Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[C0012]

Synthesis of C-Glycosylated Amino Acids – Suitable Building Blocks for the Synthesis of Glycopeptide Mimics

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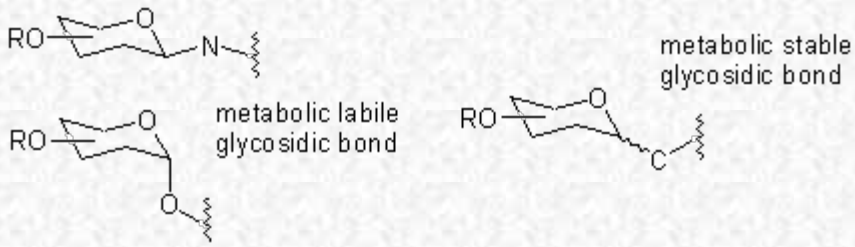
Received: 6 August 2000 / Uploaded: 9 August

Introduction

Glycopeptides are considered as a class of natural products which are responsible for a great variety of molecular recognition processes on the cellular surface including fertilization, pathogen-cell adhesion and the inflammatory response.[1] It appears that the interactions of glycopeptides with their respective ligands is in general mediated by their carbohydrate epitopes. These glycosidic moieties exhibit a great diversity and very complex structures which makes their synthesis an almost arduous task.

To elucidate the biological functions glycopeptide mimics have been envisioned as versatile tools to circumvent these obstacles in recent years. Therefore, effort has been directed towards the synthesis of these products. In particular, the glycosidic bonds between the glycosidic and the peptide moieties have been in the focus of investigations due to their low metabolic and chemical stability. Here we would like to report on our studies towards the synthesis of C-glycosylated amino acids which may be considered as suitable buiiliding blocks of glycopeptide mimics (Figure 1).

Figure 1: Linkages of glycosylic and peptide moieties.



Despite numerous contributions to synthesize C-glycosylated amino acids in recent years, they often involve a lot of steps and are of low diastereoselectivity.[2] Here, we present two independent routes whose main emphasis was directed towards the diastereoselective synthesis of this unnatural glycosidic bond. In addition, the peptide moiety should undergo no racemization.

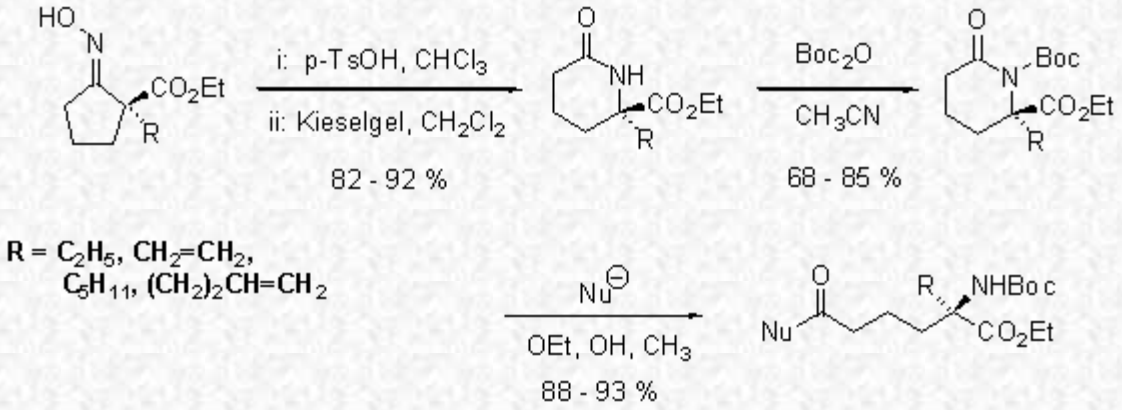
In addition, we will show that they can be attached easily to a polymeric resin to allow solid phase synthesis.

The Dianion approach

This approach is characterized by the formation of the glycosidic bond with nucleophilic glycosidic building blocks, which have been investigated thoroughly by the groups of Kessler et al. and Sinay et al.. They have demonstrated that glycosidic anions and dianions can be utilized to form the glycosidic linkage. Despite the high diastereoselectivity during C-C-bond formation, their was still an urgent need for appropriate peptide building blocks which would undergo no racemization at the stereogenic centre of the aglycon.

