.1 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ = 7.50 (bs, 1 H, NH), 7.48−7.15 (m, 15 H, 3 Ph), 6.18 (bs, 1 H, NH), 4.63 and 4.53 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.61 (d, 1 H, $J_{1',4}$ = 2.1 Hz, H-4), 4.42 and 4.26 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.41 and 4.37 (2 d, 2 H, *J* = 10.5 Hz, PhCH_2), 4.33 (dd, 1 H, $J_{1',2'}$ = 2.2 Hz, H-1′), 4.21 (q, 2 H, *J* = 7.0 Hz, CH_2-CH_3), 4.13 (ddd, 1 H, $J_{3',4'}$ = 7.8 Hz, $J_{4',5'a}$ = 3.0 Hz, $J_{4',5'b}$ = 2.8 Hz, H-4′), 4.01 (dd, 1 H, $J_{2',3'}$ = 5.5 Hz, H-3′), 3.82 (dd, 1 H, H-2′), 3.76 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.52 (dd, 1 H, H-5′b), 2.22 (s, 3 H, CH_3), 1.30 (t, 3 H, CH_2CH_3). Anal. Calcd for $C_{34}H_{38}N_2O_7$ (586.67): C, 69.61; H, 6.53; N, 4.77. Found: C, 69.55; H, 6.53; N, 4.70.

Eluted second was (*R*)-**11a** (278 mg, 47%) as a white solid. Mp: 149−150 °C (cyclohexane). $[\alpha]_D^{20}$ = −65 (*c* 0.3, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.10 (m, 15 H, 3 Ph), 7.00 (bs, 1 H, NH), 5.38 (bs, 1 H, NH), 4.57 and 4.47 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.50 (s, 2 H, PhCH_2), 4.49 and 4.44 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.26 (dd, 1 H, $J_{1',4}$ = 3.2 Hz, $J_{4,NH}$ = 6.1 Hz, H-4), 4.21 (ddd, 1 H, $J_{3',4'}$ = 4.5 Hz, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 3.9 Hz, H-4′), 4.08 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 4.06 (dd, 1 H, $J_{1',2'}$ = 5.8 Hz, H-1′), 4.01 (dd, 1 H, $J_{2',3'}$ = 5.0 Hz, H-3′), 3.88 (dd, 1 H, H-2′), 3.55 (dd, 1 H, $J_{5'a,5'b}$ = 10.5 Hz, H-5′a), 3.46 (dd, 1 H, H-5′b), 2.24 (s, 3 H, CH_3), 1.21 (t, 3 H, CH_2CH_3). Anal. Calcd for $C_{34}H_{38}N_2O_7$ (586.67): C, 69.61; H, 6.53; N, 4.77. Found: C, 69.58; H, 6.51; N, 4.76.

(4*R*)- and (4*S*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (11b). Column chromatography with 2:1 cyclohexane−AcOEt afforded first (*R*)-**11b** (383 mg, 54%) as a white foam. $[\alpha]_D^{20}$ = −101.3 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.15 (m, 20 H, 4 Ph), 6.70 (bs, 1 H, NH), 4.98 and 4.62 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.94 and 4.72 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.77 and 4.67 (2 d, 2 H, *J* = 11.0 Hz, PhCH_2), 4.51 (bs, 1 H, NH), 4.50 (d, 1 H, $J_{1',4}$ = ∼0.5 Hz, H-4), 4.42 and 4.35 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.22−4.12 (m, 2 H, CH_2CH$_3$), 3.96 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.91 (dd, 1 H, $J_{1',2'}$ = 9.2 Hz, $J_{2',3'}$ = 9.5 Hz, H-2′), 3.64 (dd, 1 H, H-3′), 3.56−3.45 (m, 3 H, H-5′, 2 H-6′), 3.23 (dd, 1 H, H-1′), 2.18 (s, 3 H, CH_3), 1.30 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{42}H_{46}N_2O_8$ (706.82): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.45; H, 6.58; N, 4.03.

Eluted second was (*S*)-**11b** (77 mg, 11%) as a white foam. $[\alpha]_D^{20}$ = 29.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (C_6D_6): δ = 8.11 (bs, 1 H, NH), 7.50−6.95 (m, 20 H, 4 Ph), 5.62 (bs, 1 H, NH), 5.00 and 4.54 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.99 and 4.54 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.90 (bs, 1 H, H-4), 4.27 and 4.21 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.27 and 4.16 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.22 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 4.05−3.88 (m, 3 H, H-1′, CH_2CH$_3$), 3.84 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.66−3.58 and 3.52−3.45 (2m, 3 H, H-5′, 2 H-6′), 3.42 (dd, 1 H, H-3′), 1.82 (s, 3 H, CH_3), 0.95 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{42}H_{46}N_2O_8$ (706.82): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.41; H, 6.51; N, 4.00.

(4*R*)- and (4*S*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (11c). Column chromatography with 2:1 cyclohexane−AcOEt afforded first (*R*)-**11c** (302 mg, 43%) as a white foam. $[\alpha]_D^{20}$ = −58.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ = 8.00 (bs, 1 H, NH), 7.50−7.10 (m, 20 H, 4 Ph), 5.74 (bs, 1 H, NH), 5.19 and 4.51 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.88 and 4.72 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.82 (s, 2 H, PhCH_2), 4.75 and 4.68 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.29 (bdd, 1 H, H-4), 4.14 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 4.02 (dd, 1 H, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 9.0 Hz, H-4′), 3.98 (dd, 1 H, $J_{1',2'}$ = ∼0.5 Hz, $J_{2',3'}$ = 2.2 Hz, H-2′), 3.82 (dd, 1 H, $J_{5',6'a}$ = 4.5 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′a), 3.72 (dd, 1 H, $J_{5',6'b}$ = 1.0 Hz, H-6′b), 3.63 (dd, 1 H, H-3′), 3.46 (ddd, 1 H, H-5′), 3.32 (bdd, 1 H, H-1′), 2.15 (s, 3 H, CH_3), 1.20 (t, 3 H, CH_2CH_3). Anal. Calcd for $C_{42}H_{46}N_2O_8$ (706.82): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.35; H, 6.55; N, 3.90.

Eluted second was (*S*)-**11c** (101 mg, 14%) as a white foam. $[\alpha]_D^{20}$ = 60.5 (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.10 (m, 20 H, 4 Ph), 6.85 (bs, 1 H, NH), 5.11 and 4.78 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.87 and 4.60 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.87 and 4.57 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.66 and 4.48 (2 d, 2 H, *J* = 12.1 Hz, PhCH_2), 4.63 (d, 1 H, $J_{1',4}$ = 8.0 Hz, H-4), 4.41 (bs, 1 H, NH), 4.22−4.08 (m, 2 H, CH_2CH$_3$), 4.04 (dd, 1 H, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 9.2 Hz, H-4′), 3.98 (dd, 1 H, $J_{1',2'}$ = ∼0.5 Hz, $J_{2',3'}$ = 2.2 Hz, H-2′), 3.75 (dd, 1 H, $J_{5',6'a}$ = 4.5 Hz, $J_{6'a,6'b}$ = 10.8 Hz, H-6′a), 3.67 (dd, 1 H, $J_{5',6'b}$ = 1.5 Hz, H-6′b), 3.59 (dd, 1 H, H-3′), 3.36 (ddd, 1 H, H-5′), 3.27 (dd, 1 H, H-1′), 2.22 (s, 3 H, CH_3), 1.24 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{42}H_{46}N_2O_8$ (706.82): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.48; H, 6.63; N, 3.99.

(4*R*)- and (4*S*)-6-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (12a). Column chromatography with 4:1 cyclohexane−AcOEt afforded first (*R*)-**12a** (149 mg, 23%) as a white foam. $[\alpha]_D^{20}$ = 25.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (C_6D_6): δ = 10.08 (bs, 1 H, NH), 7.60−6.90 (m, 20 H, 4 Ph), 6.12 (s, 1 H, H-1′), 5.44 (bs, 1 H, NH), 5.14 (d, 1 H, $J_{4,NH}$ = 3.0 Hz, H-4), 5.08 and 4.96 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.89 and 4.41 (2 d, 2 H, *J* = 12.2 Hz, PhCH_2), 4.40 (ddd, 1 H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'a}$ = 2.0 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.20 (dd, 1 H, $J_{2',3'}$ = 4.0 Hz, H-3′), 4.13 (d, 1 H, H-2′), 4.10 and 3.85 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 3.88−3.76 (m, 2 H, CH_2CH$_3$), 3.61 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.33 (dd, 1 H, H-5′b), 1.20 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{39}H_{40}N_2O_7$ (648.74): C, 72.20; H, 6.21; N, 4.32. Found: C, 72.30; H, 6.25; N, 4.41.

Eluted second was (*S*)-**12a** (448 mg, 69%) as a white foam. $[\alpha]_D^{20}$ = 139.2 (*c* 1.6, $CHCl_3$). ^{1}H NMR: δ = 9.22 (bs, 1 H, NH), 7.50−7.10 (m, 20 H, 4 Ph), 5.86 (d, 1 H, $J_{1,'2'}$ = ∼ 0.5 Hz, H-1′), 5.46 (d, 1 H, $J_{4,NH}$ = 2.2 Hz, H-4), 5.35 (bd, 1 H, NH), 4.91 and 4.73 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.82 and 4.64 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.45 and 4.31 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.29 (ddd, 1 H, $J_{3',4'}$ = 8.5 Hz, $J_{4',5'a}$ = 2.1 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.20−4.02 (m, 3 H, H-3′, CH_2CH$_3$), 3.95 (dd, 1 H, $J_{2',3'}$ = 5.0 Hz, H-2′), 3.86 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.60 (dd, 1 H, H-5′b), 1.17 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{39}H_{40}N_2O_7$ (648.74): C, 72.20; H, 6.21; N, 4.32. Found: C, 72.25; H, 6.32; N, 4.40.

