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Synthesis of *C*-glycosyl β-amino acids by asymmetric Mannich-type three-component reactions

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Abstract—*C*-Galactosyl and *C*-ribosyl β-amino acids were prepared by one-pot $InCl_3$-catalyzed Mannich-type three-component condensation (3CC) by combining the corresponding formyl C-glycoside, *p*-methoxybenzyl amine, and a ketene silyl acetal. In each case the reaction was highly stereoselective and afforded only one single product in good to excellent yields.

Multicomponent reactions (MCRs) performed either on a solid phase or in solution[1] have emerged as a powerful tool in combinatorial chemistry for the generation of small-molecule libraries with the goal of discovering new leads for drug development and optimization processes or identifying novel biologically active substances. With some exceptions,[2] most MCRs have been focused on achieving molecular diversity through functional group variation of components, whereas stereochemical aspects have so far played a secondary role. This is quite surprising in view of the above cited main fields of application of MCRs because the absolute as well as the relative configuration of a molecule can profoundly affect its pharmacological properties and biological activities.[3] Consequently the need of preparing stereodiversified libraries by varying the stereochemistry of compounds having the same constitution has been stressed by Verdine[4] and Tietze[5] and their co-workers. Moreover, the issue regarding the stereochemical induction by chiral catalysts in the Passerini reaction has been recently addressed by the Dömling group,[6] while reagent-controlled asymmetric Biginelli[7] and Hantzsch[7b,8] cyclocondensations have been investigated over the last two years in our laboratory. Indeed, the use of chiral reagents (aldehydes, ketoesters, enamines) carrying natural carbohydrate and glycinyl residues led to collections of dihydropyrimidine and pyridine glycosides and amino acids in enantiomerically pure form. In this context we would like to report below on the asymmetric version of another classical MCR, namely a Mannich-type condensation[9] that under $InCl_3$-catalysis as suggested by recent work of Loh and Chen[2g] combined an anomeric sugar aldehyde, an amine, and a ketene silyl acetal. This reaction turned out to be highly stereoselective affording in each case examined a *C*-glycosyl β-amino acid as one single stereoisomer in good yield (60–80%). These sugar amino acids exhibit two elements of structural diversity in respect to *O*- and *N*-glycosyl α-amino acids, such as the natural glycopeptide constituent *O*-glycosyl serines (threonines) and *N*-glycosyl asparagines, and therefore they possess great potential as useful probes for studies in glycobiology[10] and building blocks for the development of artificial *C*-glycopeptides.[11] The asymmetric synthesis of β-amino acids[12] is a topic of current interest due to their own pharmacological activities[13] and use as α-amino acid surrogates for the construction of hybrid α- and β-peptidic materials.[14]

The few existing syntheses of *C*-glycosyl β-amino acids have been approached via two multistep routes, both starting from sugar aldehydes. One route had relied on the Mannich-type reaction of α-amido glycoalkyl sulfones (prepared from *C*-glycosyl propionaldehydes) with the lithium enolate derived from 2-acetylisoborneol;[15] a second route was based on a Michael-type addition of amines to sugar derived γ-alkoxy α,β-unsaturated esters.[16,17] On the other hand, in order to open a rapid

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entry to this scarcely investigated class of artificial sugar amino acids, we carried out exploratory investigations of a three-component Mannich-type synthesis by treatment of the β-linked *C*-galactosyl formaldehyde[18] **1** (90 mg) with *p*-methoxybenzyl amine (PMBA, **2**) (1 equiv) and catalytic $InCl_3$ (0.2 equiv) in MeOH at rt, followed by the addition after 30 min of the third coupling partner (1.5 equiv), the commercially available ketene silyl acetal 1-methoxy-2-methyl-1-trimethylsilyloxypropene **3a** (Scheme 1). After 12 h at rt, the reaction led to the three-component coupling product *C*-galactosyl β-amino ester **4a** as a single diastereoisomer (by ^1H NMR analysis of the crude reaction mixture) in 80% isolated yield by column chromatography. The same high diastereoselectivity and yield were registered in larger scale reactions starting from 250 up to 800 mg of the sugar aldehyde **1**. While the conservation of the β-linkage at the sugar anomeric center of **4a** was easily confirmed by estimating the $J_{4,5}$ value (~9.0 Hz) in its ^1H NMR spectrum, the absolute stereochemistry of the newly formed stereocenter carrying the amino group was assigned as being '*R*' by means of ^1H NMR studies[19] and confirmed by X-ray crystal structure analysis[20] of compound **5** (Fig. 1) derived from **4a** by N-acylation, O- and N-debenzylation, and acetonization. Similar results were obtained by combining in the same way as above and in the presence of $InCl_3$ the sugar aldehyde **1**, PMBA **2**, and the readily available ketene silyl acetal, (1-ethoxyvinyloxy)trimethylsilane[21] **3b** (5 equiv) in EtOH as a solvent. Also this one-pot reaction proceeded with excellent diastereoselectivity to generate the desired three-component coupling product **4b** exclusively as judged by ^1H NMR analysis of the crude reaction mixture, although in lower isolated yield (60%). The low efficiency of the ketene silyl acetal **3b** due to the transformation into ethyl trimethylsilyl acetate has been reported.[21a] In this case the *R*-configuration of the asymmetric carbon of the β-amino acid group was assigned by analogy with **4a** and the assumption that the two reactions proceeded with the same mechanism.

