Design and Synthesis of New Classes of Heterocyclic *C*-Glycoconjugates and Carbon-Linked Sugar and Heterocyclic Amino Acids by Asymmetric Multicomponent Reactions (AMCRs)

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ABSTRACT

While chemical efficiency relies on several factors, the multicomponent reaction (MCR) approach was considered as a powerful synthetic tool for preparing target molecules of biological relevance in an efficient manner. Four classes of new bioactive molecules were designed and synthesized by asymmetric MCRs, in some cases with the cooperation of polymer-assisted solution-phase (PASP) technique. These include (a) *C*-glycosyl dihydropyrimidines and dihydropyridines via Biginelli and Hantzsch cyclocondensations, (b) *C*-glycosyl β-amino acids via Mannich- and Reformatsky-type reactions, (c) *C*-glycosyl β-lactams via Staudinger reaction, and (d) heterocyclic α-amino acids (glycine and alanine) via the Biginelli and Hantzsch reactions.

1. Introduction

Over the past four years or so our laboratory has been engaged in a research program aimed at preparing collections of novel carbohydrate and amino acid derivatives displaying molecular structure with firmly established biological activity. The a priori identification of biologically validated targets was a crucial point in our program to fulfill the requirements of the modern drug discovery paradigm. This has significantly changed from the past by focusing on the quality rather than on the size of compound libraries in both the lead optimization and lead generation phases. The validity of this new paradigm is demonstrated, for instance, by the growing number of marketed pharmaceuticals resulting from the screening of combinatorial libraries designed using natural products as scaffolds.[1] According to this trend, we considered three main classes of biologically relevant compounds, artificial nucleosides, unnatural (sugar and heterocycle) amino acids, and β-lactams. The synthesis of new families of nucleosides is, in fact, a current topic in medicinal chemistry due to the well-established anticancer, antibiotic, and antiviral activity of these molecules;[2] nonproteinogenic amino acids have gained great importance in life science both as precursors to artificial peptides and for their own biological properties;[3] finally, the search for new β-lactam containing molecules is actively pursued to find a remedy for the emergence of strains of organisms resistant to these antibiotics.[4] Another important goal of our program was addressing some aspects of the modern criteria of synthetic efficiency (see below for a detailed discussion of this topic) to achieve an easy and rapid production of collections of the above target molecules. To this aim, we considered multicomponent reactions (MCRs)[5] as a tool for the efficient generation of structurally and stereochemically diversified families of the identified biologically validated targets (focused libraries). This Account describes the rationale at the basis of our study and the experimental work that led to the development of this chemistry along with some preliminary results on the biological activity of the synthesized molecules.

About Chemical Efficiency. Chemical efficiency in modern terms implies not only the traditional concept of chemical yield but takes also into account chemo-, regio-, and stereoselectivity, atom economy, and convergence of the reaction. The compliance of these aspects has been the center of many efforts over the second half of the last century.[6] Economic, such as material, apparatus, and labor cost, and ecological aspects are also of great relevance in the choice of a synthetic strategy. Accordingly, the use of noncommon media (ionic liquids, water, supercritical fluids)[7] and environmentally benign reagents (hydrogen peroxide, oxygen)[7] has been considered to reduce the impact on the environment and hazards. Moreover, new metal-free and low-cost catalysts such as the organocatalysts[8] and new techniques based on alternative energy sources such as the microwave-assisted organic synthesis (MAOS)[9] have been introduced over the past few years. At the same time, efficiency can be also pursued by simplifying operations that have been so far carried out in a routine and traditional way such as the postreaction phases involving reaction mixture workup and product isolation and purification. To this aim, different methodologies have been developed including the solid-phase

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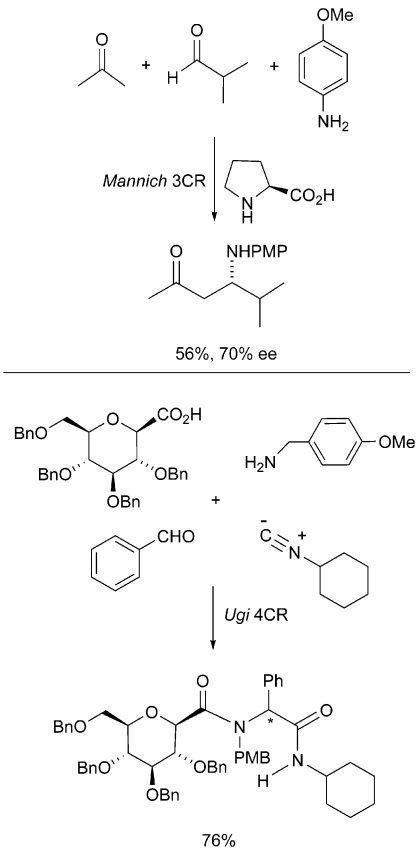
Scheme 1. Examples of Enantioselective and Diastereoselective MCRs



organic synthesis (SPOS),[10] the complementary technique called polymer-assisted solution-phase synthesis (PASPS),[10] the "light" fluorous synthesis,[10] the "tag-assisted" synthesis,[11] and the synthesis in flow mode.[12]

Maximizing Synthetic Efficiency by Asymmetric Multicomponent Reactions (AMCRs). Efficiency is also being currently pursued, when possible, by implementation of classical multicomponent reactions (MCRs), as well as the invention of new ones.[5] Since these reactions involve the stepwise one-pot transformation of three or more reactants in a single product that contains portions of all the starting components, they feature a high degree of atom economy and are especially suitable in combinatorial chemistry and diversity-oriented synthesis programs. Other benefits of MCRs are the intrinsic labor- and time-saving nature and the high purity of products they generate owing to their high selectivity. Asymmetric multicomponent reactions (AMCRs),[13] which are MCRs affording products having at least one new stereocenter, can be carried out in an enantioselective manner by the use of achiral starting materials and external asymmetric agents or in a diastereoselective manner by the use of reactants containing chiral residues. In the latter cases, the chiral group(s) becomes part of the target molecules and can be eventually removed. These approaches are illustrated in Scheme 1 by an organocatalyzed Mannich 3CR[14] and Ugi 4CR,[15] respectively. The great potential of AMCRs has been recognized recently by the synthetic organic chemistry community. The consideration for this

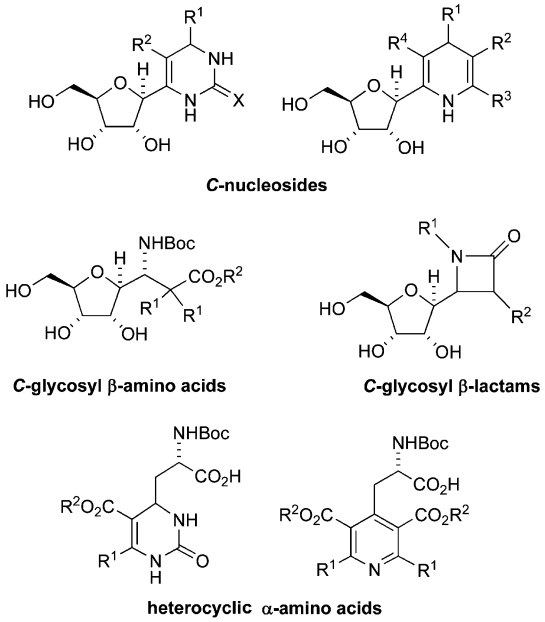


FIGURE 1. Designed biologically validated targets.

strategy relies mainly on the awareness of the tendency in modern drug discovery to develop compounds with complex chemical structures, usually with one or more stereocenters, and these are needed in highly pure enantiomeric forms. The synthesis of such drug candidates can be approached via AMCRs, since these allow for a rapid compilation of libraries with a wide range of structural and stereochemical elements of diversity simply by modulating the structure and stereochemistry of starting components, promoters, or both.

Our Study: General Strategy. The first step of our research program involved the development of optimized AMCRs for the preparation of small collections of homochiral compounds with validated structure via internal asymmetric induction (diastereoselective approach) using chiral reagents. Suitable isolation of final products in high purity, as well as the removal of protecting groups for biological testing, constituted the final operations of the whole procedure. Representative structures of biologically validated targets that were designed for this program are shown in Figure 1. They include (i) heterocyclic *C*-glycoconjugates, that is, *C*-nucleosides, via the Biginelli and Hantzsch 3CRs, (ii) *C*-glycosyl β-amino acids via the Mannich and Reformatsky 3CRs, (iii) *C*-glycosyl β-lactams by the Staudinger 3CR, and (iv) heterocyclic α-amino acids via the Biginelli and Hantzsch 3CRs. It is worth pointing out that the target glycoconjugates in Figure 1 featured the carbohydrate fragment anomerically linked to the aglycone moiety through a carbon−carbon bond. This type of linkage was a structural prerequisite to ensure high stability under both basic and acidic conditions and avoid enzyme-catalyzed transformations. In fact, it is amply demonstrated that the replacement of the anomeric C−O and C−N bond in *O*- and *N*-glycosides with a C−C bond leads to *C*-glycoside analogues displaying high stability toward chemical and enzymatic degradation.[16]

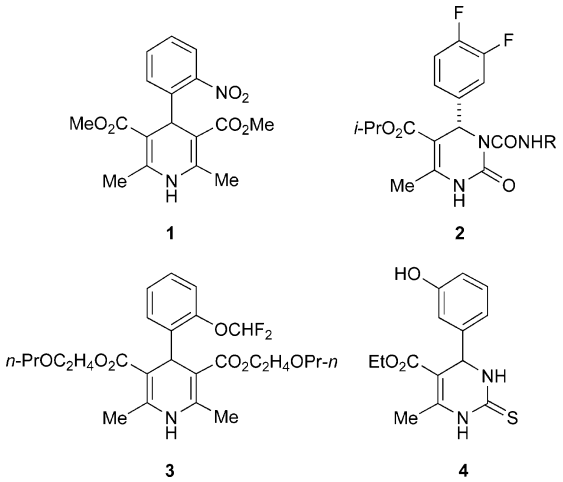


FIGURE 2. DHP and DHPM derivatives of pharmaceutical relevance.