(4*R*)- and (4*S*)-6-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (12b). Column chromatography with 10:1 diisopropyl ether−AcOEt (containing 5% of CH_2Cl_2) afforded first (*R*)-**12b** (96 mg, 13%) as a white foam: $[\alpha]_D^{20}$ = −3 (*c* 0.3, $CHCl_3$). ^{1}H NMR: δ = 7.40−7.20 (m, 25 H, 5 Ph), 7.19 (bs, 1H, NH), 5.54 (d, 1 H, $J_{1',2'}$ = 9.2 Hz, H-1′), 5.37 (d, 1 H, $J_{4,NH}$ = 2.0 Hz, H-4), 5.08 (bd, 1 H, NH), 4.95 and 4.62 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.85 and 4.61 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.75 (s, 2 H, PhCH_2), 4.48 and 4.44 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.00 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ =

∼0.5 Hz, H-4′), 3.98 and 3.78 (2dq, 2 H, J = 7.0, 11.0 Hz, CH_2-CH$_3$), 3.93 (dd, 1 H, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.71 (ddd, 1 H, $J_{5',6'a}$ = 5.5 Hz, $J_{5',6'b}$ = 7.0 Hz, H-5′), 3.68 (dd, 1 H, H-3′), 3.59 (dd, 1 H, $J_{6'a,6'b}$ = 9.5 Hz, H-6′a), 3.53 (dd, 1 H, H-6′b), 1.00 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.41; H, 6.28; N, 3.63.

Eluted second was (*S*)-**12b** (481 mg, 63%) as a white foam. $[\alpha]_D^{20}$ = 72.5 (*c* 0.9, CHCl$_3$). ^{1}H NMR: δ = 7.40−7.25, 7.18−7.00, and 6.80−6.60 (3 m, 25 H, 5 Ph), 7.20 (bs, 1 H, NH), 5.68 (d, 1 H, $J_{1',2'}$ = 9.0 Hz, H-1′), 5.47 (d, 1 H, $J_{4,NH}$ = 2.5 Hz, H-4), 5.42 (bd, 1 H, NH), 4.94 and 4.61 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.72 and 4.67 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.67 and 4.15 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.50 and 4.43 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.08−3.92 (m, 2 H, CH_2CH$_3$), 3.98 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.86 (dd, 1 H, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.70 (ddd, 1 H, $J_{5',6'a}$ = 5.8 Hz, $J_{5',6'b}$ = 6.9 Hz, H-5′), 3.69 (dd, 1 H, H-3′), 3.59 (dd, 1 H, $J_{6'a,6'b}$ = 10.0 Hz, H-6′a), 3.53 (dd, 1 H, H-6′b), 1.15 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.40; H, 6.25; N, 3.61.

(4*R*)- and (4*S*)-6-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (12c). Column chromatography with 3:1 cyclohexane−AcOEt afforded first (*S*)-**12c** (405 mg, 53%) as a white foam. $[\alpha]_D^{20}$ = 29.7 (*c* 2.1, CHCl$_3$). ^{1}H NMR: δ = 7.60 (bd, 1 H, J = ∼0.5 Hz, NH), 7.45−7.15 (m, 25 H, 5 Ph), 5.42 (bdd, 1 H, J = ∼0.5 Hz, $J_{4,NH}$ = 2.0 Hz, NH), 5.15 (s, 1 H, H-1′), 5.10 (d, 1 H, H-4), 4.92 and 4.57 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.82 and 4.64 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.81 and 4.75 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.63 and 4.59 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.35 (d, 1 H, $J_{2',3'}$ = 2.5 Hz, H-2′), 4.05−3.95 (m, 2 H, CH_2CH$_3$), 3.92 (dd, 1 H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'}$ = 9.2 Hz, H-4′), 3.79 (dd, 1 H, H-3′), 3.78 (dd, 1 H, $J_{5',6'a}$ = 1.8 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′a), 3.71 (dd, 1 H, $J_{5',6'b}$ = 5.5 Hz, H-6′b), 3.59 (ddd, 1 H, H-5′), 1.12 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.38; H, 6.34; N, 3.68.

Eluted second was (*R*)-**12c** (135 mg, 17%). $[\alpha]_D^{20}$ = 66.6 (*c* 1.0, CHCl$_3$). ^{1}H NMR: δ = 7.62 (bd, 1 H, J = ∼0.5 Hz, NH), 7.40−7.00 (m, 25 H, 5 Ph), 5.51 (d, 1 H, $J_{4,NH}$ = 2.5 Hz, H-4), 5.38 (bdd, 1 H, J = ∼0.5 Hz, $J_{4,NH}$ = 2.5 Hz, NH), 5.22 (d, 1 H, $J_{1',2'}$ = ∼0.5 Hz, H-1′), 4.87 and 4.53 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.81 and 4.38 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.71 and 4.65 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.61 (s, 2 H, PhCH_2), 4.29 (dd, 1 H, $J_{2',3'}$ = 2.5 Hz, H-2′), 4.14 (q, 2 H, J = 7.0 Hz, CH_2CH$_3$), 3.89 (dd, 1 H, $J_{3',4'}$ = 9.2 Hz, $J_{4',5'}$ = 9.5 Hz, H-4′), 3.80 (dd, 1 H, H-3′), 3.78 (dd, 1 H, $J_{5',6'a}$ = 1.0 Hz, $J_{6'a,6'b}$ = 10.8 Hz, H-6′a), 3.69 (dd, 1 H, $J_{5',6'b}$ = 5.5 Hz, H-6′b), 3.63 (ddd, 1 H, H-5′), 1.12 (t, 3 H, CH$_2$CH_3). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.45; H, 6.31; N, 3.60.

(4*R*)- and (4*S*)-6-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-[2-(trifluoromethyl)phenyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (13a). Column chromatography with 25:2:1 CH$_2$Cl$_2$−cyclohexane−AcOEt afforded first (*R*)-**13a** (196 mg, 27%) slightly contaminated by uncharacterized byproducts. ^{1}H NMR: δ = 9.60 (bs, 1 H, NH), 7.80−7.10 (m, 19 H, Ph), 6.04 (s, 1 H, H-1′), 5.85 (bs, 1 H, H-4), 5.20 (bs, 1 H, NH), 4.99 and 4.90 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.84 and 4.62 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.38 and 4.23 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.33 (ddd, 1 H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'a}$ = 2.0 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.17−4.08 (m, 2 H, H-2′, H-3′), 4.07−3.92 (m, 2 H, CH_2CH$_3$), 3.91 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.61 (dd, 1 H, H-5′b), 0.98 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3).

Eluted second was (*S*)-**13a** (392 mg, 55%) as a white foam. $[\alpha]_D^{20}$ = 92.3 (*c* 0.9, CHCl$_3$). ^{1}H NMR: δ = 9.39 (bs, 1 H, NH), 7.80−7.20 (m, 19 H, Ph), 5.99 (s, 1 H, H-1′), 5.92 (d, 1 H, $J_{4,NH}$ = 2.0 Hz, H-4), 5.15 (bd, 1 H, NH), 5.03 and 4.88 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.83 and 4.64 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.48 and 4.37 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.34 (ddd, 1 H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'a}$ = 2.5 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.21 (dd, 1 H, $J_{2',3'}$ = 4.0 Hz, H-3′), 4.13 (d, 1 H, H-2′), 4.01 (q, 2 H, J = 7.0 Hz, CH_2CH$_3$), 3.87 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.63 (dd, 1 H, H-5′b), 1.00 (t, 3 H, CH$_2$CH_3). Anal. Calcd for $C_{40}H_{39}F_3N_2O_7$ (716.74): C, 67.03; H, 5.48; F, 7.95; N, 3.91. Found: C, 67.00; H, 5.41; F, 7.91; N, 3.88.

(4*R*)- and (4*S*)-4,6-Bis(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (15a). Column chromatography with 3:1 cyclohexane−AcOEt afforded first (*S*)-**15a** (41 mg, 4%) as a white foam. $[\alpha]_D^{20}$ = 75 (*c* 0.4, CHCl$_3$). ^{1}H NMR selected data: δ = 9.41 (bs, 1 H, NH), 7.50−7.10 (m, 30 H, 6 Ph), 6.01 (bs, 1 H, NH), 5.78 (s, 1 H, H-1*r6*), 4.09−4.00 (m, 2 H, H-2*r6*, H-3*r4*), 2.92 (dd, 1 H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 10.8 Hz, H-5a*r6*), 3.89 (dd, 1 H, $J_{1,2}$ = 2.0 Hz, $J_{2,3}$ = 5.5 Hz, H-2*r4*), 3.76 (dd, 1 H, $J_{4,5a}$ = 3.0 Hz, $J_{5a,5b}$ = 10.8 Hz, H-5a*r4*), 3.60 (dd, 1 H, $J_{4,5b}$ = ∼0.5 Hz, H-5b*r6*), 3.53 (dd, 1 H, $J_{4,5b}$ = 3.2 Hz, H-5b*r4*), 1.29 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 976.1 (M$^+$ + H), 999.4 (M$^+$ + Na), 1014.7 (M$^+$ + K). Anal. Calcd for $C_{59}H_{62}N_2O_{11}$ (975.13): C, 72.67; H, 6.41; N, 2.87. Found: C, 72.61; H, 6.35; N, 2.84.

Eluted second was (*R*)-**15a** (369 mg, 38%) as a white foam. $[\alpha]_D^{20}$ = 6.4 (*c* 1.0, CHCl$_3$). ^{1}H NMR selected data: δ = 9.20 (bs, 1 H, NH), 7.50−7.10 (m, 30 H, 6 Ph), 5.76 (s, 1 H, H-1*r6*), 5.08 (bs, 1 H, NH), 3.93 (d, 1 H, $J_{2,3}$ = 4.0 Hz, H-2*r6*), 3.89 (dd, 1 H, $J_{1,2}$ = 5.5 Hz, $J_{2,3}$ = 6.5 Hz, H-2*r4*), 3.77 (dd, 1 H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 10.8 Hz, H-5a*r6*), 3.53 (dd, 1 H, $J_{4,5b}$ = ∼0.5 Hz, H-5b*r6*), 3.48 (dd, 1 H, $J_{4,5a}$ = 4.5 Hz, $J_{5a,5b}$ = 10.2 Hz, H-5a*r4*), 3.44 (dd, 1 H, $J_{4,5b}$ = 5.0 Hz, H-5b*r4*), 1.26 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 998.2 (M$^+$ + Na), 1014.4 (M$^+$ + K). Anal. Calcd for $C_{59}H_{62}N_2O_{11}$ (975.13): C, 72.67; H, 6.41; N, 2.87. Found: C, 72.60; H, 6.38; N, 2.80.

