ORGANIC LETTERS

2001
Vol. 3, No. 9
1375−1378

Chiral Auxiliary Based Approach Toward the Synthesis of C-Glycosylated Amino Acids

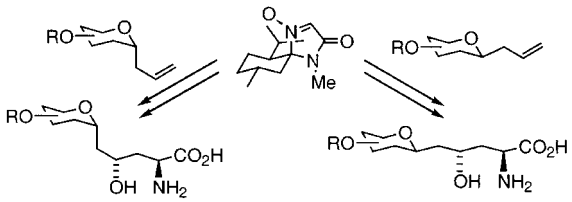
Bernhard Westermann,*,† Armin Walter,† Ulrich Flörke,† and Hans-Josef Altenbach*,‡

Universität Paderborn, Fachbereich für Chemie und Chemietechnik, Warburgerstr. 100, 33098 Paderborn, Germany, and Bergische Universität Wuppertal, Gaussstr. 20, 42097 Wuppertal, Germany

bw@fb13n.uni-paderborn.de

Received February 21, 2001

ABSTRACT



In a chiral auxiliary based method C-glycosylated amino acids can be obtained by a 1,3-dipolar cycloaddition of a chiral glycine equivalent and C-1 allyl- or vinyl-derived carbohydrate building blocks as the key step. The products are formed regio- and diastereoselectively. Reductive cleavage of the N–O bond of the isoxazolidine and of the chiral auxiliary leads to C-glycosylated amino acids. The use of (–)-menthone to (+)-menthone as the auxiliary leads to the corresponding diastereomers.

Recently, approaches toward the synthesis of glycopeptide mimics have gained considerable interest because they promise to yield biologically active derivatives without the synthesis of the complex natural derivatives.[1] In this context, much effort has been directed toward the synthesis of metabolically and chemically stable products. This has been achieved by incorporating isosteric, retro-isomeric, or peptoid building blocks as substitutes for the peptide−glycoside bond.[2] Our interest in this field is mainly concerned with the synthesis of C-glycosylated amino acids.[3] For this class of compounds a number of synthetic strategies have been described, which in addition to often being lengthy and complex exhibit limited usefulness for the stereoselective synthesis of *manno-*, *gluco-* and *galacto*-glycosylated amino acids.[4,5]

In this communication we present a very short and efficient

† Universität Paderborn.
‡ Bergische Universität Wuppertal.

(1) Reviews and concepts: Seitz, O. *ChemBioChem* **2000**, *1*, 214−246. Koeller, K. M.; Wong, C. H. *Chem. Rev.* **2000**, *100*, 4465−4494. Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495−4538. Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* **1999**, *5*, 1384−1390. Sears, P.; Wong, C. H. *Angew. Chem.* **1999**, *111*, 2446−2471; *Angew. Chem., Int. Ed.* **1999**, *38*, 2300−2324. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215−3237. Warren, D. G.; Garg, H. G. In *Glycopeptides and Related Compounds*; Warren, C. D., Large, D. G., Eds.; Marcel Dekker: New York, 1997. Bill, R. M.; Flitsch, S. L. *Chem. Biol.* **1996**, *3*, 145−149.

(2) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, *64*, 933−944. Hoffmann, M.; Burkhart, F.; Kessler, H. *Helv. Chim. Acta* **1996**, *79*, 1519−1532. Dechantsreiter, M. A.; Burkhart, F.; Kessler, H. *Tetrahedron Lett.* **1998**, *39*, 253−254. Kim, J. M.; Roy, R. *Tetrahedron Lett.* **1997**, *38*, 3487−3490 and references therein.

(3) Walter, A.; Westermann, B. *Synlett* **2000**, 1682−1684. Westermann, B.; Walter, A.; Diedrichs, N. *Angew. Chem.* **1999**, *111*, 3554−3556; Angew. *Chem., Int. Ed.* **1999**, *38*, 3384−3386. Westermann, B.; Diedrichs, N.; Gedrath, I.; Walter, A. In *Bioorganic Chemistry*; Diederichsen, U., Lindhorst, T. K., Westermann, B., Wessjohann, L. A., Eds., Wiley-VCH: Weinheim, 1999.