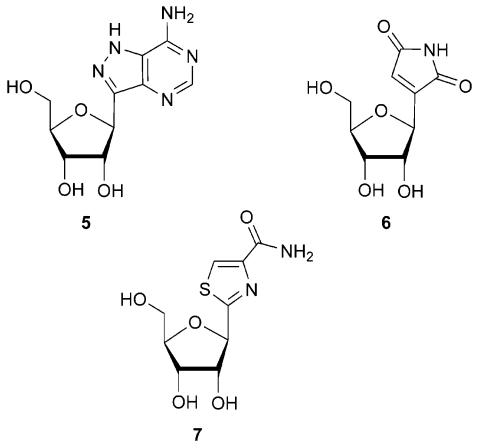


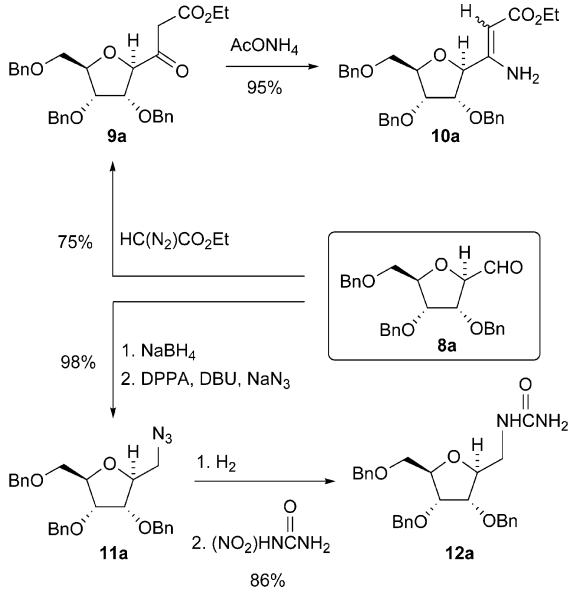
FIGURE 3. Natural and synthetic *C*-nucleosides of biological relevance.

2. Heterocyclic *C*-Glycoconjugates

Why Assemble Sugar-Decorated *N*-Heterocycles via Biginelli and Hantzsch 3CRs? Chronologically our research in this field began by considering the asymmetric synthesis of dihydropyrimidine (DHPMs) and dihydropyridine (DHPs) *C*-glycoconjugates (Figure 1). This research stemmed from the idea that carbohydrate decoration of compounds having a firmly established pharmacological activity not only can modify the pharmacokinetic or the pharmacodynamic properties but also can lead to products with new and unexpected biological functions.[17] Therefore we set for ourselves the program of preparing *C*-glycosylated DHPM and DHP derivatives via Biginelli[18] and Hantzsch[19] 3CRs because DHP and DHPM scaffolds are "privileged structures", which, depending on the substitution patterns of the heterocyclic ring, show the ability to bind to a wide range of receptors. For instance, nifedipine **1** (Figure 2) is a well-known DHP derivative used since the 1970s as an antihypertensive agent; the DHPM **2** has been identified as a drug candidate for the treatment of benign prostatic hyperplasia; cerebrocast **3** is a novel drug with antidiabetic and neuroprotectant properties; monastrol **4** is a recently identified lead compound of a new class of anticancer agents (see below for more details).

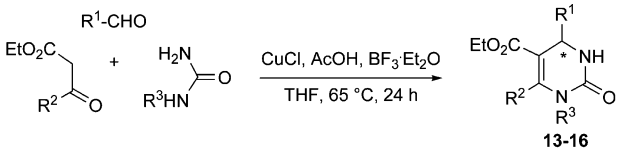
An additional reason that spurred us to enter in this field was the realization that DHPM and DHP *C*-glycosides constitute new families of *C*-nucleosides displaying two unusual heterocyclic bases. Research on *C*-nucleosides is actively pursued in medicinal chemistry as demonstrated by the isolation and synthesis of several of these glycoconjugates showing anticancer, antibiotic, and antiviral activity.[20] For instance, formycin **5** and showdomycin **6** (Figure 3) are natural antibiotics that display the D-ribofuranosyl ring β-linked by a carbon−carbon bond to an adenine and a pyrrolic nucleus, respectively. Tiazofurin **7** is instead a synthetic *C*-nucleoside with anticancer activity featuring the thiazole ring in its structure. In fact, it is well-known that the heterocyclic residue exerts a central role in *C*-nucleoside biological functions, and therefore the synthesis and biological evaluation of new classes of compounds with such structural diversity are of great interest.

Scheme 2. Synthesis of Glycosylated Reagents

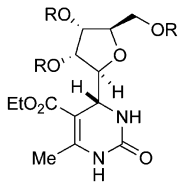
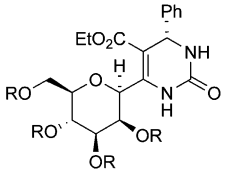
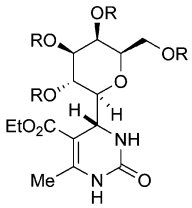
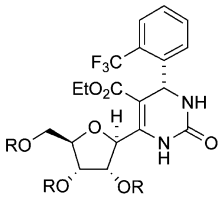
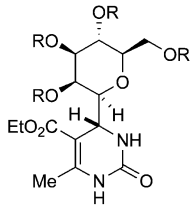
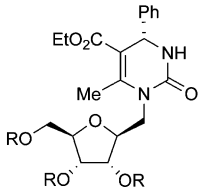
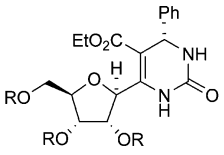
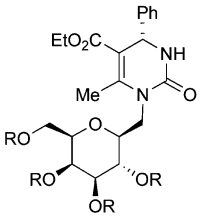
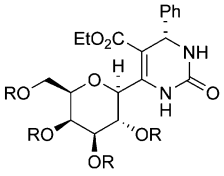
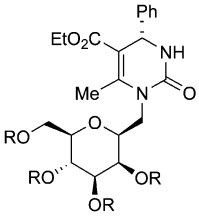


The Multigram Scale Routes to *C*-Glycosylated Reagents for the Biginelli and Hantzsch AMCRs. Considering that the Biginelli reaction involves the acid-catalyzed cyclocondensation of aldehyde, β-ketoester, urea, or thiourea derivatives and the most versatile version of the Hantzsch reaction proceeds by heating aldehyde, β-ketoester, and β-enamino ester derivatives, we focused, in a first instance, our efforts on the preparation of a small arsenal of *C*-glycosyl derivatives of each of those reagents. *C*-Glycosyl formaldehydes, readily accessible from sugar lactones via the thiazole-based route developed in our laboratory,[21] were precious tools not only as partners in the planned 3CRs but also as precursors to other *C*-glycosylated reagents. The conditions employed for the transformations[22,23] of the model β-D-*C*-ribosyl aldehyde **8a** into the ketoester **9a** and ureide **12a** through the azide **11a** are reported in Scheme 2. The access to another key reactant, the enamino ester **10a** from **9a**, is illustrated as well. In a similar way β-linked *C*-galactopyranosyl and

Table 1. DHPM Glycoconjugates Prepared via Biginelli 3CRs



13-16

R^1, R^2, R^3	Product	Yield %	de %	R^1, R^2, R^3	Product	Yield %	de %
β-ribosyl , Me, H	 **(*R*)-13a** (R = Bn) **(*R*)-13a'** (R = H)	63	50	Ph, β-mannosyl, H	 **(*S*)-14c** (R = Bn) **(*S*)-14c'** (R = H)	70	50
β-galactosyl, Me, H	 **(*R*)-13b** (R = Bn) **(*R*)-13b'** (R = H)	65	70	2-(CF_3)-C_6H_4, β-ribosyl, H	 **(*S*)-15a** (R = Bn) **(*S*)-15a'** (R = H)	82	35
β-mannosyl, Me, H	 **(*R*)-13c** (R = Bn) **(*R*)-13c'** (R = H)	57	50	Ph, Me, CH_2-β-ribosyl	 **(*S*)-16a** (R = Bn) **(*S*)-16a'** (R = H)	48	0
Ph, β-ribosyl, H	 **(*S*)-14a** (R = Bn) **(*S*)-14a'** (R = H)	92	50	Ph, Me ,CH_2-β-galactosyl	 **(*S*)-16b** (R = Bn) **(*S*)-16b'** (R = H)	41	0
Ph, β-galactosyl, H	 **(*S*)-14b** (R = Bn) **(*S*)-14b'** (R = H)	75	70	Ph, Me , CH_2-β-mannosyl	 **(*S*)-16c** (R = Bn) **(*S*)-16c'** (R = H)	40	0

C-glucopyranosyl ketoesters, ureides, and enamino esters were prepared from the corresponding readily available anomeric sugar aldehydes.