(4*R*)- and (4*S*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)-6-(2″,3″,5″-tri-*O*-benzyl-β-D-ribofuranosyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (15b). Column chromatography with 10:1 toluene−AcOEt afforded first (*S*)-**15b** (35 mg, 3%) as a white foam. $[\alpha]_D^{20}$ = −10 (*c* 0.3, CHCl$_3$). ^{1}H NMR selected data: δ = 9.18 (bs, 1 H, NH), 7.50−7.10 (m, 35 H, 7 Ph), 5.72 (d, 1 H, $J_{1,2}$ = ∼0.5 Hz, H-1*r*), 5.49 (bs, 1 H, NH), 4.65 (dd, 1 H, $J_{4,NH}$ = 2.5 Hz, $J_{4,1g}$ = 1.5 Hz, H-4), 4.48 and 4.42 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.37 and 4.24 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.05 (dd, 1 H, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 9.2 Hz, H-2*g*), 3.99 (dd, 1 H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = ∼0.5 Hz, H-4*g*), 3.91 (dd, 1 H, $J_{2,3}$ = 4.2 Hz, H-2*r*), 3.78 (dd, 1 H, $J_{4,5a}$ = 2.8 Hz, $J_{5a,5b}$ = 10.8 Hz, H-5a*r*), 3.67 (dd, 1 H, H-3*g*), 1.18 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 1118.0 (M$^+$ + Na), 1134.2 (M$^+$ + K). Anal. Calcd for $C_{67}H_{70}N_2O_{12}$ (1095.28): C, 73.47; H, 6.44; N, 2.56. Found: C, 73.41; H, 6.39; N, 2.58.

Eluted second was (*R*)-**15b** (349 mg, 32%) as a white foam. $[\alpha]_D^{20}$ = −61.6 (*c* 1.1, CHCl$_3$). ^{1}H NMR selected data: δ = 8.95 (bs, 1 H, NH), 7.50−7.10 (m, 35 H, 7 Ph), 5.92 (s, 1 H, H-1*r*), 4.61 (dd, 1 H, $J_{4,NH}$ = 2.5 Hz, $J_{4,1g}$ = ∼0.5 Hz, H-4), 4.05 (dd, 1 H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = ∼0.5 Hz, H-4*g*), 4.03 (dd, 1 H, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 8.2 Hz, H-3*r*), 3.99 (dd, 1 H, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 9.2 Hz, H-2*g*), 3.95 (d, 1 H, H-2*r*), 3.81 (dd, 1 H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 10.8 Hz, H-5a*r*), 3.68 (dd, 1 H, H-3*g*), 3.61−3.52 (m, 2 H, H-5b*r*, H-6a*g*), 3.49 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 9.5 Hz, H-6b*g*), 3.28−3.21 (m, 2 H, H-1*g*, H-5*g*), 1.29 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 1096.3 (M$^+$ + H), 1118.0 (M$^+$ + Na), 1134.2 (M$^+$ + K), 1156.9 (M$^+$ + Na + K). Anal. Calcd for $C_{67}H_{70}N_2O_{12}$ (1095.28): C, 73.47; H, 6.44; N, 2.56. Found: C, 73.40; H, 6.38; N, 2.50.

(4*R*)- and (4*S*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-6-(2″,3″,5″-tri-*O*-benzyl-β-D-ribofuranosyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (15c). Column chromatography with 3:1 cyclohexane−AcOEt afforded first (*R*)-**15c** (348 mg, 32%) as a white foam. $[\alpha]_D^{20}$ = −6.5 (*c* 1.0, CHCl$_3$). ^{1}H NMR selected data: δ = 8.90 (bs, 1 H, NH), 7.50−7.10 (m, 35 H, 7 Ph), 5.84 (d, 1 H, $J_{1,2}$ = 1.8 Hz, H-1*r*), 5.68 (bs, 1 H, NH), 5.19 and 4.72 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.33 (bdd, 1 H, H-4), 4.23 (ddd, 1 H, $J_{3,4}$ = 8.0 Hz, $J_{4,5a}$ = 2.5 Hz, $J_{4,5b}$ = 1.0 Hz, H-4*r*), 4.13 (dd, 1 H, $J_{2,3}$

= 2.5 Hz, H-3*r*), 4.03 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.2 Hz, H-4m), 3.95 (dd, 1 H, H-2*r*), 3.94 (dd, 1 H, $J_{1,2}$ = ~0.5 Hz, $J_{2,3}$ = 2.2 Hz, H-2*m*), 3.86 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a*m*), 3.73 (dd, 1 H, $J_{5a,5b}$ = 10.8 Hz, H-5a*r*), 3.61 (dd, 1 H, H-3*m*), 3.59 (dd, 1 H, $J_{5,6b}$ = 1.0 Hz, H-6b*m*), 3.53 (dd, 1 H, H-5b*r*), 3.41 (ddd, 1 H, H-5*m*), 3.24 (bdd, 1 H, H-1*m*), 1.17 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3); MALDI-TOF MS: 1118.2 (M^+ + Na), 1134.1 (M^+ + K). Anal. Calcd for $C_{67}H_{70}N_2O_{12}$ (1095.28): C, 73.47; H, 6.44; N, 2.56. Found: C, 73.55; H, 6.50; N, 2.60.

Eluted second was (*S*)-**15c** (49 mg, 4%) slightly contaminated by the major isomer. ^{1}H NMR selected data: δ = 9.28 (bs, 1 H, NH), 5.91 (d, 1 H, $J_{1,2}$ = 1.0 Hz, H-1*r*), 5.76 (bs, 1 H, NH), 1.22 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 1118.1 (M^+ + Na), 1134.0 (M^+ + K). Anal. Calcd for $C_{67}H_{70}N_2O_{12}$ (1095.28): C, 73.47; H, 6.44; N, 2.56. Found: C, 73.50; H, 6.51; N, 2.66.

General Procedure for the Synthesis of N1- and Trisglycosylated DHPMs 14a−c and 16a. A mixture of aldehyde (3.00 mmol), β-ketoester (3.00 mmol), glycosylmethyl urea (1.00 mmol), BF_3·OEt_2 (0.49 mL, 3.90 mmol), CuCl (297 mg, 3.00 mmol), glacial acetic acid (34 μL, 0.60 mmol), powdered 4-Å molecular sieves (500 mg), and anhydrous THF (8 mL) was stirred at 65 °C for 24 h. The mixture was cooled to room temperature, quenched with Et_3N, filtered through a pad of Celite, and concentrated. The residue was suspended in EtOAc (100 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 the suitable elution system to give the corresponding dihydropyrimidinones.

(4*R*)- and (4*S*)-1-[(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14a). Column chromatography with 2:1 cyclohexane−AcOEt afforded **14a** (325 mg, 48%) as a ~1:1 mixture of (4*R*)- and (4*S*)-stereoisomers. ^{1}H NMR selected data for ~1:1 mixture of stereoisomers: δ = 5.81 (d, 0.5 H, *J* = 2.5 Hz, NH), 5.77 (d, 0.5 H, *J* = 2.2 Hz, NH), 5.38 (d, 0.5 H, *J* = 2.5 Hz, H-4), 5.35 (d, 0.5 H, *J* = 2.2 Hz, H-4), 2.58 (s, 3 H, CH_3), 1.18 (t, 1.5 H, *J* = 7.0 Hz, CH_2CH_3), 1.15 (t, 1.5 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 677.5 (M^+ + H), 699.9 (M^+ + Na), 716.1 (M^+ + K). Anal. Calcd for $C_{41}H_{44}N_2O_7$ (676.80): C, 72.76; H, 6.55; N, 4.14. Found: C, 72.75; H, 6.50; N, 4.08.

(4*R*)- and (4*S*)-1-[(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14b). Column chromatography with 3:1 cyclohexane−AcOEt afforded first (*S*)-**14b** (166 mg, 21%) as a white foam. $[\alpha]_D^{20}$ = −46.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.10 (m, 25 H, 5 Ph), 5.40 (d, 1 H, $J_{4,NH}$ = 3.2 Hz, H-4), 5.32 (bd, 1 H, NH), 4.96 and 4.72 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.96 and 4.60 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.74 and 4.67 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.38 (s, 2 H, PhCH_2), 4.15−4.02 (m, 2 H, CH_2CH$_3$), 4.00 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ~0.5 Hz, H-4′), 3.70 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.61 (dd, 1 H, H-3′), 3.57−3.34 (m, 6 H, H-1′, H-5′, 2 H-6′, CH_2N), 2.55 (s, 3 H, CH_3), 1.18 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 797.1 (M^+ + H), 820.0 (M^+ + Na), 836.1 (M^+ + K). Anal. Calcd for $C_{49}H_{52}N_2O_8$ (796.95): C, 73.85; H, 6.58; N, 3.52. Found: C, 73.90; H, 6.62; N, 3.58.

Eluted second was (*R*)-**14b** (161 mg, 20%) as a white foam. $[\alpha]_D^{20}$ = −8 (*c* 0.4, $CHCl_3$). ^{1}H NMR: δ = 7.50−7.10 (m, 25 H, 5 Ph), 5.33 (s, 1 H, H-4), 5.32 (bs, 1 H, NH), 5.01 and 4.68 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.95 and 4.62 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.76 and 4.66 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.41 (s, 2 H, PhCH_2), 4.08 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 4.04 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ~0.5 Hz, H-4′), 3.76 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.63 (dd, 1 H, H-3′), 3.62−3.40 (m, 6 H, H-1′, H-5′, 2 H-6′, CH_2N), 2.48 (s, 3 H, CH_3), 1.17 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 797.1 (M^+ + H), 829.8 (M^+ + Na), 836.0 (M^+ + K). Anal. Calcd for $C_{49}H_{52}N_2O_8$ (796.95): C, 73.85; H, 6.58; N, 3.52. Found: C, 73.91; H, 6.64 N, 3.51.

