Diastereoselective Synthesis of C-Glycosylated Amino Acids with Lactams as Peptide Building Blocks**

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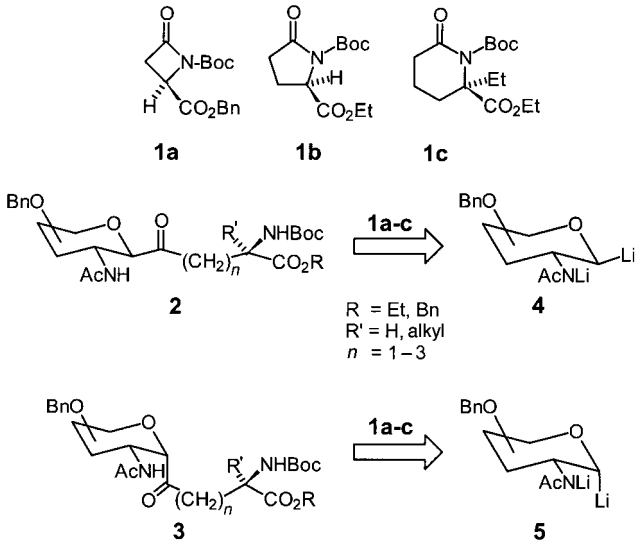
Glycopeptides are of growing interest with regard to the elucidation and utilization of their numerous biological properties.[1, 2] However, these natural products are of low metabolic and chemical stability, and their synthesis often requires complex sequences. Therefore, recent research has been focussed on the efficient synthesis of glycopeptide mimics with a stable linkage of the glycosyl and peptide moieties. Whereas natural glycopeptides bear metabolic labile O- and N-glycosidic bonds, C- and S-glycosylated mimics offer the possibility to circumvent this drawback.[3] Despite numerous contributions for the synthesis of C-glycosylated amino acids in recent years, these methods often involve a lot of steps and are of low diastereoselectivity.[4, 5]

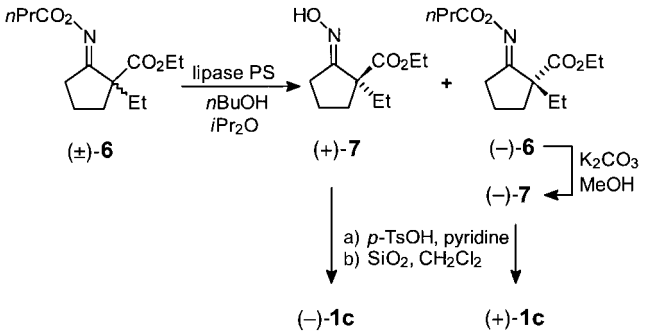
Here we present the diastereoselective synthesis of C-glycosylated amino acids **2** and **3** by utilizing enantiomerically pure lactams **1a–c** as peptide building blocks. Lactams **1a–c** can be ring-opened with the easily generated glycosyl dianions **4** and **5** (Scheme 1).[6] The lactams used in this study can be obtained from the chiral pool or synthesized by enyzme-catalyzed kinetic resolution of appropriate precursors. Therefore, they offer an easily accessible source of peptide building blocks.[7] Furthermore, for the formation of the glycosidic bond no racemization of the aglycon has to be taken into account upon utilization of **1a–c**.[8]



Scheme 1. Strategies for the synthesis of C-glycosides starting from lactams **1**.

In addition it will be shown that following this strategy, C-glycosylated α,α'-disubstituted α-amino acids can be prepared. When incorporated into oligopeptides, certain secondary peptidic structures like β turns can be adjusted through use of these conformationally restricted amino acids.[9]