***C*-Nucleosides from Asymmetric Biginelli and Hantzsch 3CRs.** We first sought suitable reaction conditions and acid promoters that would allow the assembly of the heterocyclic scaffold in high yield and, at the same time, would leave unaltered the quite sensitive sugar residues. Decomposition of these chiral fragments could arise from the removal of the acid-sensitive benzyl (Bn) protective groups and the elimination of BnOH from the C1 and C2 positions. Satisfactory results were obtained

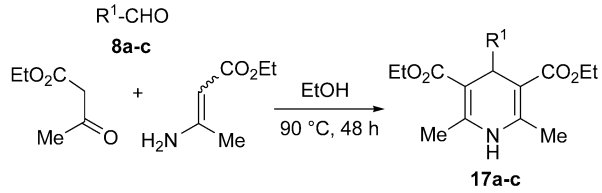
by carrying on the Biginelli reaction in refluxing THF as a solvent and in the presence of a mixture of CuCl, AcOH, and $BF_3{\cdot}Et_2O$ as an acid promoter. Also $Yb(OTf)_3$ turned out to be a good catalyst whose use, however, was conditioned by the high cost. In this way, the homochiral C4-glycosylated DHPMs **13a**−**c** and the C6-glycosylated DHPMs **14a**−**c** and **15a** (Table 1) were isolated as major products from pairs of diastereoisomers generated from various precursors.[22] While ranging from good to modest values, the registered diastereomeric excesses (de) revealed for all these 3CRs a good degree of asymmetric induction exerted by the carbohydrate residue in the formation of the C4 stereocenter of the DHPM ring. On the other hand the *C*-glycosyl DHPMs **16a**−**c** featuring the sugar residue linked to the N1 through a methylene bridge were obtained in equal amounts of their C4 epimers (Table 1). We speculated that the absence of stereoselection was due to the distance of the chiral carbohydrate residue from the C4 stereocenter of the DHPM ring under formation.

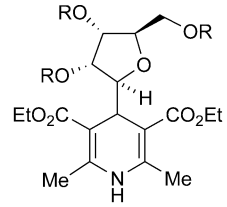
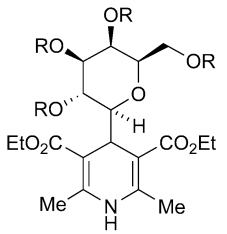
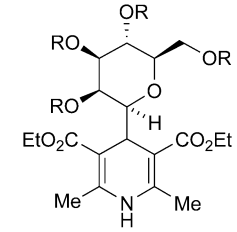
We have also considered the Hantzsch 3CR for the generation of *C*-nucleosides featuring the DHP ring as the heterocyclic moiety.[23] Symmetrically substituted and therefore achiral DHPs **17a**−**c** bearing a sugar residue at C4 were prepared in good yields by reacting *C*-glycosyl aldehydes **8a**−**c**, ethyl acetoacetate, and ethyl aminocrotonate in refluxing ethanol (Table 2). On the other hand, attempts to carrying on the synthesis of C2-glycosylated isomers by the same one-pot technique gave unsatisfactory results. In fact, two convergent routes in which the carbohydrate fragment (*β*-*C*-ribosyl) was installed in the ketoester or the enamino ester afforded the DHP in very low yields (5−10%). However, this class of *C*-nucleosides was successfully approached via a one-pot two-step variant of the Hantzsch reaction (Table 3). This involved the initial aldehyde−ketoester coupling to give the Knoevenagel adduct **18** and then treatment of the latter in the same reaction vessel in which it was formed by the *C*-glycosyl enamino ester **10**. However, this methodology led to the DHP derivatives **19a**−**c** and **20a** as the major isolated isomers (Table 3) with modest diastereoselectivities.

It is worth mentioning before closing this section that the benzyl groups of all DHPM- and DHP-based *C*-nucleosides synthesized were subsequently removed by hydrogenolysis without affecting the other functionalities of these rather complex substrates. In summary, the MC-based strategy that we adopted allowed for the rapid and efficient generation of a collection of about 50 *stereochemically pure* artificial nucleosides. Molecular diversity appears to have been explored within this collection on the basis of the nature and position of the sugar residues in the DHP and DHPM scaffolds.[24]

Biological Assays on *C*-Glycosyl DHPMs and the Lead Compound Monastrol. Although *C*-nucleosides are known to exhibit a wide spectrum of activities, we have so far assayed a selection of our DHPM-based *C*-nucleosides as antimitotic agents, specifically as inhibitors of the microtubule-associated protein Eg5. The lead compound of this

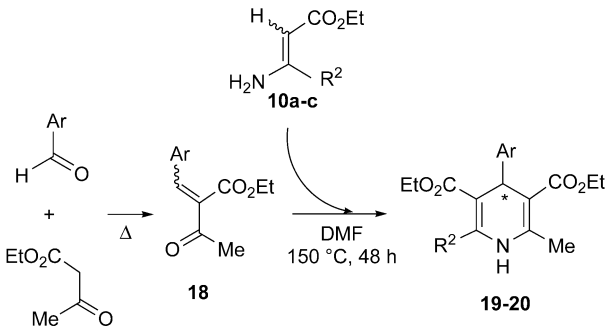
Table 2. Synthesis of C4-Glycosylated DHPs via Hantzsch 3CRs

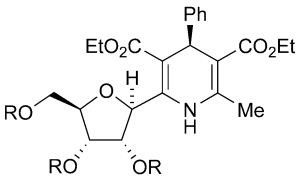
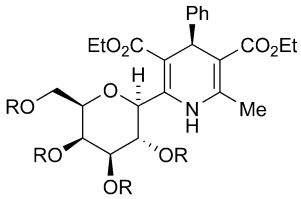
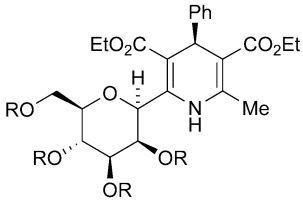
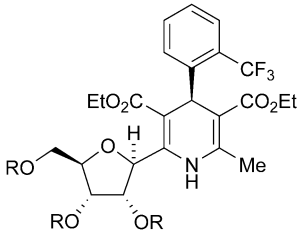


R^1	Product	Yield %
β-ribosyl, **8a**	 **17a** (R = Bn) **17a'** (R = H)	71
β-galactosyl, **8b**	 **17b** (R = Bn) **17b'** (R = H)	88
β-mannosyl, **8c**	 **17c** (R = Bn) **17c'** (R = H)	70

new class of anticancer drugs is, in fact, a sulfurated DHPM derivative named monastrol[25] whose structure **4** in a racemic form is depicted in Figure 2. Monastrol inhibits in vitro and in vivo the motor activity of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity. This novel action of monastrol differentiates it from all other known mitotic inhibitors ranging from colchine to taxanes, which instead affect microtubules, the main structural element of the mitotic spindle.[26] According to our initial idea regarding the beneficial effect of glycosylation on the pharmacokinetic profile and bioavailability of biologically active compounds, we have prepared via the Biginelli reaction compounds (4*S*)-**21** and (4*R*)-**21**, that is, analogues of monastrol, by exchange of the C6 methyl group with the *C*-ribosyl fragment (Scheme 3).[22] This sugar residue was introduced at the C6 position of the DHPM ring to leave unaltered the major structure of the molecule, particularly the aryl group at C4 and the

Table 3. Synthesis of C2-Glycosylated DHPs via Two-Step One-Pot Hantzsch 3CRs

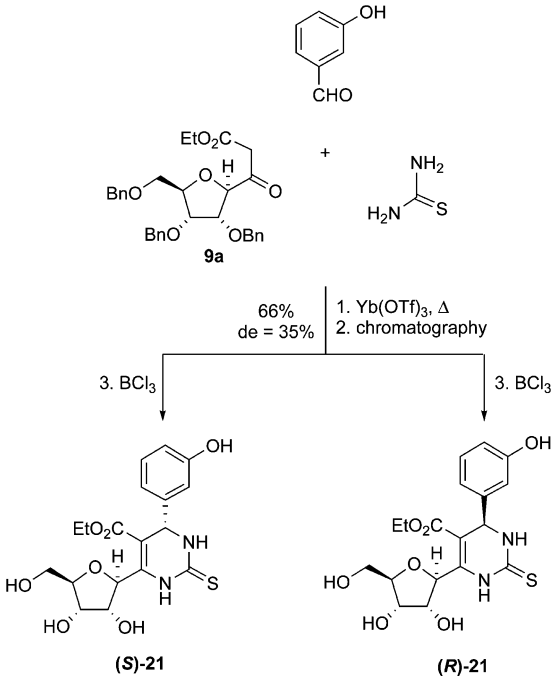


R^2	Product	Yield %	de
β-ribosyl, **10a**	 **(*S*)-19a** (R = Bn) **(*S*)-19a'** (R = H)	71	20
β-galactosyl, **10b**	 **(*S*)-19b** (R = Bn) **(*S*)-19b'** (R = H)	61	30
β-mannosyl, **10c**	 **(*S*)-19c** (R = Bn) **(*S*)-19c'** (R = H)	66	0
β-ribosyl, **10a**	 **(*S*)-20a** (R = Bn) **(*S*)-20a'** (R = H)	62	10

enamine-ester motif, which are the key sites of the pharmacological properties.