(4*R*)- and (4*S*)-1-[(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14c). Column chromatography with 3:1 cyclohexane−AcOEt afforded **14c** (318 mg, 40%) as a ~1:1 mixture of (4*R*)- and (4*S*)-stereoisomers. ^{1}H NMR selected data for ~1:1 mixture of stereoisomers: δ = 7.50−7.10 (m, 25 H, Ph), 5.40 (bs, 0.5 H, NH), 5.39 (d, 0.5 H, *J* = 3.0 Hz, H-4), 5.34 (bd, 0.5 H, *J* = 3.0 Hz, NH), 5.32 (d, 0.5 H, *J* = 3.0 Hz, H-4), 5.09 (d, 1 H, *J* = 12.0 Hz, PhCH_2), 4.92 (d, 0.5 H, *J* = 11.2 Hz, PhCH_2), 4.90 (d, 0.5 H, *J* = 11.2 Hz, PhCH_2), 2.60 (s, 1.5 H, CH_3), 2.58 (s, 1.5 H, CH_3), 1.17 (t, 1.5 H, *J* = 7.0 Hz, CH_2CH_3), 1.15 (t, 1.5 H, *J* = 7.0 Hz, CH_2CH_3). MALDI-TOF MS: 797.5 (M^+ + H), 830.2 (M^+ + Na), 836.7 (M^+ + K). Anal. Calcd for $C_{49}H_{52}N_2O_8$ (796.95): C, 73.85; H, 6.58; N, 3.52. Found: C, 73.80; H, 6.51 N, 3.43.

(4*R*)- and (4*S*)-4,6-Tris-(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (16a). MALDI-TOF MS analysis of crude **16a**: 1392.1 (M^+ + H), 1414.2 (M^+ + Na), 1430.1 (M^+ + K).

General Procedure for the Synthesis of C4-, C6-, N1-, and Bisglycosylated DHPMs 11a′−c′ to 15a′−c′. A vigorously stirred mixture of benzylated DHPM (0.30 mmol), 20% palladium hydroxide on carbon (50 w/w of substrate), AcOEt (4 mL), and EtOH (4 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. After the mixture was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 3−5 h, 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 to give the corresponding deprotected DHPM in almost quantitative yield.

(4*R*)-6-Methyl-2-oxo-4-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-11a′). Mp: 264−266 °C (MeOH). $[\alpha]_D^{20}$ = −148 (*c* 0.2, H_2O). ^{1}H NMR (DMSO-d_6 + D_2O, 70 °C): δ = 4.16−4.02 (m, 2 H, CH_2-CH$_3$), 4.10 (d, 1 H, $J_{1',4}$= 5.0 Hz, H-4), 3.86 (dd, 1 H, $J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 5.0 Hz, H-2′), 3.76 (dd, 1 H, $J_{3',4'}$ = 5.1 Hz, H-3′), 3.64 (ddd, 1 H, $J_{4',5'a}$ = 4.2 Hz, $J_{4',5'b}$ = 4.8 Hz, H-4′), 3.59 (dd, 1 H, H-1′), 3.45 (dd, 1 H, $J_{5'a,5'b}$ = 11.2 Hz, H-5′a), 3.33 (dd, 1 H, H-5′b), 2.18 (s, 3 H, CH_3), 1.20 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3). ^{13}C NMR (DMSO-d_6): δ = 165.5, 153.4, 149.9, 96.3, 85.2, 83.1, 71.1, 70.6, 61.5, 59.1, 51.6, 17.9, 14.2. MALDI-TOF MS: 340.0 (M^+ + Na), 356.0 (M^+ + K). Anal. Calcd for $C_{13}H_{20}N_2O_7$ (316.31): C, 49.36; H, 6.37; N, 8.86. Found: C, 49.38; H, 6.30; N, 8.80.

(4*S*)-6-Methyl-2-oxo-4-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-11a′). Amorphous solid. $[\alpha]_D^{20}$ = 121 (*c* 0.6, DMF). ^{1}H NMR (DMSO-d_6): δ = 9.05 (bs, 1 H, NH), 7.10 (bs, 1 H, NH), 4.21 (bdd, 1 H, $J_{1',4}$ = 3.0 Hz, $J_{4,NH}$ = 3.2 Hz, H-4), 4.08 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 3.79 (dd, 1 H, $J_{1',2'}$ = 2.8 Hz, $J_{2',3'}$ = 5.5 Hz, H-2′), 3.72 (dd, 1 H, H-1′), 3.71 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.59 (dd, 1 H, $J_{4',5'a}$ = 2.8 Hz, $J_{5'a,5'b}$ = 11.5 Hz, H-5′a), 3.55 (ddd, 1 H, $J_{4',5'b}$ = 3.5 Hz, H-4′), 3.43 (dd, 1 H, H-5′b), 2.18 (s, 3 H, CH_3), 1.20 (t, 3 H, CH_2CH_3). ^{13}C NMR (DMSO-d_6): δ = 165.4, 152.2, 149.7, 95.2, 87.1, 82.1, 70.5, 60.6, 59.2, 52.7, 18.0, 14.2. MALDI-TOF MS: 317.9 (M^+ + H), 324.0 (M^+ + Li), 339.6 (M^+ + Na). Anal. Calcd for $C_{13}H_{20}N_2O_7$ (316.31): C, 49.36; H, 6.37; N, 8.86. Found: C, 49.30; H, 6.36; N, 8.83.

(4*R*)-4-(β-D-Galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-11b′). Amorphous solid. $[\alpha]_D^{20}$ = −117.3 (*c* 0.9, MeOH). ^{1}H NMR (CD_3OD): δ = 4.66 (d, 1 H, $J_{1',4}$= 2.8 Hz, H-4), 4.19 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 3.85 (dd, 1 H, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = ~0.5 Hz, H-4′), 3.71 (dd, 1 H, $J_{1',2'}$ = 9.5 Hz, $J_{2',3'}$ = 9.3 Hz, H-2′), 3.68 (dd, 1 H, $J_{5',6'a}$ = 6.0 Hz, $J_{6'a,6'b}$ = 10.8 Hz, H-6′a), 3.63 (dd, 1 H, $J_{5',6'b}$ = 6.2 Hz, H-6′b), 3.45 (dd, 1 H, H-3′), 3.42 (ddd, 1 H, H-5′), 3.14 (dd, 1 H, H-1′), 2.28 (s, 3 H, CH_3), 1.28 (t, 3 H, CH_2CH_3). ^{13}C NMR (CD_3OD): δ = 167.8, 156.9, 150.8,

98.9, 83.4, 80.1, 76.6, 70.7, 68.1, 62.5, 61.0, 52.2, 18.3, 14.6. MALDI-TOF MS: 347.0 ($M^+ + H$), 353.5 ($M^+ + Li$), 369.5 ($M^+ + Na$), 385.8 ($M^+ + K$). Anal. Calcd for $C_{14}H_{22}N_2O_8$ (346.33): C, 48.55; H, 6.40; N. 8.09. Found: C, 48.60; H, 6.45; N, 8.12.

(4*R*)-4-(β-D-Mannopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid Ethyl Ester ((*R*)-11c′). Amorphous solid. $[\alpha]_D^{20} = -175.4$ (*c* 0.5, MeOH). ^{1}H NMR (CD_3OD): $\delta = 4.44$ (d, 1 H, $J_{1',4} = 7.0$ Hz, H-4), 4.30−4.16 (m, 2 H, CH_2CH$_3$), 3.89 (dd, 1 H, $J_{5',6'a} = 2.5$ Hz, $J_{6'a,6'b} = 11.8$ Hz, H-6′a), 3.69 (dd, 1 H, $J_{1',2'} = \sim 0.5$ Hz, $J_{2',3'} = 3.5$ Hz, H-2′), 3.67 (dd, 1 H, $J_{5',6'b} = 6.2$ Hz, H-6′b), 3.55 (dd, 1 H, $J_{3',4'} = 9.5$ Hz, $J_{4',5'} = 9.2$ Hz, H-4′), 3.41 (dd, 1 H, H-3′), 3.36 (dd, 1 H, H-1′), 3.21 (ddd, 1 H, H-5′), 2.30 (s, 3 H, CH_3), 1.33 (t, 3 H, $J = 7.0$ Hz, CH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 169.0$, 156.6, 151.5, 98.6, 82.0, 80.7, 76.0, 71.2, 69.1, 63.6, 61.8, 53.3, 18.7, 14.6. MALDI-TOF MS: 347.5 ($M^+ + H$), 353.6 ($M^+ + Li$), 369.6 ($M^+ + Na$), 385.8 ($M^+ + K$). Anal. Calcd for $C_{14}H_{22}N_2O_8$ (346.33): C, 48.55; H, 6.40; N. 8.09. Found: C, 48.51; H, 6.32; N, 8.00.

(4*S*)-4-(β-D-Mannopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-11c′). The compound was recovered slightly contaminated by uncharacterized byproducts. ^{1}H NMR (CD_3OD): $\delta = 4.66$ (d, 1 H, $J_{1',4} = 7.8$ Hz, H-4), 4.28−4.12 (m, 2 H, CH_2CH$_3$), 3.92 (dd, 1 H, $J_{1',2'} = \sim 0.5$ Hz, $J_{2',3'} = 3.5$ Hz, H-2′), 3.78 (dd, 1 H, $J_{5',6'a} = 2.5$ Hz, $J_{6'a,6'b}$= 11.2 Hz, H-6′a), 3.70 (dd, 1 H, $J_{5',6'b} = 4.5$ Hz, H-6′b), 3.64 (dd, 1 H, $J_{3',4'} = 9.5$ Hz, $J_{4',5'} = 9.2$ Hz, H-4′), 3.42 (dd, 1 H, H-3′), 3.41 (dd, 1 H, H-1′), 3.15 (ddd, 1 H, H-5′), 2.24 (s, 3 H, CH_3), 1.31 (t, 3 H, $J = 7.0$ Hz, CH$_2$CH_3); ^{13}C NMR (CD_3OD): $\delta = 168.6$, 156.0, 148.3, 100.6, 82.0, 80.1, 76.5, 69.7, 68.7, 63.0, 61.3, 52.2, 18.0, 14.6; MALDI-TOF MS: 347.2 ($M^+ + H$), 353.5 ($M^+ + Li$), 369.5 ($M^+ + Na$), 385.7 ($M^+ + K$).