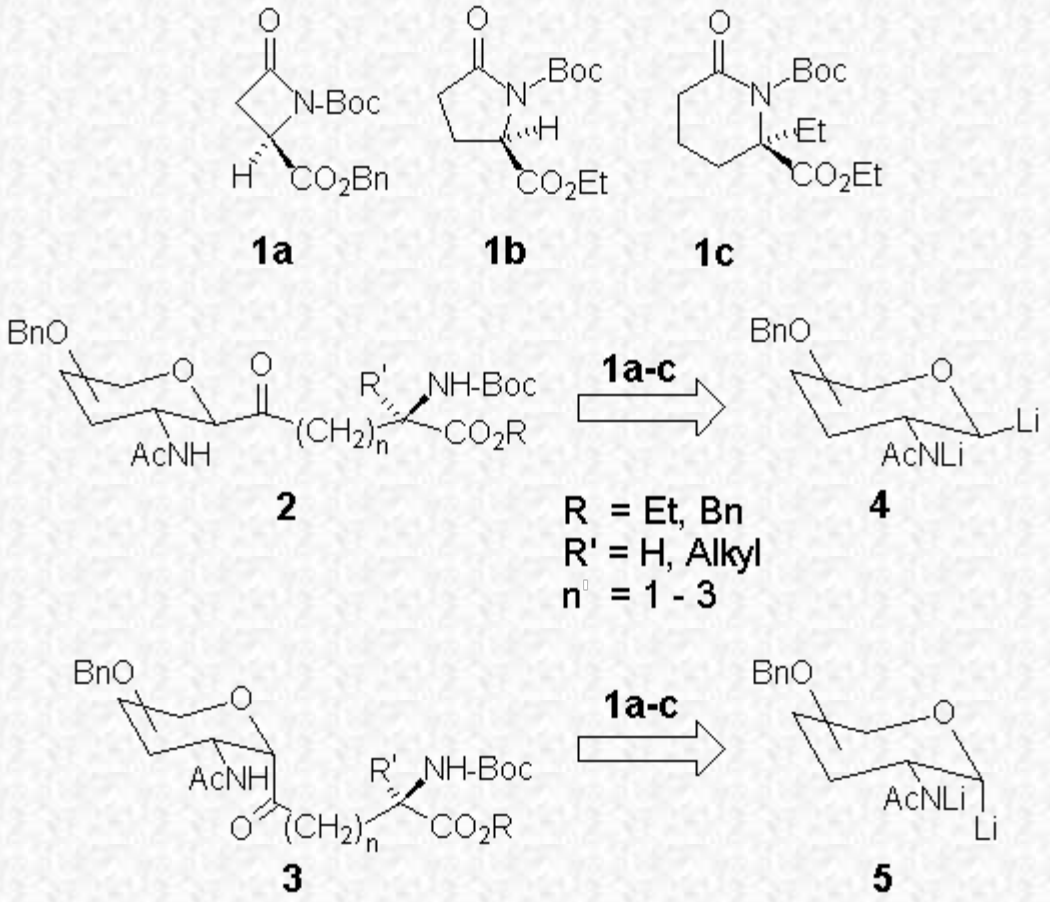
In recent studies we demonstrated that lactames can be used as precursors of amino acids. They can be easily ringopened with nucleophiles, during this reaction no racemization of the stereogenic centre occurs (Scheme 1).

Scheme 1: Synthesis of a ,a -disubstituted amino acids by nucleophilic ring opening of lactams.