The sugar−monastrol analogues (4*S*)-**21** and (4*R*)-**21** and other selected C4- and C6-glycosylated DHPMs were tested as inhibitors of Eg5 activity in vitro and in vivo.[27] (*S*)-Monastrol (IC_{50} = 14 μM; EC_{50} = 22 μM) served as reference compound, and its activity was set at 100% in

Scheme 3. Synthesis of Monastrol Analogues via Biginelli 3CRs



the diagram that reports the percentages of inhibition of all the compounds examined (Figure 4). Although less active than (4*S*)-monastrol, the glycosylated analogue (4*S*)-**21** resulted to be the most active among the synthesized DHPM derivatives. A common property displayed by the majority of the tested compounds, including (4*S*)-monastrol, was the higher activity in vivo than in vitro. This behavior is still a matter of speculation.

Synthesis of Multivalent *C*-Glycosyl DHPMs via Biginelli 3CRs. The idea of assembling DHPM scaffolds decorated with more than one carbon-linked sugar stemmed from parallel work in our laboratory on the synthesis of glycoclusters.[28] The basis of this research is the so-called glycoside cluster effect, a phenomenon whose mechanism is not yet well understood and that implies the augmentation of the biological activity by a factor much higher than expected by a simple effect of concentration increase.[29] Hence we carried out one-pot Biginelli reactions in which two components, the aldehyde and the ketoester, bore a *C*-glycosyl residue. In Table 4 are shown the three major products, (*R*)-**22a**−**c**, that were

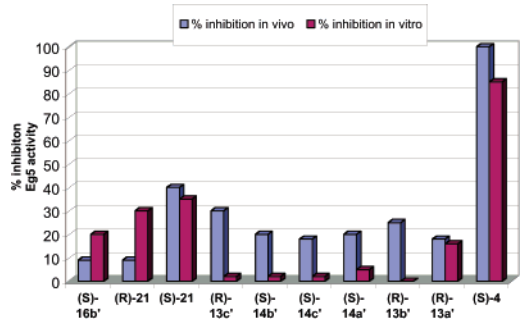
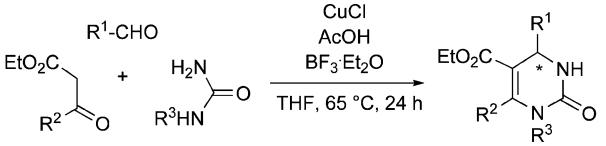
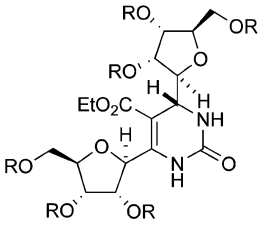
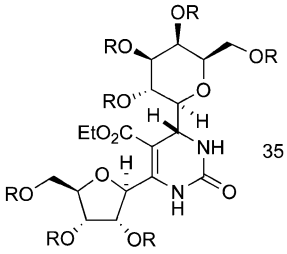
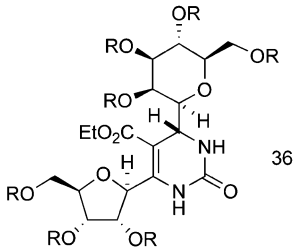
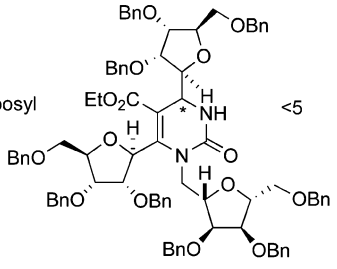


FIGURE 4. Inhibition in vivo and in vitro of mitotic kinesin Eg5 activity by selected glycosylated DHPMs and the (4*S*)-monastrol enantiomer (*S*)-**4** (reported with kind permission of Prof. F. Kozielski).

Table 4. Multivalent *C*-Glycosyl DHPMs Prepared via Biginelli 3CRs



22-23

R^1, R^2, R^3	Product	Yield %	de %
β-ribosyl, β-ribosyl, H		42	80
	(*R*)-22a (R = Bn) **(*R*)-22a'** (R = H)		
β-galactosyl, β-ribosyl, H		35	82
	(*R*)-22b (R = Bn) **(*R*)-22b'** (R = H)		
β-mannosyl, β-ribosyl, H		36	76
	(*R*)-22c (R = Bn) **(*R*)-22c'** (R = H)		
β-ribosyl, β-ribosyl, β-ribosyl		<5	/
	23a		

prepared featuring two sugar units, one attached to C4 and the other to C6 of the DHPM ring. The reactions leading to these products appeared to proceed with some difficulty as shown by the modest yields very likely because of their highly congested transition states. However the diastereoselectivity was in all cases more than satisfactory. Attempts to prepare a tris-glycosylated DHPM derivative by reacting three *C*-glycosylated reactants afforded the target product **23a** in such a small amount to be detectable only by MS analysis of the crude reaction mixture.

3. *C*-Glycosyl β-Amino Acids

***C*-Glycosyl β-Amino Acids as Precursors to Artificial Glycopeptides.** There is abundant evidence that the structure and biological functions of cell surface glycoproteins are greatly affected by their saccharide portions.[30] Some of these biological functions are beneficial (fertilization, immune response), while some others are detrimental (cancer metastasis, viral and bacterial infections). The modulation or inhibition of these phenomena by the use of artificial glycopeptides is an attractive strategy. The design of these compounds can be made by considering two drastic changes with respect to their native analogues. One is the replacement of the *O*- and *N*-glycosidic linkages anchoring the sugar fragments to the polyamide backbone by a carbon−carbon bond to ensure higher resistance of the glycosidic portion toward chemical and enzymatic degradation.[31] The other is the exchange of the α-amidic with the β-amidic bond in the peptide chain to induce increased stability toward proteolysis and new folding patterns, especially β-turn conformations.[32] Evidently, *C*-glycosyl β-amino acids are crucial building blocks in a cotranslational synthetic approach to these artificial glycopeptides.[33] When we addressed this issue a few years ago, there was only one report by Palomo and co-workers[34] describing the multistep synthesis of *C*-glycosyl β-amino acid derivatives from *C*-glycosyl propanals. The few compounds prepared in this way displayed the carbohydrate and β-amino acid moieties spaced out by an ethylene bridge.

Scheme 4. Complementary Mannich and Reformatsky One-Pot Routes to *C*-Glycosyl β-Amino Esters

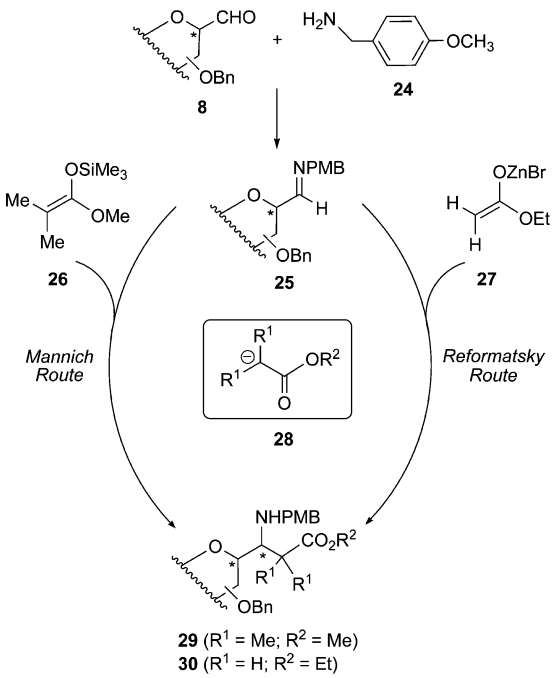
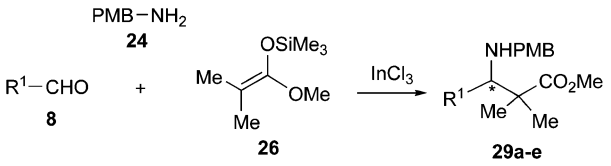