(4*S*)-2-Oxo-4-phenyl-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-12a′). Amorphous solid. $[\alpha]_D^{20} = 58.5$ (*c* 1.5, MeOH). ^{1}H NMR (pyridine-d_5): $\delta = 10.58$ (bs, 1 H, NH), 9.00 (bd, 1 H, $J_{4,NH} = 1.0$ Hz, NH), 7.80−7.00 (m, 5 H, Ph), 6.35 (s, 1 H, H-1′), 5.72 (d, 1 H, H-4), 5.08 (dd, 1 H, $J_{2',3'} = 4.5$ Hz, $J_{3',4'} = 8.2$ Hz, H-3′), 4.79 (d, 1 H, H-2′), 4.70 (ddd, 1 H, $J_{4',5'a} = 2.0$ Hz, $J_{4',5'b} = \sim 0.5$ Hz, H-4′), 4.46 (dd, 1 H, $J_{5'a,5'b} = 11.0$ Hz, H-5′a), 4.35 (dd, 1 H, H-5′b), 4.10−3.40 (m, 2 H, CH_2CH$_3$), 1.04 (t, 3 H, $J = 7.0$ Hz, CH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 166.6$, 154.6, 151.0, 145.4, 129.7, 129.6, 128.9, 128.8, 127.6, 101.1, 83.6, 81.3, 79.6, 71.0, 61.4, 60.5, 56.4, 14.5. MALDI-TOF MS: 379.8 ($M^+ + H$), 386.1 ($M^+ + Li$), 402.1 ($M^+ + Na$), 418.2 ($M^+ + K$). Anal. Calcd for $C_{18}H_{22}N_2O_7$ (378.38): C, 57.14; H, 5.86; N, 7.40. Found: C, 57.12; H, 5.80; N, 7.32.

(4*R*)-2-Oxo-4-phenyl-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-12a′). The compound was recovered slightly contaminated by uncharacterized byproducts. ^{1}H NMR (pyridine-d_5): $\delta = 10.75$ (bs, 1 H, NH), 9.08 (bd, 1 H, $J_{4,NH} = 3.0$ Hz, NH), 7.80−7.00 (m, 5 H, Ph), 6.37 (d, 1 H, $J_{1',2'} = 1.0$ Hz, H-1′), 5.68 (d, 1 H, H-4), 5.05 (dd, 1 H, $J_{2',3'} = 4.5$ Hz, $J_{3',4'} = 8.0$ Hz, H-3′), 4.76 (dd, 1 H, H-2′), 4.66 (ddd, 1 H, $J_{4',5'a} = 2.0$ Hz, $J_{4',5'b} = \sim 0.5$ Hz, H-4′), 4.47 (dd, 1 H, $J_{5'a,5'b} = 11.0$ Hz, H-5′a), 4.38 (dd, 1 H, H-5′b), 4.05 (q, 2 H, $J = 7.0$ Hz, CH_2CH$_3$), 1.08 (t, 3 H, CH$_2$CH_3). MALDI-TOF MS: 379.7 ($M^+ + H$), 402.2 ($M^+ + Na$).

(4*S*)-6-(β-D-Galactopyranosyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-12b′). Amorphous solid. $[\alpha]_D^{20} = 62.5$ (*c* 0.4, MeOH). ^{1}H NMR (pyridine-d_5): $\delta = 9.77$ (bs, 1 H, NH), 9.24 (bd, 1 H, $J_{4,NH} = 3.0$ Hz, NH), 7.87−7.81 and 7.25−7.10 (2m, 5 H, Ph), 6.29 (d, 1 H, $J_{1',2'} = 9.5$ Hz, H-1′), 5.78 (d, 1 H, H-4), 4.88 (dd, 1 H, $J_{2',3'} = 9.1$ Hz, H-2′), 4.57 (dd, 1 H, $J_{3',4'} = 2.8$ Hz, $J_{4',5'} = \sim 0.5$ Hz, H-4′), 4.46 (dd, 1 H, $J_{5',6'a} = 6.5$ Hz, $J_{6'a,6'b} = 11.8$ Hz, H-6′a), 4.37 (dd, 1 H, $J_{5',6'b} = 5.0$ Hz, H-6′b), 4.24 (ddd, 1 H, H-5′), 4.22 (dd, 1 H, H-3′), 4.02−3.82 (m, 2 H, CH_2CH$_3$), 0.94 (t, 3 H, $J = 7.0$ Hz, CH_2CH$_3$). ^{13}C NMR (pyridine-d_5): $\delta = 166.2$, 153.8, 150.3, 145.3, 129.0, 127.8, 127.7, 123.9, 123.8, 103.0, 82.0, 77.3, 75.8, 71.1, 71.0, 62.6, 60.2, 56.4, 14.0. MALDI-TOF MS: 409.6 ($M^+ + H$), 415.6 ($M^+ + Li$), 431.7 ($M^+ + Na$), 448.3 ($M^+ + K$). Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.40): C, 55.88; H, 5.92; N, 6.86. Found: C, 55.81; H, 5.97; N, 6.80.

(4*S*)-6-(β-D-Mannopyranosyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-12c′). Amorphous solid. $[\alpha]_D^{20} = 27.9$ (*c* 1.1, MeOH). ^{1}H NMR (pyridine-d_5): $\delta = 9.15$ (bs, 2 H, 2 NH), 7.70−7.50 and 7.30−7.10 (2m, 5 H, Ph), 5.91 (s, 1 H, H-1′), 5.57 (d, 1 H, $J_{4,NH} = 2.8$ Hz, H-4), 5.03 (d, 1 H, $J_{2',3'} = 2.5$ Hz, H-2′), 4.86 (dd, 1 H, $J_{3',4'} = 9.2$ Hz, $J_{4',5'} = 9.5$ Hz, H-4′), 4.52 (dd, 1 H, $J_{5',6'a} = 1.5$ Hz, $J_{6'a,6'b} = 11.0$ Hz, H-6′a), 4.43 (dd, 1 H, $J_{5',6'b} = 5.0$ Hz, H-6′b), 4.39 (dd, 1 H, H-3′), 4.06−3.98 (m, 3 H, CH_2CH$_3$, H-5′), 0.98 (t, 3 H, $J = 7.0$ Hz, CH_2CH$_3$). ^{13}C NMR (pyridine-d_5): $\delta = 165.5$, 153.3, 150.1, 145.5, 128.9, 128.8, 127.8, 127.2, 127.1, 99.5, 83.0, 76.2, 76.0, 72.4, 68.0, 62.4, 60.1, 55.7, 14.1. MALDI-TOF MS: 409.5 ($M^+ + H$), 431.5 ($M^+ + Na$), 448.2 ($M^+ + K$). Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.40): C, 55.88; H, 5.92; N, 6.86. Found: C, 55.93; H, 5.99; N, 6.98.

(4*S*)-4-[2-(Trifluoromethyl)phenyl]-2-oxo-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-13a′). Amorphous solid. $[\alpha]_D^{20} = 48.5$ (*c* 1.2, MeOH). ^{1}H NMR (CD_3OD): $\delta = 7.80-7.40$ (m, 4 H, Ph), 5.86 (s, 1 H, H-4), 5.66 (d, 1 H, $J_{1',2'} = 2.0$ Hz, H-1′), 4.32 (dd, 1 H, $J_{2',3'} = 4.5$ Hz, $J_{3',4'} = 8.0$ Hz, H-3′), 4.25 (dd, 1 H, H-2′), 4.06 (ddd, 1 H, $J_{4',5'a} = 2.0$ Hz, $J_{4',5'b} = \sim 0.5$ Hz, H-4′), 4.02 (dd, 1 H, $J_{5'a,5'b} = 10.8$ Hz, H-5′a), 4.00 (q, 2 H, $J = 7.0$ Hz, CH_2CH$_3$), 3.83 (dd, 1 H, H-5′b), 0.98 (t, 3 H, CH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 166.1$, 153.5, 152.7, 143.5, 134.8, 129.6, 129.5, 127.6, 127.2, 127.1, 99.8, 83.9, 81.6, 79.5, 71.2, 61.3, 60.6, 52.6, 14.2. MALDI-TOF MS: 447.6 ($M^+ + H$), 469.9 ($M^+ + Na$), 485.9 ($M^+ + K$). Anal. Calcd for $C_{19}H_{21}F_3N_2O_7$ (446.37): C, 51.12; H, 4.74; F, 12.77; N, 6.28. Found: C, 51.15; H, 4.78; F, 12.70; N, 6.30.

(4*R*)-4-[2-(Trifluoromethyl)phenyl]-2-oxo-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-13a′). The compound was recovered slightly contaminated by uncharacterized byproducts. ^{1}H NMR (CD_3OD): $\delta = 7.80-7.20$ (m, 4 H, Ph), 5.79 (s, 1 H, H-4), 5.74 (d, 1 H, $J_{1',2'} = 2.0$ Hz, H-1′), 4.23 (dd, 1 H, $J_{2',3'} = 4.5$ Hz, $J_{3',4'} = 7.5$ Hz, H-3′), 4.16 (dd, 1 H, H-2′), 4.04 (ddd, 1 H, $J_{4',5'a} = 2.0$ Hz, $J_{4';5'b} = \sim 0.5$ Hz, H-4′), 4.01 (dd, 1 H, $J_{5'a,5'b} = 10.8$ Hz, H-5′a), 3.99 (q, 2 H, $J = 7.0$ Hz, CH_2CH$_3$), 3.83 (dd, 1 H, H-5′b), 0.99 (t, 3 H, CH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 166.1$, 153.8, 152.7, 143.3, 134.4, 129.6, 129.4, 127.7, 127.1, 127.0, 100.1, 84.1, 81.6, 79.3, 71.3, 61.3, 60.7, 52.4, 14.2. MALDI-TOF MS: 447.5 ($M^+ + H$), 469.7 ($M^+ + Na$).

(4*R*)- and (4*S*)-6-Methyl-2-oxo-4-phenyl-1-[(β-D-ribofuranosyl)methyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14a′). ^{1}H NMR (pyridine-d_5) selected data for ∼1:1 mixture of (4*R*)- and (4*S*)-stereoisomers: $\delta = 9.22$ (d, 0.5 H, $J = 2.5$ Hz, NH), 9.15 (d, 0.5 H, $J = 2.2$ Hz, NH), 5.70 (d, 0.5 H, $J = 2.5$ Hz, H-4), 5.68 (d, 0.5 H, $J = 2.2$ Hz, H-4), 2.83 (s, 1.5 H, CH_3), 2.74 (s, 1.5 H, CH_3), 1.02 (t, 1.5 H, $J = 7.0$ Hz, CH$_2$CH_3), 0.99 (t, 1.5 H, $J = 7.0$ Hz, CH$_2$CH_3). ^{13}C NMR (pyridine-d_5) selected data for ∼1:1 mixture of (4*R*)- and (4*S*)-stereoisomers: $\delta = 165.9$, 154.6, 153.8, 147.8, 147.4, 105.6, 104.8, 14.1, 14.0. MALDI-TOF MS: 413.8 ($M^+ + Li$), 429.8 ($M^+ + Na$), 445.6 ($M^+ + K$). Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.43): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.19; H, 6.48; N, 6.73.