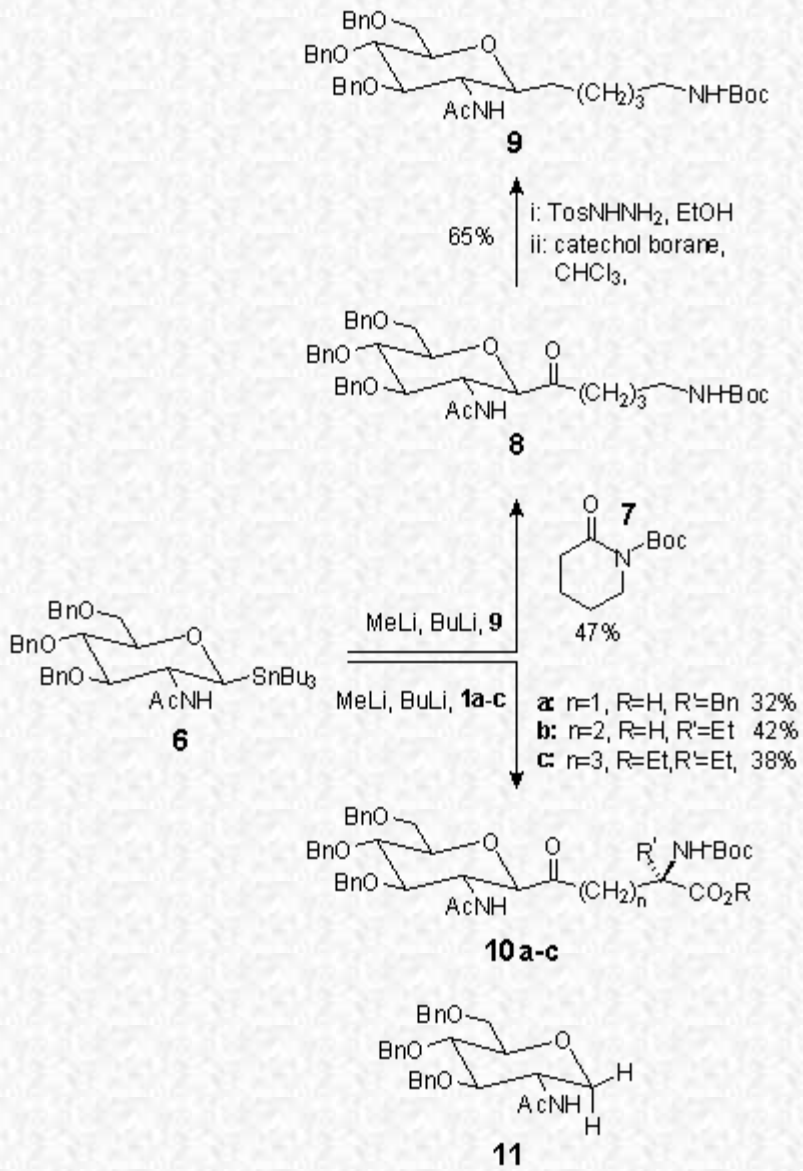
Therefore, we thought it might be possible to utilize glycosidic dianions **4,5** for this reaction (Scheme 2).

Scheme 2: Planned synthesis of C-glycosylated amino acids by the glycosidic dianion approach.



To prove our approach to synthesize C-glycosylated amino acids from **1**, a modell reaction using *N*-Boc protected, unsubstituted valero lactam **7** was applied (Scheme 3). Starting from the b -configured stannyl derivative **6**,[6] the glycosyl dianion **4** was generated at -78 °C by subsequent addition of one equivalent of MeLi and BuLi, each, and **7** was added. The C-glycoside **8** was obtained in 47 % yield as the only diastereoisomer. The product was proven to be of b -configuration as determined by extensive NMR-experiments. Reduction of **8** to **9** was carried out by synthesizing the tosyl hydrazone and subsequent reduction with catechol borane in 65 % overall yield.

Scheme 3: Synthesis of C-glycosylated amino acids.



In analogy, the reactions of **6** with substituted lactams **1 a-c** were carried out as described above. The C-glycosylated amino acids **10 a-c** could be isolated in satisfactory yields (**10a**:32%; **10b**:42%; **10c**:38%). At this stage, the investigation of the configuration at the anomeric center and a possible racemization of the stereogenic center of the peptidic moiety was of high interest. To prove that no racemization occured, the pyroglutamic derivative **1b** was employed enantiomerically pure [(+)-**1b** and (–)-**1b**] and as a racemic mixture (±)-**1b**. The analysis of the ^{1}H-NMR spectra for (+)-**10b** and (–)-**10b** revealed only one singlett for the *t*-Butyl moiety, whereas the ^{1}H-NMR spectra for (±)-**10b** showed two baseline separated singletts. Therefore, it can be conluded that no racemization took place during the nucleophilic ring opening of the

enantiomerically pure lactams.

To obtain a -configured glycosylated amino acid **3**, glycosyl dianion **5**[6] was used. To date, this reaction could not be carried out successfully, only **11** could be isolated as the sole product. We believe that steric reasons are responsible for this failure.

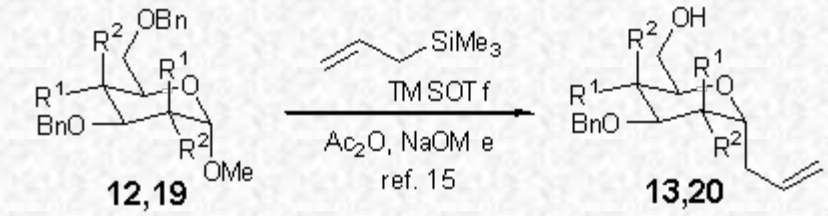
The results presented above clearly indicate that lactams are suitable building blocks for the synthesis of C-glycopeptides. They can be obtained easily provided by the chiral pool or by enzyme catalyzed kinetic resolution of suitable derivatives. Furthermore, it should be pointed out that the products are orthogonally protected.