Table 5. *C*-Glycosyl *β*-Amino Esters Prepared via Mannich 3CRs



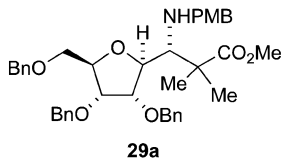
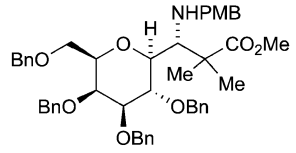
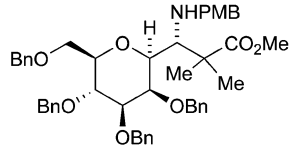
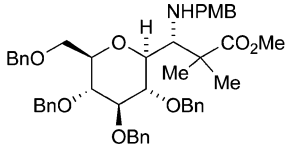
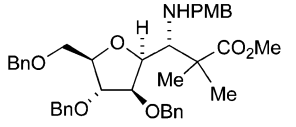
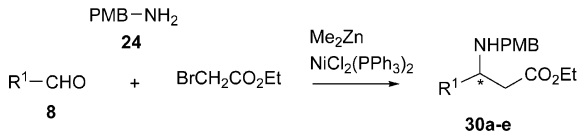
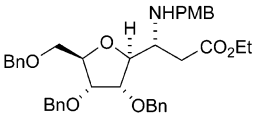
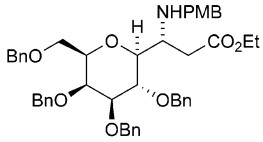
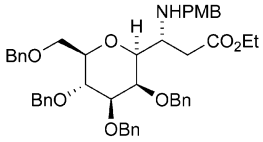
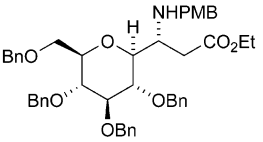
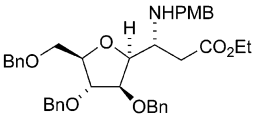
R^1	β-amino ester	Yield %	de %
β-ribosyl, **8a**	 **29a**	85	100
β-galactosyl, **8b**	 **29b**	80	100
β-mannosyl, **8c**	 **29c**	60	100
β-glucosyl, **8d**	 **29d**	90	100
β-arabinosyl, **8e**	 **29e**	75	100

Table 6. *C*-Glycosyl *β*-Amino Esters Prepared via Reformatsky 3CRs

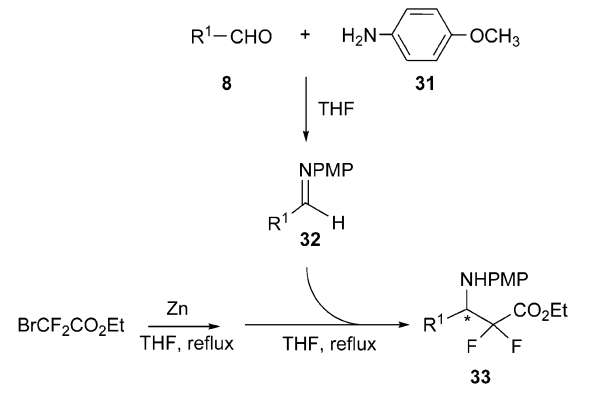


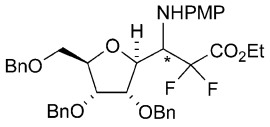
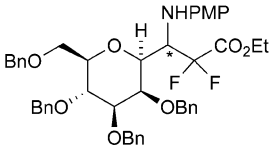
R^1	β-amino ester	Yield %	de %
β-ribosyl, **8a**	 **30a**	72	100
β-galactosyl, **8b**	 **30b**	78	100
β-mannosyl, **8c**	 **30c**	60	100
β-glucosyl, **8d**	 **30d**	70	100
β-arabinosyl, **8e**	 **30e**	45	100

Synthesis of *C*-Glycosyl *β*-Amino Acids via One-Pot Mannich and Reformatsky 3CRs. Opening two complementary AMCR routes allowed access to the classes of *C*-glycosyl *β*-amino acids **29** and **30** (Scheme 4), which differ in the extent of substitution at the central carbon atom of the amino acid group.[35] These routes represent one-pot versions of the classical stepwise Mannich and Reformatsky reactions. They involve the initial coupling of a *C*-glycosyl aldehyde **8** with *p*-methoxybenzylamine (PMBA, **24**) to give the imine **25**, which is then treated with a suitable *C*-nucleophile acting as the equivalent of the carboxylate-stabilized α-carbanion **28**. Convenient reagents serving for that purpose were the commercially available ketene silyl acetal 1-methoxy-2-methyl-1-trimethylsilyloxypropene **26** in the $InCl_3$-promoted Mannich-type synthesis and the in situ prepared bromozinc enolate **27** (from Me_2Zn, $BrCH_2CO_2Et$, $NiCl_2(PPh_3)_2$) in the Reformatsky method. In both routes, a diversity element was introduced by changing the sugar fragment in the aldehyde **8**. Hence reactions were carried out with *O*-perbenzylated *β*-linked *C*-glycosyl aldehydes **8a**−**e** (**a**, D-ribo; **b**, D-galacto; **c**, D-manno; **d**, D-gluco; **e**, D-arabino) to give two sets of *C*-glycosyl *β*-amino esters, that is, the α,α-dimethyl derivatives **29a**−**e** via the Mannich route (Table 5) and the α-unsubstituted compounds **30a**−**e** via the Reformatsky route (Table 6). The most striking feature of these reactions was their high stereoselectivity because compounds **29a**−**e** and **30a**−**e** were isolated as *single* diastereoisomers. The replacement of the *N*-PMB protective group in these compounds with the *tert*-butoxycarbonyl (Boc) group was carried out as well, thus providing a small yet significant collection of *C*-glycosyl *β*-amino esters suitably *N*-protected for their cotranslational incorporation into α-peptides en route to artificial derivatives.[33]

Stepwise Synthesis of *C*-Glycosyl α,α-Difluoro *β*-Amino Acids. Establishing a wide scope multicomponent

Table 7. Stepwise Synthesis of *C*-Glycosyl α,α-Difluoro *β*-Amino Esters



R^1	β-amino ester	Yield %	de %
β-ribosyl, **8a**	 **33a**	32	100
β-galactosyl, **8b**	 **33b**	30	100

reaction as a means for the target-oriented preparation of special libraries of compounds is by far a nontrivial task. This problem became apparent to us when we decided to employ the above one-pot Reformatsky-type reaction for the synthesis of *C*-glycosyl α,α-difluoro *β*-amino acids, that is, the fluorinated isosteres of the α-unsubstituted *C*-glycosyl *β*-amino esters **30**. It is well-known that hydrogen/fluorine exchange in a biologically active compound often dramatically alters its physicochemical properties and pharmacological profile.[36] Quite disappointingly, the one-pot Reformatsky-type reaction of the *C*-galactosyl formaldehyde **8b**, PMBA **24**, the zinc source Me_2Zn, and the *C*-nucleophile precursor $BrCF_2CO_2Et$ in the presence of the catalyst $NiCl_2(PPh_3)_2$ failed to give the target fluorinated *β*-amino ester. We suggested that the instability of the Reformatsky reagent $BrZnCF_2CO_2Et$ and the required long reaction time concurred to the failure of this three-component coupling. Fortunately enough, the target *β*-amino esters **33a** and **33b** (ribo and galacto series) became accessible via the classical Reformatsky method (Table 7). This involved the preparation of the imine **32** from the aldehyde **8** and *p*-methoxyphenylamine (PMPA, **31**), followed by the addition of **32** to a solution of the Reformatsky reagent $BrZnCF_2CO_2Et$ generated in refluxing THF from Zn powder and $BrCF_2CO_2Et$. In this way, the α,α-difluorinated *β*-amino esters **33a** and **33b** were obtained as single diastereoisomers in ca. 30% isolated yield.[35]

4. *C*-Glycosyl *β*-Lactams

The Need for New *β*-Lactam Inhibitors of Methicillin-Resistant *Staphylococcus aureus*. It is worth introducing this section by reminding readers that *β*-lactams inhibit bacterial growth by inactivation of a set of bacterial enzymes named penicillin binding proteins (PBPs), which catalyze the final cross-linking of the peptidoglycan, the main component of the bacterial cell wall.[37] PBPs are bifunctional and retain both transglycosidase and transpeptidase activity. *β*-Lactams lock PBPs only in their transpeptidase domain, leaving free the transglycosidase domain. The resistance mechanism of some bacteria, like the methicillin-resistant *Staphylococcus aureus*, involves the biosynthesis of a new transpeptidase (PBP2A), which couples with the transglycosidase domain of the locked PBPs thus restoring the biosynthesis of peptidoglycan.[37] The interruption of the PBP2A−transglycosidase coupling can be the Achilles' heel of this resistance mechanism. We envisaged the introduction of carbon-linked sugar residues in the *β*-lactam ring as a way for reaching this goal based on the expectation that sugar-decorated *β*-lactams can simultaneously lock the transglycosidase and transpeptidase domains in resistant bacteria.