We showed earlier that *N*-Boc-protected lactams can be easily ring-opened by nucleophiles to afford α,α'-disubstituted amino acids.[10] Although lactams **1a**, **b** can be taken from the chiral pool,[11] others such as lactam **1c** can be obtained enantiomerically pure by a lipase-catalyzed kinetic resolution. When (±)-**6**[12] is submitted to lipase-catalyzed transacylation in the presence of *n*-butanol, (+)-**7** and (−)-**7** (from (−)-**6** after cleavage of the butyrate moiety with K_2CO_3/methanol) can be obtained in high enantiomeric excess and high yields. The enantiomeric excess was determined to be 93% *ee* for (+)-**7** and 98% *ee* for (−)-**7**.[13] This, to our knowledge, is the first example of successful kinetic resolution of oxime esters by an enzyme-catalyzed transacylation.[14] A stereospecific Beckmann rearrangement and protection of the lactam led to the desired lactams (+)-**1c** and (−)-**1c** (Scheme 2). As shown earlier, no racemization takes place during this rearrangement.[10]



Scheme 2. Lipase-catalyzed transacylation of oxime esters (±)-**6** to(+)-**7** and (−)-**6** as well as Beckmann rearrangement to **1c**. Ts = tosyl = toluenesulfonyl.

To prove our approach for the synthesis of C-glycosylated amino acids from **1**, a model reaction using *N*-Boc-protected, unsubstituted valerolactam **9** was carried out (Scheme 3). Starting from the β-configured stannyl derivative **8**, the glycosyl dianion **4** was generated at −78 °C by subsequent addition of one equivalent each of MeLi and BuLi, and then allowed to react with **9**. The C-glycoside **10** was obtained in 47% yield as the only diastereoisomer. The product was of β-configuration, as determined by extensive NMR experiments. Reduction of **10** to **11** was accomplished by synthesis of the tosyl hydrazone and subsequent reduction with catecholborane in 65% overall yield.[15]

In analogy, the reactions of **8** with lactams **1a–c** were carried out as described above. The C-glycosylated amino acids **12a–c** could be isolated in satisfactory yields (**12a**: 32%; **12b**: 42%; **12c**: 38%). 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

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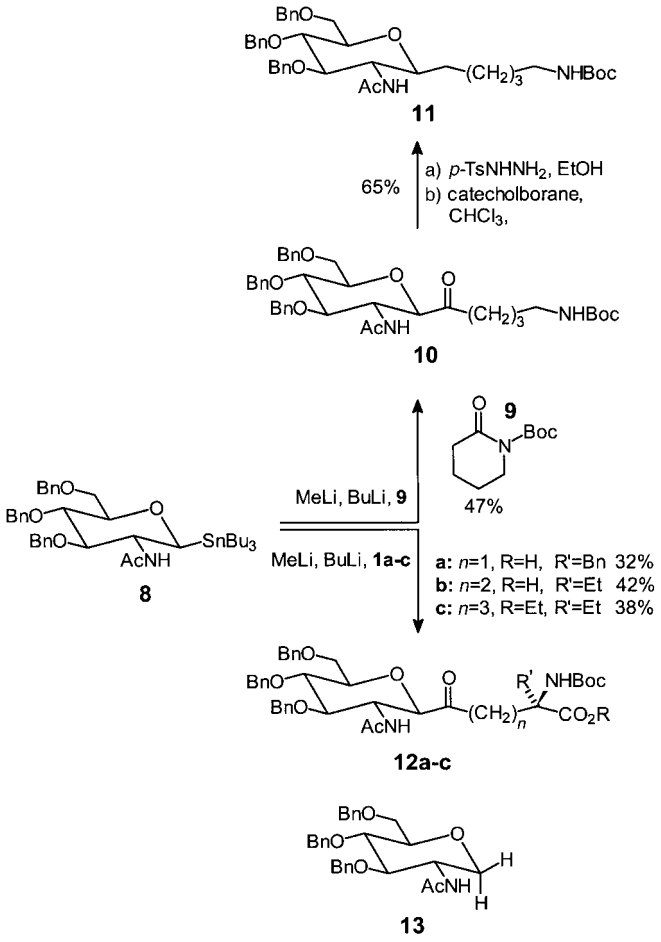

Scheme 3. Nucleophilic ring opening of lactams **1a–c** and **9** by reaction with glycosyl dianions.

pyroglutamic derivative **1b** was employed enantiomerically pure, (+)-**1b** and (−)-**1b**, and as a racemate, (±)-**1b**. The ^{1}H NMR spectra for the products obtained from (+)-**1b** and (−)-**1b** revealed only one singlet for the *tert*-butyl moiety, whereas the ^{1}H NMR spectra for the product from (±)-**1b** showed two baseline-separated singlets.[16] Therefore, it can be concluded that no racemization took place during the nucleophilic ring opening of the enantiomerically pure lactams.