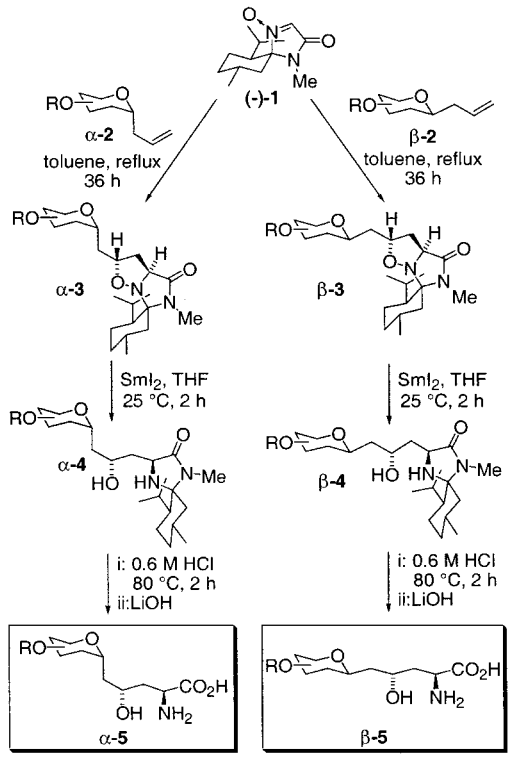
(4) Reviews: Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395−4422. Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959. Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317−11362. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599.

(5) Selected publications: Wellner, E.; Gustaffsson, T.; Bäcklund, J.; Holmdahl, R.; Kihlberg, J. *ChemBioChem* **2000**, *1*, 272−280. Vincent, S. P.; Schleyer, A.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 4440−4443. Lundquist, J. J.; Debenham, S. D.; Toone, E. J. *J. Org. Chem.* **2000**, *65*, 8245−8250. SanMartin, R.; Tavassoli, B.; Walsh, K. E. *Org. Lett.* **2000**, *2*, 4051−4054. Dominique, R.; Liu, B. C.; Das, S. K.; Roy, R. *Synthesis* **2000**, 862−868.

10.1021/ol015743j CCC: $20.00
Published on Web 04/05/2001

approach toward this class of building blocks suitable for incorporation in glycopeptide mimics. Several prerequisites were established for the synthesis of C-glycosylated amino acids: (criterion a) easy and broadly applicable approach to a large variety of products with different configurations in the glycosidic and aglycosidic moieties, and (criterion b) orthogonal protecting group strategies. To meet these criteria, we designed a chiral auxiliary based approach with a [2 + 3] cycloaddition of appropriate precursors as the key step. With (−)-menthone-derived chiral nitrone (−)-**1** as a glycine equivalent and allyl-substituted glycosidic building blocks **2** as starting materials, cycloadditions exhibiting a high degree of regio- and diastereoselectivity should occur (Scheme 1).

Scheme 1



The C-1-allylated *manno-, gluco- and galacto*-configured C-glycosides β-**2a** and α-**2b**−**e** are known products, which can be obtained easily from common sources (criterion a).[6] The protecting groups can be varied; in this study we only used acetyl- and benzyl-protected derivatives (criterion b). The nitrone (−)-**1** can be obtained in a two-step procedure by condensation of (−)-menthone and glycine methyl amide and subsequent oxidation with *m*-chloro perbenzoic acid.[7] It should be mentioned at this point that the chiral auxiliary menthone can be obtained as its D- and L-isomer; it is thus possible to synthesize (+)- and (−)-**1**. Therefore, both diastereomers of the glycosylated amino acids, exhibiting different configurations at the stereogenic center of the amino acid moiety, are accessible (criterion a).