Synthesis of *C*-Glycosyl *β*-Lactams by One-Pot Staudinger 3CR. The venerable Staudinger [2 + 2] imine−ketene cycloaddition[38] is by far the most versatile and simplest entry to the *β*-lactam fragment. The ketene is

Scheme 5. Modern Synthesis of a *β*-Lactam *C*-Glycoconjugate by a Two-Step One-Pot Staudinger 3CR

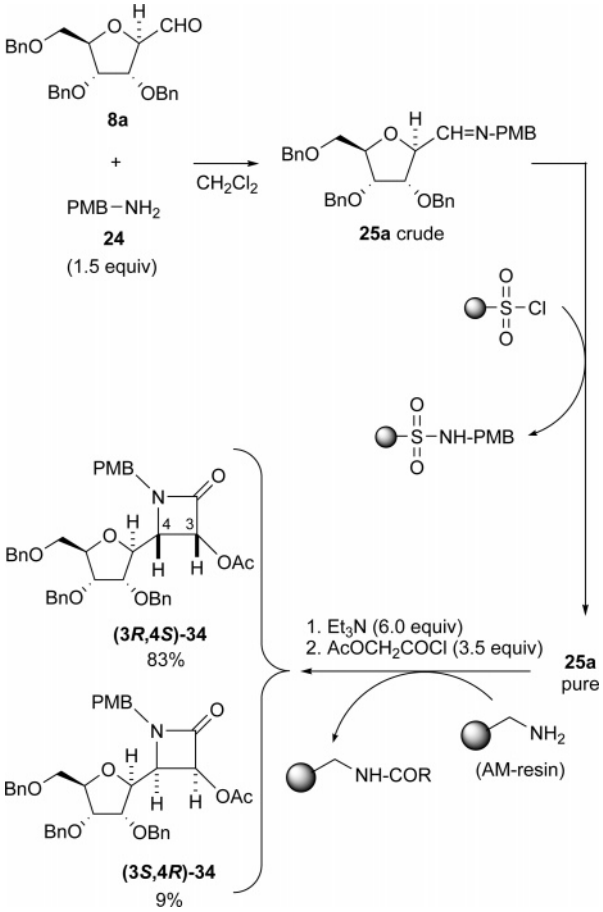
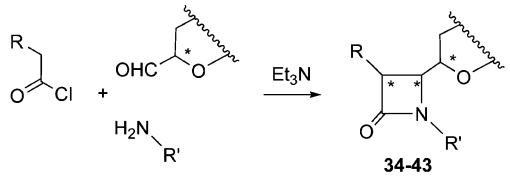
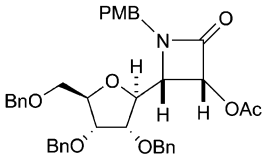
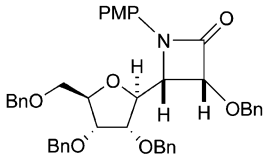
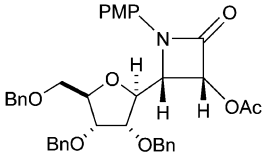
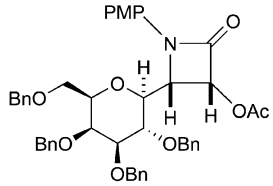
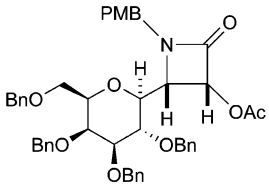
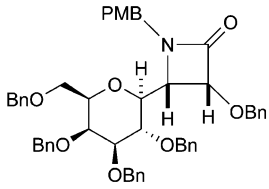
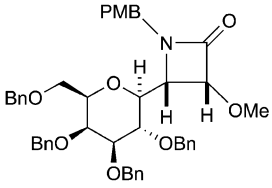
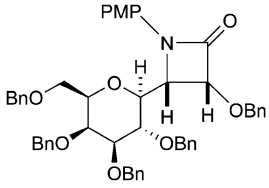
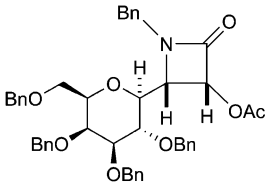
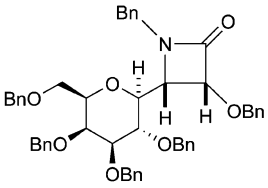


Table 8. *C*-Glycosyl *β*-Lactams Prepared via Two-Step One-Pot Staudinger 3CRs



Product	Product
 **34**	 **35**
 **36**	 **37**
 **38**	 **39**
 **40**	 **41**
 **42**	 **43**

generated in situ by dehydrohalogenation of a suitable acyl halide in the presence of a preformed imine derived from aldehyde and amine coupling. We have carried out for the first time the synthesis of *C*-glycosyl *β*-lactams by generation of the cycloaddition partners in the same reaction vessel from mixtures of sugar aldehyde, amine, and acyl chloride. Chemical efficiency in this new 3CR-based methodology was achieved by the use of an excess of amine and acyl chloride and application of the polymer-assisted solution-phase (PASP) technique[10] for intermediate purification and product isolation. A typical example

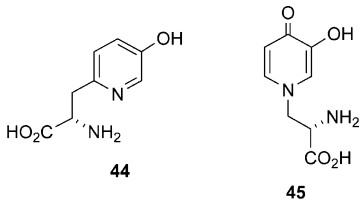


FIGURE 5. Heterocycle α-amino acids of biological relevance.

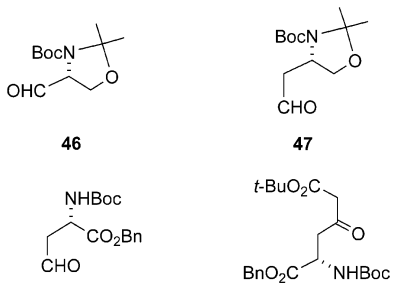


FIGURE 6. Aldehydes and ketoesters bearing masked and protected glycinyl moieties.

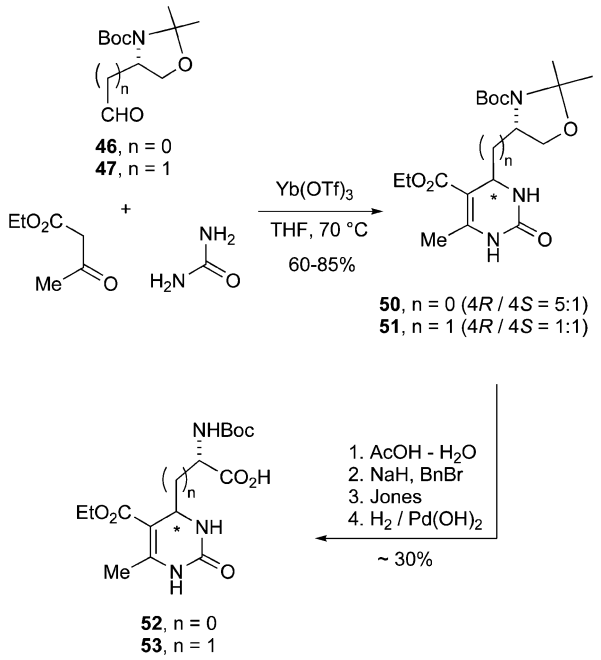
of this approach is illustrated in Scheme 5. The *β*-linked *C*-ribosyl *N*-PMB imine **25a** was generated in CH_2Cl_2 by mixing the *C*-ribosyl formaldehyde **8a** with an excess (1.5 equiv) of *p*-methoxybenzylamine **24**. These unusual reaction conditions ensured the complete consumption of the most expensive reagent, **8a**. The unreacted PMBA **24** was sequestered by treatment with resin-supported sulfonyl chloride. To the resulting heterogeneous mixture was then added (acetoxy)acetyl chloride (3.5 equiv) and Et_3N (6.0 equiv) to produce the corresponding acetoxy-substituted ketene. After a suitable period of time, the reaction mixture was treated with nucleophilic aminomethylated polystyrene (AM-resin) to remove the excess of ketene and its precursor acetyl chloride, as well as the acid arising from the hydrolysis of the latter. The same resin served also to sequester the aldehyde **8a**, which was formed from the partial hydrolysis of the imine **25a**. Simple workup (filtration and washing with water) of the resulting suspension and solvent evaporation afforded a mixture of 4-(*C*-ribosyl)-*β*-lactam stereoisomers (3*R*,4*S*)-**34** (major, 83%) and (3*S*,4*R*)-**34** (minor, 9%).[39]

By the same technique illustrated above, a collection of 10 pairs of 4-(*C*-ribosyl)- and 4-(*C*-galactosyl)-*β*-lactams featuring different protective groups at nitrogen and substituents at C3 was prepared. The major isomers are presented in Table 8. The minor products (not shown) featured opposite configuration at C3 and C4. It is important to point out that simple reaction sequences were established for the oxidative removal with ammonium cerium nitrate (CAN) of the *N*-PMB and *N*-PMP protective groups as well as the reductive removal with $H_2/Pd(OH)_2$ of the *O*-Bn groups. Assays on the biological activity of these compounds are still underway.