The Metathesis approach

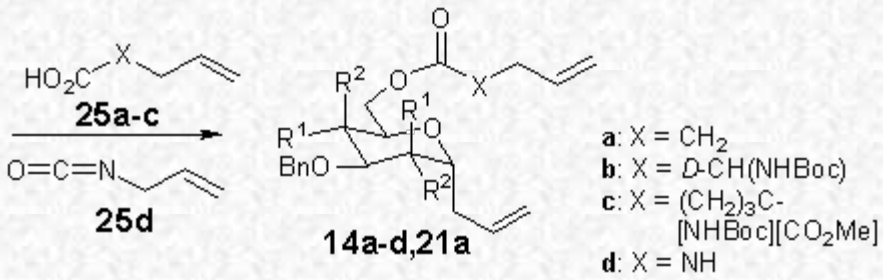
Due to its simplicity and selectivity the ring closing olefin metathesis has emerged itself as one of leading methods to provide C=C-coupled products. For the synthesis of neoglycoproteins, several preparations have been published for these classes of compounds using the RCM-approach, most of them being intermolecular.[7] Two major drawbacks have to be encountered following this method: a: the formation of homo-dimerized products and b: the formation of E/Z-mixtures. Therefore, an intramolecular approach is likely to circumvent these obstacles.

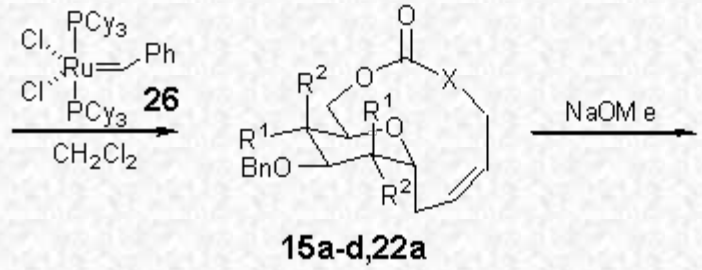
The a -configured C-allylated derived glycosidic building blocks **13** and **20** (*galacto*- and *manno*-configuration) have been envisaged as suitable starting materials for the RCM (Scheme 4). Their synthesis by Sakurai reaction and regioselective deprotection at C-6 can be initiated while starting from readily available tetrabenzyl protected glycosides **12** and **18**.[8] (In our hands a two step prodecure – Sakurai reaction and selective deprotection at C-6 has led consistently to higher yields). The deprotection can be carried out as a one pot reaction, first regioselective acetylation using acetic anhydride in the presence of TMS-triflate followed by transacylation with sodium methylate. Subsequent derivatization to diolefinic products **14** and **21** is carried out according to known procedures.

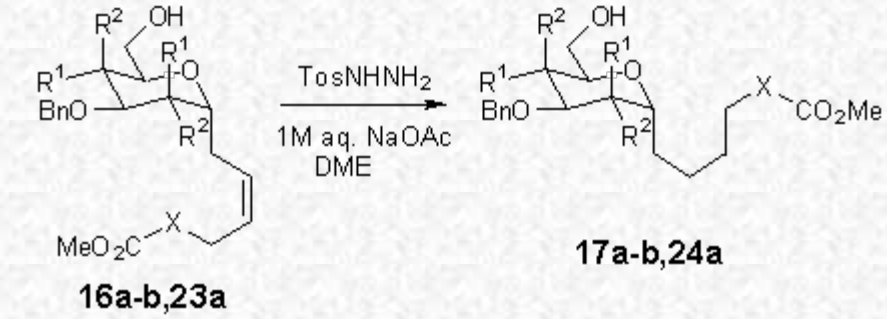
Scheme 4: Synthesis of C-glycosylated amino acids via RCM.