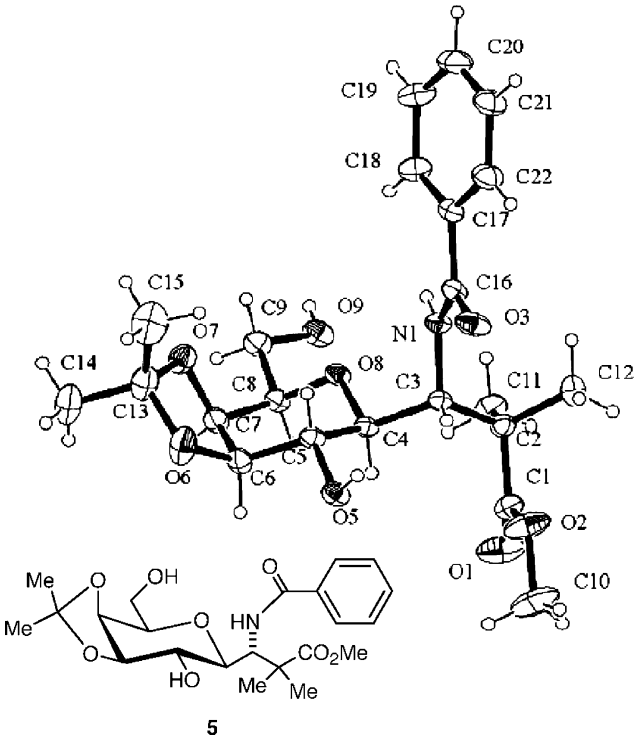
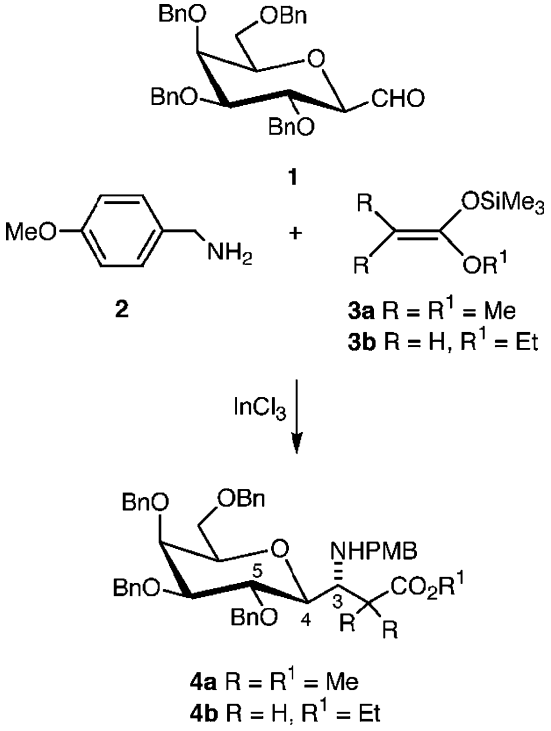
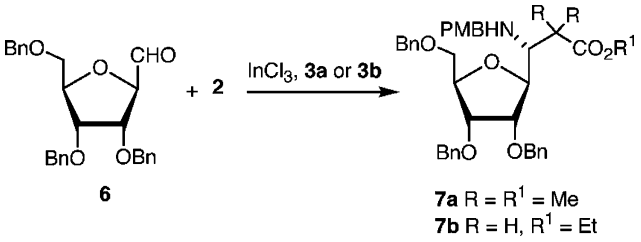


Figure 1. An ORTEP view of the *C*-galactosyl β-amino ester **5** displaying the thermal ellipsoids at a 30% probability level.

The effectiveness of this MCR3 approach to other sugar β-amino acids was demonstrated by the successful $InCl_3$-catalyzed reactions of the *C*-ribosyl formaldehyde[18] **6**, with PMBA **2** and ketene silyl acetals **3a** and **3b** (Scheme 2). Each reaction led to a single three-component coupling product, namely the *C*-ribosyl β-amino ester **7a** (82%) in one case and the ester **7b** (60%) in the other. The *R*-configuration of the carbon bearing the amino group of product **7a** was established by ^1H NMR studies[19] whereas that of **7b** was assigned by analogy.