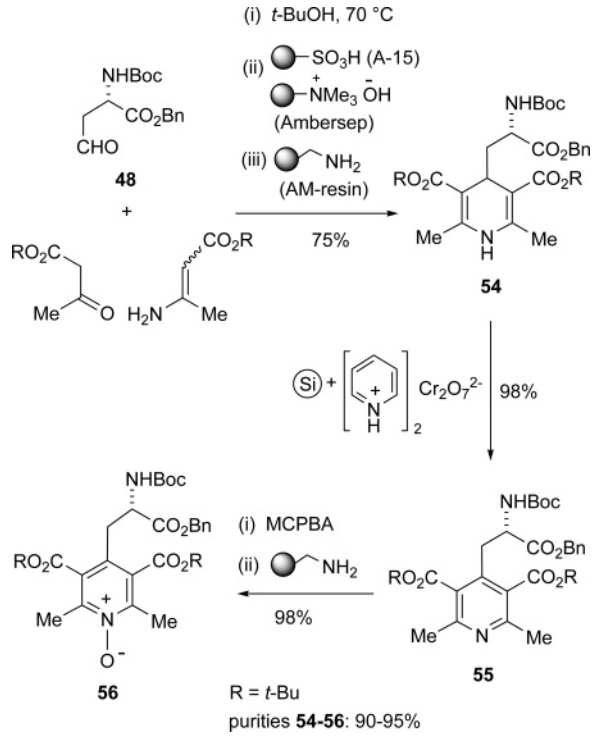
5. Heterocyclic α-Amino Acids (HAAs)

The Design of Related Families of HAAs. In 2003, we became interested in the class of heterocycle-substituted α-amino acids. The potential of these compounds in

Scheme 6. Synthesis of 4-Dihydropyrimidinyl-α-glycines and 4-Dihydropyrimidinyl-α-alanines via Biginelli 3CRs



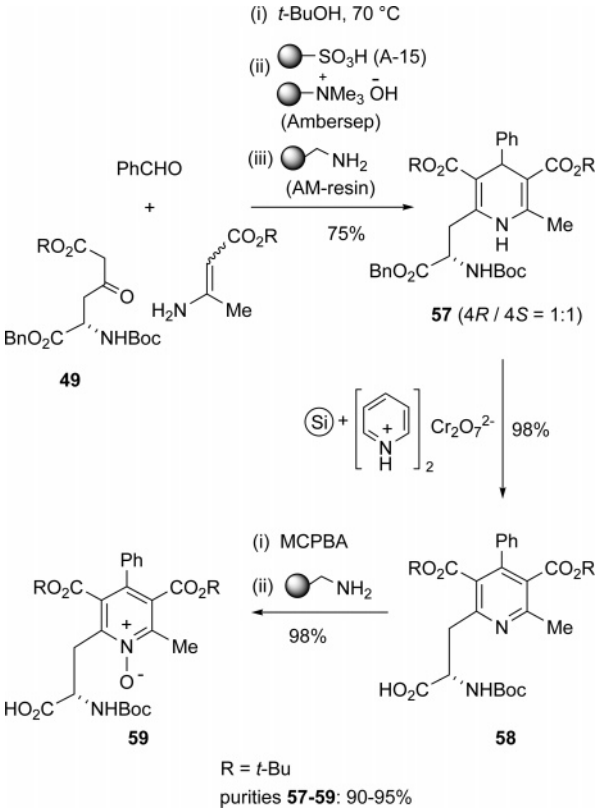
Scheme 7. Synthesis of 4-DHP-, 4-Py-, and 4-Py-*N*O-α-alanines via Hantzsch 3CRs



biology and medicine was foreseen as components of artificial peptides,[40] building blocks of peptide nucleic acids (PNAs),[41] and leads in new drug discovery. The antitumor and antibiotic properties of natural products of this type such as L-azatyrosine **44**,[42] a pyridine isostere of L-tyrosine, and L-mimosine **45** (Figure 5) have been amply documented.[42]

We envisaged a facile access to new classes of HAAs such as dihydropyrimidine (DHPM) and dihydropyridine

Scheme 8. Synthesis of 2-DHP-, 2-Py-, and 2-Py-*N*O-α-alanines via Hantzsch 3CRs



(DHP) derivatives via Biginelli and Hantzsch 3CRs, respectively, using reactants bearing a masked or protected glycinyl moiety (Figure 6). The Garner aldehyde **46** and the one-carbon homologue **47** were considered for that purpose because the easy cleavage of the *N*-Boc oxazolidine ring to the *N*-Boc glycinyl group is known to occur with conservation of the configurational integrity of its stereocenter.[43]

Synthesis of Dihydropyrimidinyl (DHPM) Glycines and Alanines via Biginelli 3CR. We were well aware that crucial in this program was performing the Biginelli reaction under conditions that left unaltered the oxazolidine ring and the configuration of the stereocenter of the aldehydes **46** and **47**. Quite gratifyingly, the Lewis acid $Yb(OTf)_3$ previously exploited in our laboratory[22] proved to be the catalyst of choice as the Biginelli 3CRs of aldehydes **46** and **47** afforded the DHPMs **50** and **51**, each one as a mixture of C4 epimers, in good overall yields (Scheme 6).[44] Suitable elaboration of individual diastereoisomers including the oxazolidinyl-to-glycinyl group transformation was carried out to give the corresponding 4-DHPM-α-glycines **52** and 4-DHPM-α-alanines **53**.

Synthesis of Dihydropyridyl (DHP), Pyridyl (Py), and Pyridyl *N*-Oxide (Py-*N*O) Alanines via Hantzsch 3CRs. The synthesis of these HAAs was performed via the Hantzsch aldehyde−ketoester−enamine cyclocondensation and then elaboration of the DHP ring. In each step, the reaction processing was simplified by using an orchestrated sequence of polymer-supported reagents and sequestrants. This avoided aqueous work up and chro-

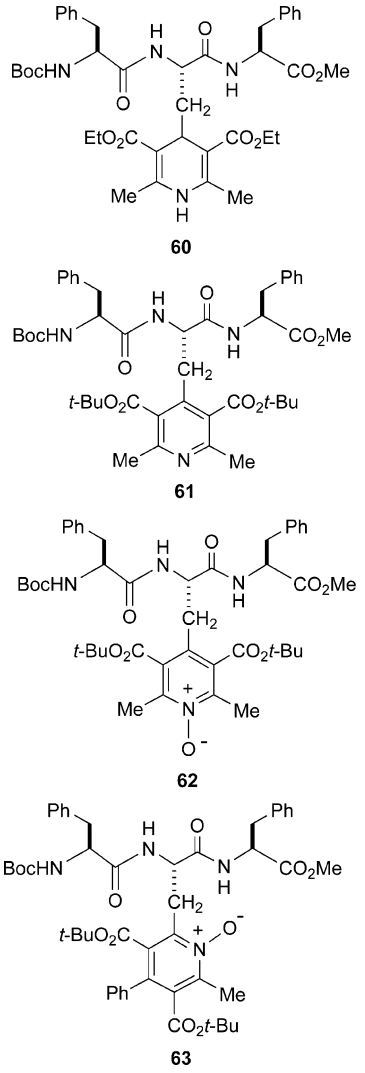


FIGURE 7. Tripeptides prepared using DHP-, Py-, and Py-*N*O-α-alanines.

matographic separation thus maximizing the efficiency of the whole procedure. At first 4-DHP-α-alanine **54** was targeted by reacting the aldehyde **48** bearing the *N*-Boc benzyl glycinate group, *tert*-butyl acetoacetate, and *tert*-butyl aminocrotonate (Scheme 7).[45] The amino ester **54** was isolated in 75% yield and 95% purity by the action of the acidic resin Amberlyst 15 (A-15) and basic resin Ambersep 900 OH to scavenge unreacted enamine and ketoester, respectively, and then by the use of the nucleophilic AM-resin to remove the unreacted aldehyde. The subsequent conversion of **54** into the 4-Py-α-alanine **55** was carried out in an almost quantitative way by using pyridinium chlorochromate (PCC) immobilized on silica, which facilitated the removal of chromium salts. Finally, the 4-Py-*N*O-α-alanine **56** was obtained by oxidation of **55** with *m*-chloroperoxybenzoic acid (MCPBA) and purification by sequestering the excess oxidant and *m*-chlorobenzoic acid with AM-resin.

The same reaction sequence and PASP technique starting from benzaldehyde, the ketoester **49**, and *tert*-butyl aminocrotonate was employed[45] for the preparation of the 2-DHP-α-alanine **57** as a 1:1 mixture of C4 epimers, 2-Py-α-alanine **58**, and its *N*-oxide **59** (Scheme 8). Finally, the potential of these highly functionalized HAAs as components of peptides was subsequently demonstrated by their efficient insertion into tripeptides (Figure 7).

6. Conclusions

It was intended that this Account provide testimony to the potential of the solution-phase multicomponent reactions, eventually combined with the use of polymer-supported reagents, as a formidable tool for achieving chemical efficiency, one of the leading criteria in modern organic synthesis, spanning from chemical yield, selectivity, and atom economy to labor and material cost, product isolation, and environmental aspect. Accordingly, we have described our efforts toward the synthesis of new classes of chiral molecules of biological relevance, that is, glycoconjugates and amino acids, via operationally simple and efficient one-pot asymmetric multicomponent processes. Crucial issues that we have faced and solved for the effective production of collections of the above multifunctional chiral molecules included the compatibility of catalyst(s) with the nature of all reactants and reaction conditions, the conservation of the configurational integrity of stereocenter(s), and the orthogonality of the protective group arrays. It is our intention to continue the research in a similar fashion with studies of other MC-based routes for the synthesis of different classes of biologically relevant molecules.