(4*S*)-1-[(β-D-Galactopyranosyl)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*S*)-14b′). Syrup. $[\alpha]_D^{20} = -62.6$ (*c* 0.8, MeOH). ^{1}H NMR (DMSO-d_6) selected data: $\delta = 7.90$ (d, 1 H, $J_{4,NH} = 3.0$ Hz, NH), 7.40−7.10 (m, 5 H, Ph), 5.07 (d, 1 H, H-4), 4.05−3.90 (m, 2 H, CH_2CH$_3$), 1.08 (t, 3 H, $J = 7.0$ Hz, CH$_2$CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 165.5$, 152.3, 151.7, 144.0, 128.4, 128.3, 127.2, 126.4, 126.3, 102.6, 79.7, 78.2, 74.4, 69.1, 67.8, 59.6, 59.3, 52.8, 42.9, 16.3, 14.0. MALDI-TOF MS: 437.7 ($M^+ + H$), 459.9 ($M^+ + Na$). Anal. Calcd for $C_{21}H_{28}N_2O_8$ (436.46): C, 57.79; H, 6.47; N, 6.42. Found: C, 57.70; H, 6.48; N, 6.51.

(4*R*)- and (4*S*)-1-[(β-D-Mannopyranosyl)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Esters (14c′). Syrup. ^{1}H NMR (DMSO-d_6) selected data for ∼1:1 mixture of (4*R*)- and (4*S*)-stereoisomers: δ = 8.00 (d, 0.5 H, J = 3.5 Hz, NH), 7.95 (d, 0.5 H, J = 3.5 Hz, NH), 7.40−7.10 (m, 5 H, Ph), 5.18 (d, 0.5 H, J = 3.5 Hz, H-4), 5.09 (d, 0.5 H, J = 3.5 Hz, H-4), 2.57 (s, 1.5 H, CH_3), 2.56 (s, 1.5 H, CH_3), 1.14 (t, 1.5 H, J = 7.0 Hz, CH_2CH_3), 1.09 (t, 1.5 H, J = 7.0 Hz, CH_2CH_3). ^{13}C NMR (DMSO-d_6) selected data for ∼1:1 mixture of (4*R*)- and (4*S*)-stereoisomers: δ = 167.8, 167.7, 156.0, 155.7, 151.9, 150.7, 145.0, 144.9, 106.4, 105.6, 16.9, 16.7, 14.5, 14.2. MALDI-TOF MS: 437.5 (M^+ + H), 459.8 (M^+ + Na). Anal. Calcd for $C_{21}H_{28}N_2O_8$ (436.46): C, 57.79; H, 6.47; N, 6.42. Found: C, 57.83; H, 6.41; N, 6.40.

(4*R*)-2-Oxo-4,6-bis-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-15a′). Amorphous solid. $[\alpha]_D^{20}$ = −72.5 (*c* 1.3, MeOH). ^{1}H NMR (pyridine-d_5): δ = 10.42 (bs, 1 H, NH), 8.83 (s, 1 H, NH), 6.32 (s, 1 H, H-1*r6*), 5.07 (dd, 1 H, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.5 Hz, H-3*r6*), 5.05 (d, 1 H, $J_{4,1r4}$ = 4.0 Hz, H-4), 4.87 (dd, 1 H, $J_{1,2}$ = 6.5 Hz, $J_{2,3}$ = 4.8 Hz, H-2*r4*), 4.86 (d, 1 H, H-2*r6*), 4.67 (dd, 1 H, $J_{3,4}$ = 6.0 Hz, H-3*r4*), 4.64 (ddd, 1 H, $J_{4,5a}$ = 2.0 Hz, $J_{4,5b}$ = ∼0.5 Hz, H-4*r6*), 4.52 (dd, 1 H, $J_{1,2}$ = 6.5 Hz, H-1*r4*), 4.44 (ddd, 1 H, $J_{4,5a}$ = 4.5 Hz, $J_{4,5b}$ = 4.8 Hz, H-4*r4*), 4.40 (dd, 1 H, $J_{5a,5b}$ = 12.0 Hz, H-5a*r6*), 4.30 (dd, 1 H, H-5b*r6*), 4.11 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 4.06 (dd, 1 H, $J_{5a,5b}$ = 12.0 Hz, H-5a*r4*), 4.00 (dd, 1 H, H-5b*r4*), 1.12 (t, 3 H, CH_3). ^{13}C NMR (D_2O): δ = 166.5, 155.4, 150.9, 96.9, 85.0, 83.2, 81.5, 80.0, 77.8, 72.0, 71.5, 69.3, 62.4, 61.8, 59.1, 52.4, 13.6. MALDI-TOF MS: 441.8 (M^+ + Li), 458.6 (M^+ + Na). Anal. Calcd for $C_{17}H_{26}N_2O_{11}$ (434.40): C, 47.00; H, 6.03; N, 6.45. Found: C, 47.10; H, 6.05; N, 6.40.

(4*R*)-4-(β-D-Galactopyranosyl)-2-oxo-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-15b′). Amorphous solid. $[\alpha]_D^{20}$ = −43.8 (*c* 0.7, MeOH). ^{1}H NMR (pyridine-d_5): δ = 10.42 (s, 1 H, NH), 8.78 (bd, 1 H, $J_{4,NH}$ = 2.0 Hz, NH), 6.53 (d, 1 H, $J_{1,2}$ = 0.8 Hz, H-1*r*), 5.51 (dd, 1 H, $J_{4,1g}$= 2.8 Hz, H-4), 5.16 (dd, 1 H, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 8.0 Hz, H-3*r*), 5.08 (dd, 1 H, H-2*r*), 4.87 (dd, 1 H, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 9.2 Hz, H-2*g*), 4.72 (ddd, 1 H, $J_{4,5a}$ = 2.0 Hz, $J_{4,5b}$ = ∼0.5 Hz, H-4*r*), 4.57 (dd, 1 H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = ∼0.5 Hz, H-4*g*), 4.47 (dd, 1 H, $J_{5a,5b}$ = 11.5 Hz, H-5a*r*), 4.37 (dd, 1 H, H-5b*r*), 4.33 (dd, 1 H, $J_{5,6a}$ = 6.2 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a*g*), 4.27 (dd, 1 H, $J_{5,6b}$ = 6.0 Hz, H-6b*g*), 4.22 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 4.12 (dd, 1 H, H-3*g*), 3.88 (ddd, 1 H, H-5*g*), 3.85 (dd, 1 H, H-1*g*), 1.19 (t, 3 H, CH_3). ^{13}C NMR (pyridine-d_5): δ = 166.0, 154.9, 153.9, 96.3, 83.7, 83.5, 81.6, 80.5, 79.6, 77.1, 71.1, 70.3, 68.1, 62.2, 60.1, 59.8, 52.6, 14.5. MALDI-TOF MS: 471.8 (M^+ + Li), 487.7 (M^+ + Na), 503.9 (M^+ + K). Anal. Calcd for $C_{18}H_{28}N_2O_{12}$ (464.42): C. 46.55; H, 6.08; N, 6.03. Found: C, 46.60; H, 6.10, N, 6.09.

(4*R*)-4-(β-D-Mannopyranosyl)-2-oxo-6-(β-D-ribofuranosyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester ((*R*)-15c′). Amorphous solid. $[\alpha]_D^{20}$ = −62.4 (*c* 0.6, MeOH). ^{1}H NMR (pyridine-d_5): δ = 10.42 (bs, 1 H, NH), 7.90 (bs, 1 H, NH), 6.24 (d, 1 H, $J_{1,2}$ = 1.0 Hz, H-1*r*), 5.09 (dd, 1 H, $J_{4,NH}$ = 2.5 Hz, $J_{4,1m}$ = 4.5 Hz, H-4), 5.05 (dd, 1 H, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 8.2 Hz, H-3*r*), 4.80 (dd, 1 H, H-2*r*), 4.64 (ddd, 1 H, $J_{4,5a}$ = 2.0 Hz, $J_{4,5b}$ = ∼0.5 Hz, H-4*r*), 4.47 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.2 Hz, H-4*m*), 4.39 (d, 1 H, $J_{2,3}$ = 3.5 Hz, H-2*m*), 4.38 (dd, 1 H, $J_{5a,5b}$ = 10.8 Hz, H-5a*r*), 4.29 (dd, 1 H, H-5b*r*), 4.29 (dd, 1 H, $J_{5,6a}$ = 2.5 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a*m*), 4.24−4.10 (m, 2 H, CH_2CH_3), 4.13 (dd, 1 H, $J_{5,6b}$ = 5.0 Hz, H-6b*m*), 3.96 (dd, 1 H, H-3*m*), 3.87 (d, 1 H, H-1*m*), 3.64 (ddd, 1 H, H-5*m*), 1.18 (t, 3 H, J = 7.0 Hz, CH_2CH_3). ^{13}C NMR (pyridine-d_5): δ = 166.5, 155.5, 153.9, 96.7, 83.7, 81.9, 81.5, 81.0, 80.0, 76.3, 72.5, 71.0, 68.9, 63.5, 60.5, 60.0, 54.5, 14.4. MALDI-TOF MS: 487.8 (M^+ + Na), 503.8 (M^+ + K). Anal. Calcd for $C_{18}H_{28}N_2O_{12}$ (464.42): C. 46.55; H, 6.08; N, 6.03. Found: C, 46.51; H, 6.00, N, 6.01.