The cycloadditions of (−)-**1** and **2** were performed in toluene under reflux; in all cases the yield was >82% (Table 1). It could be demonstrated that the α- and β-configurated glycosides did not differ in reactivity and selectivity. Spectroscopic analysis of the products (β-**3a**, α-**3b**−**e**) revealed that the reaction was completely diastereo- and regioselective. These stereochemical results were as devised in our blueprints: nitrones and olefins tend strongly to form the C−C bond with the lowest substitution count.[8,9] In terms

Table 1. Results of the [2 + 3] Cycloaddition of Nitrone (−)-**1** and Allyl Glycosides **2** To Give **3**, Followed by SmI_2 Cleavage to **4**[a]

2	**3** yield [%] $[\alpha]_{20}^{D}$ (c)[1]	**4** yield [%]
β-**2a**	β-**3a** 92 37.6 (0.84)	β-**4a** 78
α-**2b**	α-**3b** 85 58.9 (0.87)	α-**4b** 80
α-**2c**	α-**3c** 88 65.7 (0.73)	α-**4c** 78
α-**2d**	α-**3d** 82 56.1 (0.9)	α-**4d** 79
α-**2e**	α-**3e** 90 23.7 (1.17)	α-**4e** 81
α-**2f**	α-**3f** 87 53.0 (1.0)	α-**4f** 81

[a] (Note 1): in $CHCl_3$.

(6) β-**2a**, **6**: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4974−4978. Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752−753. α-**2b**,**d**,**e**: Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223−232. α-**2c**: Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479−1482. α-**2f**: Horton, D. In *Methods in Carbohydrate Chemistry*; Whistler, R. J., BeMiller, J. N., Eds.; Academic Press: New York, 1972; Vol. 6, pp 282−285. Cui, J.; Horton, D. *Carbohydr. Res.* **1998**, *309*, 319−330.

(7) Vogt, A.; Altenbach, H.-J.; Kirschbaum, M.; Hahn, M. G.; Matthäus, M. S. P.; Herrmann, A. R. EP 976721, 2000; *Chem. Abstr.* **2000**, *132*, 108296. Altenbach, H.-J.; Hahn, M.; Matthäus, M. S. P. *N,N-Acetals from Menthone with* α*-Aminocarboxylic acid and N*-Methylamides. 12th International Conference on Organic Synthesis, Venice, Italy, 1998, OC-68.

(8) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. Little, R. D. Thermal Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991, Vol. 5.

of diastereoselectivity, a β-facial/exo-attack can be assumed, with the isopropyl moiety of the chiral auxiliary determining the site selectivtiy (Figure 1).[10] The absolute configuration

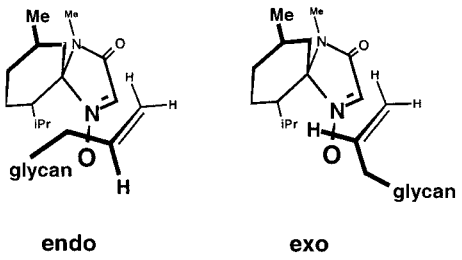


Figure 1. *exo*- vs. *endo*-configurated transition states during the cycoaddition step of (−)-**1** and **2**.

at the newly created stereogenic centers could be confirmed by X-ray crystallography of the crystalline cycloadduct **12** (Figure 2).

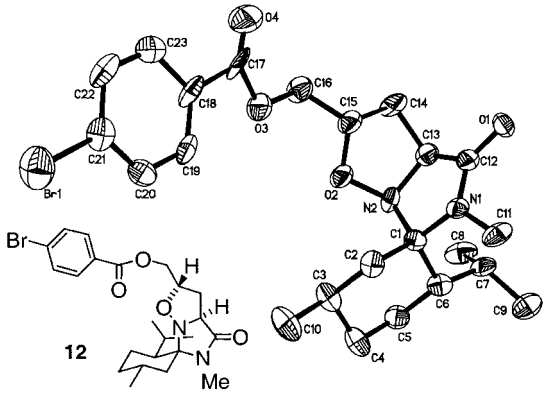


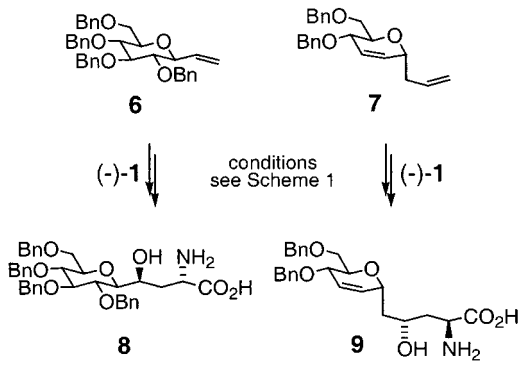
Figure 2. Molecular structure of **12**. Displacement ellopsoids shown at the 50% level; H atoms are omitted for clarity.