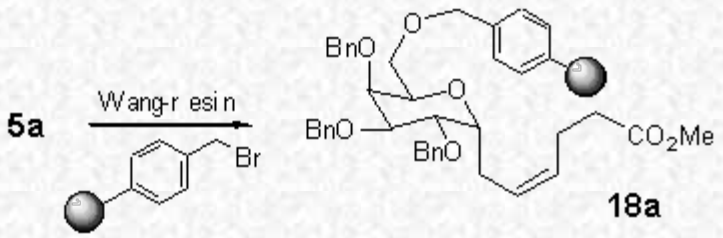


12-18 (*galacto*): R^1 = H, R^2 = OBn
19-24 (*manno*): R^1 = OBn, R^2 = H









Esterification of C-6-unproteceted *galacto*-configured **13** and *manno*-configured **20** with pentenoic acid **25a** leads to **14a** and **21a**, amino acids **14b**,**c** are prepared under classic coupling conditions (DCC, DMAP; no racemization was observed) and **14d** is synthesized with allyl isocyanate **25d**.

With these diolefines in hand, the RCM has been carried using Grubbs'-ruthenium catalyst. In the presence of 10 mol% of **26** in all runs, cyclized products **15a-c** and **22a** could be isolated in high yields (Table 1). The allyl carbamate derived RCM-precursor **15d** yielded only 26 % of the cyclized product. Cyclizations to **15a-d**

and **22a** are highly *cis*-selective, the formation of *trans*-products could be observed only for **15c** (cis/trans = 4:1).

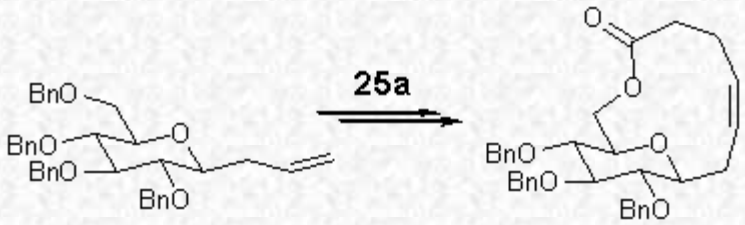
Table 1 Results of the Ruthenium-catalyzed RCM of **14a-d**, **21a** and **27**.

Substrate	Product	Time [d]	Yield [%]	(cis/trans-ratio)	$[\alpha]_D^{20}$ (c)[a]
14a	**15a**	1	84	100 : 0	+ 62.2 (0.64)
14b	**15b**	2	80	100 : 0	+20.4 (0.99)
14c	**15c**	2	77	80 : 20	_[b]
14d	**15d**	5	26	100 : 0	+63.0 (0.53)
27[c]	**28**	2	82	100 : 0	+24.0 (0.73)

a in CH_2Cl_2; [b] employed as epimer; [c] yield of the RCM-reaction

Subsequent cleavage of the formed macrocycles (12- and 15-membered) can be carried out at the predetermined cleavage functionality at C-6. The transesterification using sodium methylate accomplished the desired products **16a-b** and **23a** in quantitative yields. Reduction of the double bond to yield **17a-d** and **24a** can be achieved selectively in the presence of tosyl hydrazine without cleaving the protecting groups on the glycosidic- (Benzyl) and on the aglycon-moiety (Boc, methyl ester).

Scheme 5 Synthesis of b -configured products.



27 **28**

While starting from the b -configured allylated *gluco* derivative **27**, the metathesis product **28** can be synthesized in high yields, too (Scheme 5, Table 1). It can be demonstrated, that the b -configured derivative has no significant altering reactivity in comparison to their a -configured congeners.

We think, that the *cis*-selective formation of the double bond (exception **15c**) is due to the fact, the a bicyclic product is formed. In cases of cyclization reactions towards monocyclized products a non-stereoselective formation of the products has been obtained. Therefore some conformational constraints to support this stereoselective formation can be taken into account.

Further elaboration of the synthetic values of these compounds include attachment of the C-glycosylated products (i. a. **16a**) to a solid phase. This can be achieved easily due to the at C-6 partially deprotected carbohydrate moiety. We used benzyl bromide modified Wang-resin as solid support. Advantageously, both the glycosidic protecting groups and the resin can be removed using the same strategy.

Therefore, we think that this highly stereoselective approach towards C-glycosylated neoglycoconjugates is of wide utility. Currently, we are exploiting this approach towards solid phase synthesis as indicated by the synthesis of **22a**.

4 Conclusion

We have shown that C-glycosylated amino acids can be synthesized diastereomerically pure by two independent routes. Both routes provide the target products in a very short reaction sequence. It should be pointed out, the metathesis approach affords both the a - and b -configured glycosylated amino acids, whereas the dianion approach only gives b -configured products.

A combinatioral approach towards glycopeptides has been opened up due to the attachment to a polymeric resin. This approach is further elaborated.

Acknoledgement

The authors appreciate the support by the DFG and the Fonds der Chemischen Industrie.