To obtain α-configured glycosylated amino acid **3**, glycosyl dianion **5** was used. To date, this reaction has not been carried out successfully; only **13** 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, easily obtainable building blocks for the synthesis of C-glycopeptides. The products are orthogonally protected. Thus, by incorporation of these conformationally restricted amino acids in oligopeptides new hybrids can be synthesized that stabilize secondary structural elements in the peptide moiety and, in addition, contain a glycosidic adhesion ligand through a metabolic stable linkage.[17]

Experimental Section

(+)-**12b**: Stannane **8** (250 mg, 0.33 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. Within 5–10 min MeLi (0.33 mL, 0.33 mmol, 1 M in hexane) was added, followed by warming to −65 °C and addition of BuLi (0.30 mL, 0.45 mmol, 1.5 M in hexane) in 5–10 min. After addition of (+)-**1b** (105 mg, 0.43 mmol) the dark red reaction solution became colorless. After 30 min of stirring, a saturated NH_4Cl solution was added to stop the reaction. The reaction mixture was warmed to room temperature in an ultrasound bath, and extracted with ethyl acetate (2 × 20 mL). The extract was dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (petrol ether/ethyl acetate 1/1) yielded **12b** (97 mg, 42%) as a colorless oil. $R_f = 0.27$; $[\alpha]_D^{20} = +24.3$ ($c = 0.82$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.42 (s, 9H, CH_3), 1.78 (s, 3H, CH_3), 2.09–2.14 (m, 2H, CH_2), 2.61–2.87 (m, 2H, CH_2), 3.48–3.51 (m, 1H, 5-H), 3.55–3.64 (m, 2H, 4-H, 2-H), 3.70 (d, $J = 2.9$ Hz, 2H, 6-H), 3.89 (d, $J = 10.1$ Hz, 1H, 1-H), 3.97–4.03 (m, 1H, 3-H), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2), 4.10–4.21 (m, 1H, CH_α), 4.51–4.85 (m, 6H, $PhCH_2$), 5.29 (d, $J = 8.6$ Hz, 1H, BocNH), 5.72 (d, $J = 7.6$ Hz, 1H, NH), 7.18–7.35 (m, 15H, aromat. CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 14.57, 23.57, 25.72, 28.76, 33.37, 52.97, 54.26, 61.74, 69.32, 73.85, 75.12, 75.39, 79.34, 79.57, 80.57, 81.83, 83.21, 128.12, 128.25, 128.37, 128.43, 128.52, 128.84, 128.91, 129.04, 133.32, 133.42, 133.82, 151.11, 166.34, 167.99, 201.88.

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[13] The enantiomeric excesses were determined by GC (Lipodex β-PM, Macherey-Nagel) for (+)-**7** and (−)-**7** and by HPLC (Chiraldex OB-H, Baker) for (−)-**6**.
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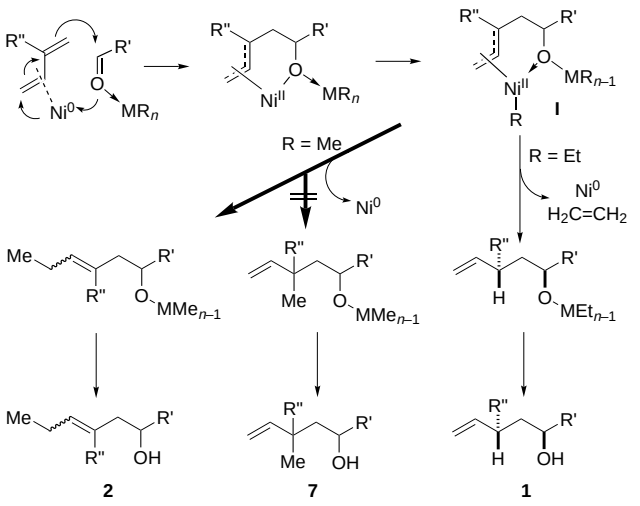


Scheme 1. Nickel-catalyzed coupling of 1,3-dienes with alkylmetal reagents and carbonyl compounds.