(4*R*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid ((*R*)-17b). A mixture of aldehyde **5b** (1.10 g, 2.00 mmol), benzyl acetoacetetate (346 μL, 2.00 mmol), urea (180 mg, 3.00 mmol), $Yb(OTf)_3$ (1.24 g, 2.00 mmol), and anhydrous THF (10 mL) was stirred under reflux for 20 h. The mixture was cooled to room temperature, diluted with EtOAc (100 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 first (4*R*)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester (833 mg, 54%) as a white foam. ^{1}H NMR: δ = 7.50−7.20 (m, 25 H, 5 Ph), 6.18 (bd, 1 H, J = ∼0.5 Hz, NH), 5.20 (s, 2 H, $PhCH_2$), 4.95 and 4.62 (2 d, 2 H, J = 12.0 Hz, $PhCH_2$), 4.94 and 4.67 (2 d, 2 H, J = 11.8 Hz, $PhCH_2$), 4.78 and 4.73 (2 d, 2 H, J = 11.2 Hz, $PhCH_2$), 4.49 (bdd, 1 H, $J_{4,NH}$ = 4.5 Hz, $J_{1',4}$ = 1.0 Hz, H-4), 4.41 and 4.35 (2 d, 2 H, J = 11.5 Hz, $PhCH_2$), 4.05 (bdd, 1 H, J = ∼0.5 Hz, $J_{4,NH}$ = 4.5 Hz, NH), 3.95 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.88 (dd, 1 H, $J_{1',2'}$ = 9.5 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.61 (dd, 1 H, H-3′), 3.54−3.41 (m, 3 H, H-5′, 2 H-6′), 3.22 (dd, 1 H, H-1′), 2.17 (s, 3 H, CH_3). MALDI-TOF MS: 791.7 (M^+ + Na), 807.5 (M^+ + K). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.40; H, 6.22; N, 3.58.

Eluted second was (4*S*)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester (167 mg, 11%) as a white foam. ^{1}H NMR: δ = 7.50−7.10 (m, 25 H, 5 Ph), 6.39 (bs, 1 H, NH), 5.55 (bs, 1 H, NH), 5.21 and 5.07 (2 d, 2 H, J = 12.0 Hz, $PhCH_2$), 5.09 and 4.54 (2 d, 2 H, J = 11.8 Hz, $PhCH_2$), 4.95 and 4.55 (2 d, 2 H, J = 11.5 Hz, $PhCH_2$), 4.72 (bs, 1 H, H-4), 4.71 and 4.59 (2 d, 2 H, J = 12.1 Hz, $PhCH_2$), 4.46 and 4.41 (2 d, 2 H, J = 11.2 Hz, $PhCH_2$), 4.09 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.1 Hz, H-2′), 3.97 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.65 (dd, 1 H, H-3′), 3.62 (dd, 1 H, H-1′), 3.55−4.80 (m, 3 H, H-5′, 2 H-6′), 1.92 (s, 3 H, CH_3). MALDI-TOF MS: 792.0 (M^+ + Na), 808.1 (M^+ + K). Anal. Calcd for $C_{47}H_{48}N_2O_8$ (768.89): C, 73.42; H, 6.29; N, 3.64. Found: C, 73.50; H, 6.31; N, 3.65.

A vigorously stirred mixture of 20% palladium hydroxide on carbon (150 mg), Ambersep 900 OH (300 mg),[38] AcOEt (2 mL), and CH_2Cl_2 (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 (4*R*)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester (100 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) previously degassed and saturated with hydrogen as described before. After the mixture was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 1.5 h, palladium hydroxide on carbon and Ambersep 900 OH were filtered off through a pad of Celite and the mixture was then suspended in CH_2Cl_2 (4 mL). This mixture was diluted with AcOH (0.5 mL) and shaken for 30 min. Then palladium hydroxide on carbon and Ambersep 900 OH were filtered off through a pad of Celite and washed thoroughly with CH_2Cl_2 and MeOH. The combined filtrates were concentrated to give (*R*)-**17b** (70 mg, 78%) as a white solid at least 95% pure by NMR analysis. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ = 7.50−7.10 (m, 20 H, 4 Ph), 6.82 (bs, 1 H, NH), 4.96 and 4.62 (2 d, 2 H, J = 11.8 Hz, $PhCH_2$), 4.94 and 4.77 (2 d, 2 H, J = 11.5 Hz, $PhCH_2$), 4.75 and 4.65 (2 d, 2 H, J = 11.2 Hz, $PhCH_2$), 4.46 (bs, 1 H, H-4), 4.40 and 4.34 (2 d, 2 H, J = 11.0 Hz, $PhCH_2$), 3.94 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.1 Hz, H-2′), 3.93 (dd, 1 H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.65 (dd, 1 H, H-3′), 3.62 (bs, 1 H, NH), 3.54−3.42 (m, 3 H, H-5′, 2 H-6′), 3.32 (dd, 1 H, $J_{1',4}$ = ∼0.5 Hz, H-1′), 2.19 (s, 3 H, CH_3). MALDI-TOF MS: 701.9 (M^+ + Na), 717.8 (M^+ + K).

Crystallization from ethanol afforded small crystals of (*R*)-**17b** suitable for elemental and X-ray diffraction analysis. Anal. Calcd for $C_{40}H_{42}N_2O_8$ (678.77): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.77; H, 6.23; N, 4.12.

(38) Ambersep 900 OH was purchased from Fluka. This resin was washed with methanol and dried in vacuo before use.

(4*R*)-4-(β-D-Galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid ((*R*)-17b′). A vigorously stirred mixture of (4*R*)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester (300 mg, 0.39 mmol), 20% palladium hydroxide on carbon (200 mg), CH_2Cl_2 (4 mL), AcOEt (2 mL), and MeOH (4 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. After the mixture was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 8 h, palladium hydroxide on carbon was filtered off through a plug of cotton and the mixture washed thoroughly with MeOH (2 mL), H_2O (0.5 mL), and DMF (2 mL). The combined filtrates were concentrated to give (*R*)-**17b′** (118 mg, 95%) as a white amorphous solid. ^{1}H NMR ($CD_3OD + D_2O$): δ = 4.65 (bs, 1 H, H-4), 3.87 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = ∼0.5 Hz, H-4′), 3.72 (dd, 1 H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.1 Hz, H-2′), 3.68 (dd, 1 H, $J_{5',6'a}$ = 4.5 Hz, $J_{6'a,6'b}$ = 11.5 Hz, H-6′a), 3.63 (dd, 1 H, $J_{5',6'b}$ = 6.2 Hz, H-6′b), 3.47 (dd, 1 H, H-3′), 3.44 (ddd, 1 H, H-5′), 3.19 (dd, 1 H, $J_{1',4}$ = 2.5 Hz, H-1′), 2.28 (s, 3 H, CH_3). MALDI-TOF MS: 341.5 (M^+ + Na), 357.4 (M^+ + K). Anal. Calcd for $C_{12}H_{18}N_2O_8$ (318.28): C, 45.28; H, 5.70; N, 8.80. Found: C, 45.21; H, 5.68; N, 8.75.

(4*S*)-6-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (18a) and (4*R*)-6-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (18b). A mixture of 3-hydroxybenzaldehyde (122 mg, 1.00 mmol), β-ketoester **6a** (518 mg, 1.00 mmol), thiourea (228 mg, 3.00 mmol), Yb(OTf)$_3$ (310 mg, 0.50 mmol), and anhydrous THF (5 mL) was stirred under reflux for 20 h. The mixture was cooled to room temperature, diluted with EtOAc (100 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 4:1 cyclohexane−AcOEt to give first **18b** (150 mg, 22%) as a white foam. $[\alpha]_D^{20}$ = −24.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ = 10.38 (bs, 1 H, NH), 7.60−7.10 and 6.90−6.70 (2m, 19 H, Ph), 7.08 (bs, 1 H, OH), 5.90 (d, 1 H, $J_{1',2'}$ = ∼0.5 Hz, H-1′), 5.43 (bs, 1 H, NH), 5.32 (d, 1 H, $J_{4,NH}$ = 2.8 Hz, H-4), 5.18 and 4.70 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.90 and 4.83 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.40 and 4.28 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.28 (ddd, 1 H, $J_{3',4'}$ = 8.8 Hz, $J_{4',5'a}$ = 2.5 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.21−4.08 (m, 3 H, CH_2CH$_3$, H-3′), 4.05 (dd, 1 H, $J_{2',3'}$ = 5.0 Hz, H-2′), 3.86 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.58 (dd, 1 H, H-5′b), 1.17 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{39}H_{40}N_2O_7S$ (680.81): C, 68.80; H, 5.92; N, 4.11; S, 4.71. Found: C, 68.81; H, 5.93; N, 4.15, S, 4.76.

Eluted second was **18a** (299 mg, 44%) as a white foam. $[\alpha]_D^{20}$ = 59.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ = 10.32 (bs, 1 H, NH), 7.55−7.15 and 6.90−6.70 (2m, 20 H, Ph, OH), 5.83 (d, 1 H, $J_{1',2'}$ = ∼0.5 Hz, H-1′), 5.66 (bs, 1 H, NH), 5.39 (d, 1 H, $J_{4,NH}$ = 2.8 Hz, H-4), 5.06 and 4.74 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.86 and 4.69 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.40 and 4.29 (2 d, 2 H, *J* = 11.2 Hz, PhCH_2), 4.28 (ddd, 1 H, $J_{3',4'}$ = 8.5 Hz, $J_{4',5'a}$ = 2.5 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.21−4.04 (m, 2 H, CH_2CH$_3$), 4.08 (dd, 1 H, $J_{2',3'}$ = 4.5 Hz, H-3′), 3.95 (dd, 1 H, H-2′), 3.87 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 3.57 (dd, 1 H, H-5′b), 1.18 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). Anal. Calcd for $C_{39}H_{40}N_2O_7S$ (680.81): C, 68.80; H, 5.92; N, 4.11; S, 4.71. Found: C, 68.85; H, 5.95; N, 4.10, S, 4.78.