Scheme 1. Reagents and conditions: **1**, **2**, and $InCl_3$, 4-Å MS, R^1OH, rt, 30 min, then **3a** or **3b**, rt, 12 h.



Scheme 2. Reagents and conditions: **6**, **2**, and $InCl_3$, 4-Å MS, R^1OH, rt, 30 min, then **3a** or **3b**, rt, 12 h.

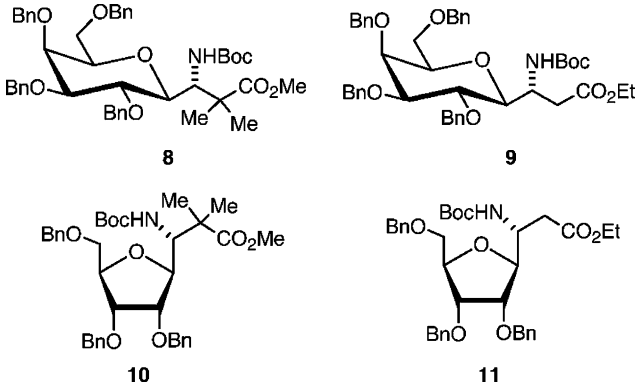


Figure 2. *C*-glycosyl β-amino esters prepared.

In view of the use of the *C*-glycosyl β-amino acids as building blocks for the preparation of glycopeptides, a standard protection of the amino group is required. Therefore it was demonstrated that the *N*-PMB protected sugar amino esters **4a**–**b** and **7a**–**b** can be suitably elaborated toward that goal. In fact these Mannich products were readily transformed into the *N*-Boc derivatives **8**–**11**[22] (80–85%) (Fig. 2) via an optimized one-pot reaction sequence involving the removal of the PMB group with CAN (4 equiv in MeCN–H_2O at rt for 6 h) followed by the introduction of the *tert*-butoxycarbonyl with Boc_2O (3 equiv in dioxane-saturated $NaHCO_3$ at rt for 12 h). Compounds **8**–**11** should be suitable substrates for *N*-Boc-based peptide synthesis.[23]

In conclusion an efficient and highly stereoselective entry to the family of *C*-glycosyl β-amino acids appears to be at hand via a Mannich-type MCR3 employing simple and readily available starting materials. In fact a collection of α- and β-linked formyl C-glycosides, the key components in this synthesis, are available via the thiazole-based formylation of a variety of sugars.[18] Hence we foresee the implementation of this method for the preparation of libraries of these sugar amino acids exhibiting both structural and stereochemical diversities.

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19. Following the protocol developed for chiral amines (Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925), compound **4a** was transformed into the corresponding hydroxy-free (*R*)- and (*S*)-methoxytrifluoromethylacetic amides, which in turn were analyzed by ^{1}H NMR spectroscopy. Configuration assignment of the carbon bearing the amino group followed the calculation of suitable $\Delta\delta^{RS}$ values.
20. Complete crystallographic data (excluding structural factors) for the structure of compound **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications number CCDC 225844. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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22. **8**: $[\alpha]_D = +31.4$ (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.25 (m, 20H, 4Ph), 5.42 (d, 1H, $J_{NH,3} = 10.5$ Hz, NH), 5.01 and 4.58 (2d, 2H, $J = 12.0$ Hz, PhCH_2), 4.86 and 4.77 (2d, 2H, $J = 10.5$ Hz, PhCH_2), 4.78 and 4.71 (2d, 2H, $J = 11.5$ Hz, PhCH_2), 4.47 and 4.42 (2d, 2H, $J = 11.8$ Hz, PhCH_2), 4.26 (d, 1H, H-3), 4.00 (dd, 1H, $J_{6,7} = 2.8$, $J_{7,8} = \sim 0.5$ Hz, H-7), 3.73 (dd, 1H, $J_{4,5} = 9.0$, $J_{5,6} = 9.1$ Hz, H-5), 3.61 (dd, 1H, H-6), 3.59 (ddd, 1H, $J_{8,9a} = 6.5$, $J_{8.9b} = 5.0$ Hz, H-8), 3.56 (s, 3H, OCH_3), 3.52 (dd, 1H, $J_{6a,6b} = 11.5$ Hz, H-9a), 3.45 (dd, 1H, H-9b), 3.44 (d, 1H, H-4), 1.42 (s, 9H, *t*-Bu), 1.22 (s, 6H, $2CH_3$). **9**: $[\alpha]_D = +26.2$ (*c* 0.8, $CHCl_3$). **10**: $[\alpha]_D = +2.6$ (*c* 1.2, $CHCl_3$). **11**: $[\alpha]_D = +14.9$ (*c* 0.7, $CHCl_3$).
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