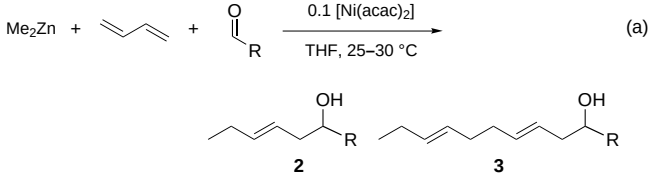
Nickel(0)-Catalyzed Three-Component Connection Reaction of Dimethylzinc, 1,3-Dienes, and Carbonyl Compounds**

Masanari Kimura, Shintaro Matsuo, Kazufumi Shibata, and Yoshinao Tamaru*

Since the discoveries of the thermal [4+2] cycloaddition reaction by Diels and Alder and nickel-catalyzed oligomerization by Wilke,[1] 1,3-dienes have been recognized to be among the most useful synthetic blocks in organic synthesis. Significant expansion of their synthetic utility has been brought about by recent studies on transition metal catalyzed cyclizations[2] and 1,2-/1,4-difunctionalization of 1,3-dienes (H, B;[3] H, Si;[4] H, Sn;[5] B, B;[6] B, Si;[7] B, Sn;[8] C, Si;[9] Si, Si;[10] Sn, Sn;[11] etc.).[12] In most cases, the products of the latter reactions are allylic metalloids that are capable of regio- and stereoselective allylation of carbonyl compounds.

We previously reported that, in the presence of a catalytic amount of [Ni(acac)$_2$] (acac = acetylacetonato) and a stoichiometric amount of triethylborane or diethylzinc, 1,3-dienes serve as a homoallyl anion equivalent and react with a wide range of carbonyl compounds to furnish bishomoallyl alcohols **1** in high yields and with high regio- and stereoselectivities[13] (Scheme 1). A proposed mechanism involves nucleophilic addition of diene–nickel(0) complexes to carbonyl compounds coordinated by MR_n ($MR_n = Et_2Zn$ or Et_3B) and ethyl group migration from M to Ni^{II} to yield an intermediate **I** (R = Et). This is followed by β-dehydronickelation and reductive elimination to furnish **1** and ethylene and regenerate Ni^0.

This sequence of reactions suggested to us that if dimethylzinc were used in place of diethylzinc, the β-dehydronickelation in the final step might be inhibited, and the intermediates **I** (R = Me) would undergo reductive elimination to provide homoallyl alcohols **2** or bis-homoallyl alcohols **7**. In fact, when dimethylzinc (4.8 mmol), 1,3-butadiene (8.0 mmol), and benzaldehyde (2.0 mmol) were exposed to [Ni(acac)$_2$] (0.2 mmol) in dry THF (5 mL) at room temperature for 2 h under N_2, the methyl group was transferred selectively to the distal allylic terminus, and homoallyl alcohol **2a** (R′ = Ph, R″ = H in Scheme 1) was obtained in almost quantitative yield [Eq. (a), R = Ph; Table 1, entry 1]. In the product mixture, the corresponding regioisomeric product **7** (R′ = Ph, R″ = H) was not detected at all.[14]



A number of nickel-catalyzed three-component connection reactions between organometallic compounds, alkynes (or strained alkenes), and carbonyl compounds have been reported;[15] however, the present reaction, to the best of our knowledge, is the first example that utilizes conjugated dienes as the unsaturated hydrocarbon component.[16] Although $CrCl_2$ also mediates a similar coupling reaction of alkyl iodides, 1,3-dienes, and carbonyl compounds, this reaction displays contrasting regioselectivity: The alkyl and carbonyl groups combine with 1,3-dienes at the C1 and C2 positions, respectively, to provide 2-alkylmethyl-3-buten-1-ols.[17]

Intrigued by the synthetic possibilities and the facility with which dimethylzinc, 1,3-butadiene, and benzaldehyde combine with one another linearly in this sequence under very mild conditions with catalysis by Ni^0 in the absence of any

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