(4*S*)-4-(3-Hydroxyphenyl)-6-(β-D-ribofuranosyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (19a). To a cooled (−70 °C), stirred solution of **18a** (200 mg, 0.29 mmol) in anhydrous CH_2Cl_2 was added boron trichloride (1.0 M solution in CH_2Cl_2, 2.64 mL, 2.64 mmol) dropwise, and stirring was continued at −70 °C for 10 min. The solution was then warmed to 0 °C and stirred for an additional 1.5 h. The excess of boron trichloride was quenched at −70 °C with EtOH/CH_2Cl_2 (1:1, 5 mL). The solution was warmed to room temperature and adjusted to pH 5 with 3 N aqueous sodium hydroxide. A minimal amount of silica gel was added and the solvent evaporated. The compound (absorbed on silica gel) was subjected to column chromatography with 10:1:0.1 CH_2Cl_2−MeOH−28% NH_4OH to give, following solvent evaporation, **19a** (90 mg, 75%) as a white solid. $[\alpha]_D^{20}$ = 56.8 (*c* 1.6, MeOH). ^{1}H NMR (pyridine-d_5): δ = 11.60 (bs, 1 H, OH), 11.24 (bs, 1 H, NH), 8.01 (bs, 1 H, NH), 7.46 (dd, 1 H, *J* = 1.0, 1.2 Hz, H-2*Ph*), 7.18 (ddd, 1 H, *J* = 1.0, 1.5, 7.5 Hz, H-4*Ph*), 7.13 (dd, 1 H, *J* = 7.5, 7.8 Hz, H-5*Ph*), 7.01 (ddd, 1 H, *J* = 1.2, 1.5, 7.8 Hz, H-6*Ph*), 6.31 (d, 1 H, $J_{1',2'}$ = ∼0.5 Hz, H-1′), 5.75 (d, 1 H, $J_{4,NH}$ = ∼0.5 Hz, H-4), 4.98 (dd, 1 H, $J_{2',3'}$ = 4.5 Hz, $J_{3',4'}$ = 8.0 Hz, H-3′), 4.74 (dd, 1 H, H-2′), 4.69 (ddd, 1 H, $J_{4',5'a}$ = 2.2 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.46 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 4.32 (dd, 1 H, H-5′b), 4.14−3.98 (m, 2 H, CH_2CH$_3$), 1.09 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). ^{13}C NMR (pyridine-d_5): δ = 176.1, 165.5, 159.4, 148.2, 146.7, 130.4, 117.8, 115.9, 114.7, 100.9, 83.6, 81.2, 79.6, 71.3, 60.4, 59.9, 56.1, 14.1. MALDI-TOF MS: 434.1 (M^+ + Na). Anal. Calcd for $C_{18}H_{22}N_2O_7S$ (410.44): C, 52.67; H, 5.40; N, 6.83; S, 7.81. Found: C, 52.60; H, 5.41; N, 6.80; S, 7.85.

(4*R*)-4-(3-Hydroxyphenyl)-6-(β-D-ribofuranosyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (19b). Dihydropyrimidinethione **18b** (200 mg, 0.29 mmol) was treated as described for the preparation of **19a** to give **19b** (90 mg, 75%) as a white solid. $[\alpha]_D^{20}$ = −80.8 (*c* 0.9, MeOH). ^{1}H NMR (pyridine-d_5 + D_2O): δ = 7.54 (dd, 1 H, *J* = 1.0, 1.2 Hz, H-2*Ph*), 7.21 (ddd, 1 H, *J* = 1.0, 3.0, 7.8 Hz, H-4*Ph*), 7.19 (dd, 1 H, *J* = 7.5, 7.8 Hz, H-5*Ph*), 7.08 (ddd, 1 H, *J* = 1.2, 3.0, 7.5 Hz, H-6*Ph*), 6.32 (d, 1 H, $J_{1',2'}$ = 2.0 Hz, H-1′), 5.73 (s 1 H, H-4), 5.02 (dd, 1 H, $J_{2',3'}$ = 4.5 Hz, $J_{3',4'}$ = 8.0 Hz, H-3′), 4.73 (dd, 1 H, H-2′), 4.68 (ddd, 1 H, $J_{4',5'a}$ = 2.0 Hz, $J_{4',5'b}$ = ∼0.5 Hz, H-4′), 4.42 (dd, 1 H, $J_{5'a,5'b}$ = 10.8 Hz, H-5′a), 4.37 (dd, 1 H, H-5′b), 4.14−4.00 (m, 2 H, CH_2CH$_3$), 1.10 (t, 3 H, *J* = 7.0 Hz, CH$_2$CH_3). ^{13}C NMR (pyridine-d_5): δ = 176.4, 165.9, 159.3, 148.1, 146.4, 130.5, 118.2, 116.0, 114.8, 101.9, 84.1, 81.6, 78.9, 71.8, 60.7, 60.2, 56.0, 14.4. MALDI-TOF MS: 411.7 (M^+ + H), 433.7 (M^+ + Na), 449.9 (M^+ + K). Anal. Calcd for $C_{18}H_{22}N_2O_7S$ (410.44): C, 52.67; H, 5.40; N, 6.83; S, 7.81. Found: C, 52.61; H, 5.45; N, 6.83; S, 7.84.

6-(5-Benzoyloxymethylfuran-2-yl)-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (21) and 4-(3-Acetoxyphenyl)-6-(5-benzoyloxymethylfuran-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (22). A mixture of 3-acetoxybenzaldehyde (164 mg, 1.00 mmol), β-ketoester **20**[33] (560 mg, 1.00 mmol), thiourea (228 mg, 3.00 mmol), Yb(OTf)$_3$ (620 mg, 1.00 mmol), and anhydrous THF (5 mL) was stirred under reflux for 20 h. The mixture was cooled to room temperature, diluted with EtOAc (100 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 3:1 cyclohexane−AcOEt to give first **22** (120 mg, 23%) as a yellow syrup. $[\alpha]_D^{20}$ = 0.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ = 8.28 (bs, 1 H, NH), 8.12−8.07 and 7.63−7.02 (2m, 9 H, Ph), 7.38 and 6.66 (2 d, 2 H, *J* = 3.5 Hz, H-3*Fur*, H-4*Fur*), 5.59 (d, 1 H, $J_{4,NH}$ = 3.0 Hz, H-4), 5.44 (bs, 1 H, NH), 5.37 (s, 2 H, CH_2OBz), 4.17 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 2.31 (s, 3 H, CH_3), 1.16 (t, 3 H, CH$_2$CH_3). Anal. Calcd for $C_{27}H_{24}N_2O_7S$ (520.55): C, 62.30; H, 4.65; N, 5.38; S, 6.16. Found: C, 62.35; H, 4.66; N, 5.40; S, 6.21.

Eluted second was **21** (220 mg, 46%) as yellow syrup. $[\alpha]_D^{20}$ = 0.0 (*c* = 1.4, $CHCl_3$). ^{1}H NMR: δ = 8.30 (bs, 1 H, NH), 8.11−8.05 and 7.63−7.34 (2m, 5 H, Ph), 7.54 (bs, 1 H, OH), 7.32 and 6.65 (2 d, 2 H, *J* = 3.5 Hz, H-3*Fur*, H-4*Fur*), 7.22−7.14 and 6.92−6.74 (2m, 4 H, Ph), 5.95 (bs, 1 H, NH), 5.53 (d, 1 H, $J_{4,NH}$ = 3.0 Hz, H-4), 5.35 (s, 2 H, CH_2OBz), 4.17 (q, 2 H, *J* = 7.0 Hz, CH_2CH$_3$), 1.15 (t, 3 H, CH$_2$CH_3). Anal. Calcd for $C_{25}H_{22}N_2O_6S$ (478.52): C, 62.75; H, 4.63; N, 5.85; S, 6.70. Found: C, 62.70, H, 4.61; N, 5.80.

6-(5-Hydroxymethylfuran-2-yl)-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (23). To a stirred solution of **21** (200 mg, 0.42 mmol) in MeOH (2 mL) was added NaOMe (0.5 M solution in

MeOH, 2 mL), and stirring was continued at room temperature for 1 h. The solution was then neutralized with AcOH. A minimal amount of silica gel was added and the solvent evaporated. The compound (absorbed on silica gel) was subjected to column chromatography with 1:1 cyclohexane−AcOEt to give, following solvent evaporation, **23** (149 mg, 95%) as a yellow syrup. $[\alpha]_D^{20} = 0.0$ ($c = 1.2$, MeOH). ^{1}H NMR (CD_3OD): $\delta = 7.22-7.14$, 6.90−6.84, and 6.77−6.70 (3m, 4 H, Ph), 7.03 and 6.48 (2 d, 2 H, $J = 3.5$ Hz, H-3*Fur*, H-4*Fur*), 5.38 (s, 1 H, H-4), 4.58 (s, 2 H, CH_2OH), 4.08 (q, 2 H, $J = 7.0$ Hz, CH_2-CH_3), 1.12 (t, 3 H, CH$_2$CH_3). MALDI-TOF MS: 375.8 ($M^+ + H$), 397.6 ($M^+ + Na$), 413.8 ($M^+ + K$). Anal. Calcd for $C_{18}H_{18}N_2O_5S$ (374.41): C, 57.74; H, 4.85; N, 7.48; S, 8.56. Found: C, 57.83; H, 4.89; N, 7.50; S, 8.65.

Treatment of dihydropyrimidinethione **22** (200 mg, 0.38 mmol) under the above conditions afforded **23** in comparable yield**.**

Crystal data for compound (*R*)-17b: $C_{40}H_{42}N_2O_8$, $M_r = 678.76$, colorless crystal (0.07 × 0.26 × 0.28 mm), orthorhombic, space group $P2_12_12_1$ (no. 19) with $a = 8.7960(2)$ Å, $b = 14.8824(3)$ Å, $c = 28.4846(7)$ Å, $V = 3728.8(2)$ Å^3, $Z = 4$, $D_c = 1.209$ g cm^{-3}, 19 593 reflections measured, 8067 indipendent, $R_{int} = 0.052$ ($2.54 < \theta < 27.5°$, $T = 150$ K, Mo Kα radiation, $\lambda = 0.710\ 73$ Å) on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SIR92) and refined on F^2 (SHELXL-97) for 464 parameters. Refinement converged at a final wR2 value of 0.0976, R1 = 0.0516 (for 5511 reflections with $I > 2\sigma(I)$), $S = 1.074$. All non-H atoms were refined anisotropically; the N−H and O−H hydrogen atoms were refined isotropically; all other hydrogen atoms were included on calculated positions, riding on their carrier atoms. A final difference Fourier showed no residual density outside −0.20 and 0.21 Å^{-3}.

Acknowledgment. We gratefully acknowledge MURST and University of Ferrara for financial support. We thank Professor G. Vertuani for the assistance in CD spectra recording and the Department of Pharmaceutical Chemistry for the access to the relevant instrumentation.

Supporting Information Available: CIF of compound (*R*)-**17b** and an ORTEP plot of (*R*)-**17b** drawn at 40% probability level. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0202076