Subsequently, classical methods (H_2/Pd or Zn/acetic acid) for the reductive cleavage of the N−O bond in isoxazolidines **4a**−**e** could not be used because they interfered with the protecting groups on the glycosidic moiety. Therefore, we turned our attention to the Sm^{II}-mediated cleavage of N−O bonds, which was described first by Natale.[11] In all cases the cleavage could be obtained in high yields, leading to the corresponding 1,3-amino alcohols **4**. The protecting groups remained intact.

The *N*,*N*-acetal **4** was quantitavely hydrolyzed on being stirred in 0.6 M aqueous HCl and a small amount of acetic acid. Cleavage of the amide bond could be achieved with an equimolar amount of lithium hydroxide. Both hydrolytic steps were quantitative. Under these conditions, no cleavage of the acetyl protecting groups in **5** was observed. During these two steps the presence of the free hydroxy group at C-4 of the aglycosidic moiety turned out to be crucial, presumably as a result of some neighboring effect. After protection (e.g., benzylation) no cleavage occurred.

To demonstrate the broad applicability of the aglycosidic building block, the GlcNAc derivative **2f**,[6] the β-configurated vinyl derivative **6**[6], and the pseudo-glucal **7**[12] were also utilized (Scheme 2). In these cases, the same regio- and

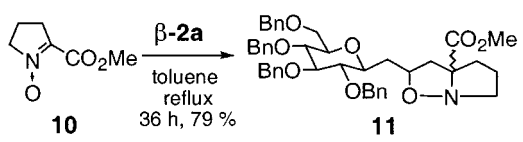
Scheme 2



diastereoselectivities were observed as in the previous cycloadditions. As described earlier, the endocyclic double bond in **7** is not susceptible to cycloaddition reactions; therefore only the exocyclic double bond underwent reaction.[13]

During our studies the question arose as to whether the stereochemical information provided by the glycosidic moiety alone may account for the observed diastereoselectivity. To test this, we utilized nitrone **10**[14] (from proline) in the cycloaddition with β-**2a** (Scheme 3). Two diastereomers **11a,b** (1:1) were obtained and were, unfortunately, insepa-

Scheme 3



(9) Selected publications: Cardona, F.; Valenzy, S.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1999**, 1319−1323. Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311−7318. Tamura, O.; Kuraki, T.; Sakai, Y.; Takizawa, J. I.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett.* **1999**, *40*, 895−898. Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819−6822. Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725−5746.

(10) The determined configuration is in strong correlation to previous results; see ref 9.

(11) Myers, R. M.; Langston, S. P.; Conway, S. P.; Abell, C. *Org. Lett.* **2000**, *2*, 1349−1352. Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755−11772. Natale, N. R. *Tetrahedron Lett.* **1982**, *23*, 5009−5012.

(12) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307−2313.

(13) Cardona, F.; Salanski, P.; Chmielewski, M.; Valenza, S.; Goti, A.; Brandi, A. *Synlett* **1998**, 1444−1446.

(14) Bernotas, R. C.; Sabol, J. S.; Sing, L.; Friedrich, D. *Synlett* **1999**, 653−655.

rable. NMR spectroscopy (DEPT-135) revealed, however, that only the one expected regioisomer was formed. It was thus proven that a chiral glycine equivalent is necessary to produce diastereomerically pure cycloaddition products.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (We1826/3-1) and the Fonds der Chemischen Industrie is highly appreciated. We thank Haarmann & Reimer GmbH, Germany, for a gift of D- and L-menthol.

Supporting Information Available: General experimental procedures, characterization data for compounds β-**3b**, **4b** and **5b**, and X-ray data of **12** to confirm the relative stereochemistry of cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015743J