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References

(1) Breinbauer, R.; Vetter, I. R.; Waldmann, H. From protein domains to drug candidates-natural products as guiding principles in the design and synthesis of compound libraries. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878−2890.
(2) *Perspectives in Nucleosides and Nucleic Acid Chemistry*; Kisakürek, M. V., Rosemeyer, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001.
(3) Izawa, K. Synthesis of unnatural amino acids and application to pharmaceuticals. *Farumashia* **2005**, *41*, 319−323.
(4) For several articles concerning β-lactam synthesis and biological activity, see the thematic issue of *Tetrahedron* **2000**, *56*, 5553−5742.
(5) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
(6) Andraos, J. Unification of reaction metrics for green chemistry II: Evaluation of named organic reactions and application to reaction discovery. *Org. Process Res. Dev.* **2005**, *9*, 149−163.
(7) Adams, D. J.; Dyson, P. J.; Tavenerg, S. T. *Chemistry In Alternative Reaction Media*; John Wiley & Son, Ltd: Chichester, U.K., 2004.
(8) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
(9) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.
(10) *Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis*; Wipf, P., Ed.; John Wiley & Son, Ltd: Chichester, U.K., 2005 and references therein.
(11) Yoshida, J.; Itami, K. Tag Strategy for Separation and Recovery. *Chem. Rev.* **2002**, *102*, 3693−3716.
(12) Jas, G.; Kirschning, A. Continuous Flow Techniques in Organic Synthesis. *Chem.—Eur. J.* **2003**, *9*, 5708−5723.

(13) Ramón, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634.
(14) List, B. Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res.* **2004**, *37*, 548−557.
(15) Lockhoff, O. An Access to Glycoconjugate Libraries through Multicomponent Reactions. *Angew. Chem., Int. Ed.* **1998**, *37*, 3436−3439.
(16) Postema, M. H. D.; Calimente, D. In *Glycochemistry: Principles, Synthesis and Applications*; Wang, P. G., Bertozzi, C., Eds.; Marcel Dekker: New York, 2000; Chapter 4, pp 77−131.
(17) For a typical and recent case, see the effect of glycosylation in guanidines: Lin, P.; Lee, C. L.; Sim, M. M. Synthesis of Novel Guanidinoglycoside: 2-Glycosylamino 4,5-Dihydro-6-Pyrimidinone. *J. Org. Chem.* **2001**, *66*, 8243−8247.
(18) For a review, see: Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, *33*, 879−888.
(19) For a review, see: Lavilla, R. Recent Developments in the Chemistry of Dihydropyridines. *J. Chem. Soc., Perkin Trans. 1* **2002**, *9*, 1141−1156.
(20) Wu, Q.; Simons, C. Synthetic Methodologies for *C*-Nucleosides. *Synthesis* **2004**, *10*, 1533−1553 and references therein.
(21) Dondoni, A. Formylation of Carbohydrates and the Evolution of Synthetic Routes to Artificial Oligosaccharides and Glycoconjugates. *Pure Appl. Chem.* **2000**, *72*, 1577−1588.
(22) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. Three-component Biginelli Cyclocondensation Reaction Using *C*-glycosylated Substrates. Preparation of a Collection of Dihydropyrimidinone Glycoconjugates and the Synthesis of *C*-glycosylated Monastrol Analogues. *J. Org. Chem.* **2002**, *67*, 6979−6994.
(23) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Dihydropyridine *C*-Glycoconjugates by Hantzsch Cyclocondensation. Synthesis of a C(6)-Glycosylated Nifedipine Analogue. *Helv. Chim. Acta* **2002**, *85*, 3331−3348.
(24) Dondoni, A.; Massi, A. Decoration of Dihydropyrimidine and Dihydropyridine Scaffolds with Sugars via Biginelli and Hantzsch Multicomponent Reactions: An Efficient Entry to a Collection of Artificial Nucleosides. *Mol. Diversity* **2003**, *6*, 261−270.
(25) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in a Phenotype-Based Screen. *Science* **1999**, *286*, 971−974.
(26) Marcus, A. I.; Peters, U.; Thomas, S. L.; Garrett, S.; Zelnak, A.; Kapoor, T. M.; Giannakakou, P. Mitotic Kinesin Inhibitors Induce Mitotic Arrest and Cell Death in Taxol-resistant and-sensitive Cancer Cells. *J. Biol. Chem.* **2005**, *280*, 11569−11577.
(27) Experiments performed in the laboratory of Prof. F. Kozielski in Grenoble, France. We thank Prof. F. Kozielski for the permission to report here these results.
(28) Dondoni, A.; Marra, A.; Zampolli, M. G. Synthesis of All Carbon Linked Glycoside Clusters Round Benzene Scaffold via Sonogashira-Heck-Cassar Cross-Coupling of Iodobenzenes with Ethynyl *C*-Glycosides. *Synlett* **2002**, *11*, 1850−1854.
(29) Lundquist, J. J.; Toone, E. J. The Cluster Effect. *Chem. Rev.* **2002**, *102*, 555−578.
(30) Bertozzi, C. R.; Kiessling, L. L. Chemical Glycobiology. *Science* **2001**, *291*, 2357−2364.
(31) Dondoni, A.; Marra, A. Methods for Anomeric Carbon-Linked and Fused Sugar Amino Acid Synthesis: The Gateway to Artificial Glycopeptides. *Chem. Rev.* **2000**, *100*, 4395−4421 and references therein.
(32) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. β-Peptides: From Structure to Function. *Chem. Rev.* **2001**, *101*, 3219−3232.
(33) McGarvey, G. J.; Benedum, T. E.; Schmidtmann, F. W. Development of Co- and Post-translational Synthetic Strategies to *C*-Neoglycopeptides. *Org. Lett.* **2002**, *4*, 3591−3594.
(34) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. Design and Synthesis of a Novel Class of Sugar-Peptide Hybrids: *C*-Linked Glyco β-Amino Acids through a Stereoselective "Acetate" Mannich Reaction as the Key Strategic Element. *J. Am. Chem. Soc.* **2002**, *124*, 8637−8643.
(35) Dondoni, A.; Massi, A.; Sabbatini, S. Multiple Component Approaches to *C*-Glycosyl β-Amino Acids by Complementary One-pot Mannich-Type and Reformatsky-Type Reactions. *Chem.—Eur. J.* **2005**, *11*, 7110−7125.
(36) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley & Son, Ltd: Chichester, U.K., 1999.
(37) Guignard, B.; Entenza, J. M.; Moreillon, P. β-Lactams against Methicillin-Resistant *Staphylococcus aureus*. *Curr. Opin. Pharmacol.* **2005**, *5*, 479−489.
(38) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide M. Asymmetric Synthesis of β-Lactams by Staudinger Ketene−Imine Cycloaddition Reaction. *Eur. J. Org. Chem.* **1954**, *19*, 3223−3235.
(39) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. Three-Component Staudinger-Type Stereoselective Synthesis of *C*-Glycosyl-β-Lactams and their Use as Precursors for *C*-Glycosyl Isoserines and Dipeptides. A Polymer-Assisted Solution-Phase Approach. *Adv. Synth. Catal.* **2004**, *346*, 1355−1360.
(40) *Peptides 2000: Proceedings of the Twenty-Sixth European Peptide Symposium*; Martinez, J., Fehrentz, J. A., Eds.; EDK: Paris, 2001.
(41) Kuwahara, M.; Arimitsu, M.; Sisido, M. Synthesis of δ-Amino Acids with an Ether Linkage in the Main Chain and Nucleobases on the Side Chain as Monomer Units for Oxy-Peptide Nucleic Acids. *Tetrahedron* **1999**, *55*, 10067−10078 and references therein.
(42) Rosenthal, G. A. *Plant Nonprotein Amino and Imino Acids. Biological, Biochemical, and Toxicological Properties*; Academic Press: New York, 1982.
(43) Garner, P.; Yoo, J. U.; Sarubu, R.; Kennedy, V. O.; Youngs, W. J. Stereocontrolled and Enantioselective Synthesis of the Branched 6-Amino-4,6-Deoxyheptopyranuronic Acid Component of Amipurimycin. *Tetrahedron* **1998**, *54*, 9303−9316.
(44) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertolasi, V. Model Studies Toward the Synthesis of Dihydropyrimidinyl and Pyridyl α-Amino Acids via Three-Component Biginelli and Hantzsch Cyclocondensations. *J. Org. Chem.* **2003**, *68*, 6172−6183.
(45) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Multicomponent Hantzsch Cyclocondensation as a Route to Highly Functionalized 2- and 4-Dihydropyridylalanines, 2- and 4-Pyridylalanines, and Their *N*-oxides: Preparation via a Polymer-Assisted Solution-Phase Approach. *Tetrahedron* **2004**, *60*, 2311−2326.

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