Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 375–378

TETRAHEDRON: *ASYMMETRY*

Glycosylation-induced asymmetric synthesis: β-amino acid esters via Mannich reactions

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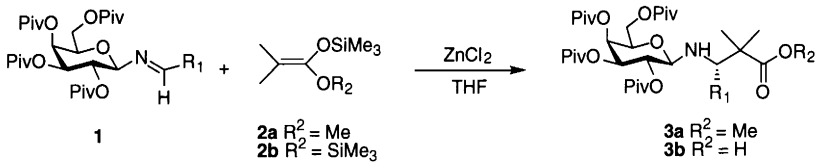
Received 3 November 1999; accepted 24 November 1999

Abstract

Activation of Schiff bases by *N*-glycosylation induces asymmetric Mannich reactions with *O*-silyl ketene acetals to give β-amino acid esters in good yields.

β-Amino acids are important constituents of natural products with pronounced pharmacological activities.[1] The enantiomerically pure β-amino acids have received increasing interest recently,[2] e.g. as building blocks for β-peptides.[3] A number of diastereoselective[2,4] and enantioselective[5] Mannich reactions to give β-amino acid derivatives have been reported. The diastereoselective Mannich reaction of *O*-pivaloylated *N*-galactosyl imines **1** with *O*-silyl ketene acetals **2a**[6] or bis-silyl ketene acetals[7] **2b** proved an efficient stereoselective access to chiral β-amino acid derivatives **3** (Scheme 1). The *N*-glycosidic bond of compounds **3** was readily cleaved under mildly acidic conditions to give enantiomerically pure β-amino acids or their esters, respectively.



Scheme 1.

In order to extend the scope of asymmetric reactions using *N*-glycosyl imines to *N*-alkyl or *N*-aryl amino acid derivatives interesting for combinatorial applications, *O*-pivaloylated galactosyl bromide[8] **4** was reacted with the *N*-butylimine **5** of acetophenone in the presence of silver triflate and the iminium intermediate trapped with trimethylsilylcyanide (Scheme 2).

The amino nitrile **6** was isolated in a yield of 30% and a diastereomeric ratio of 2:1. Obviously, the intermediate iminium ion easily forms the enamine which is responsible for the low yield and the

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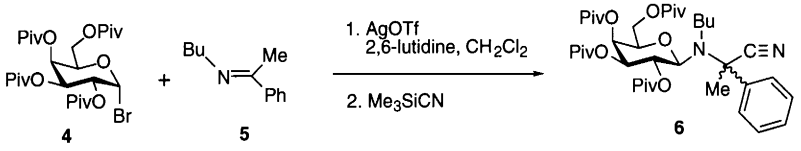
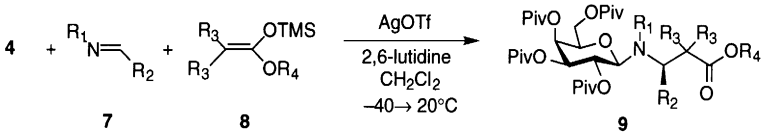
0957-4166/00/$ - see front matter
PII: S0957-4166(99)00541-8



Scheme 2.

insufficient stereoselectivity. Nevertheless, the formation of **6** showed that *N*-glycosylation at the same time activates imines and induces stereodifferentiation.

As a consequence this principle was transferred to the Mannich reaction of *N*-alkyl and *N*-aryl aldimines **7** with *O*-trimethylsilyl ketene acetals **8** (Scheme 3).[9]



Scheme 3.

The reactions were carried out in a one-pot procedure. In dry dichloromethane at –40°C, the imine **7** (1 equiv.), 2,6-lutidine (2 equiv.), the ketene acetal (3 equiv.) and silver triflate (1.2 equiv.) were dissolved. The mixture was allowed to warm up to room temperature over 15 h. The Mannich reactions proceeded between −10°C and +10°C to give the β-amino acid esters **9** in high yield and with moderate diastereoselectivity (Table 1). In all cases except for **9f**, the diastereomers **9** could be separated by preparative HPLC (reversed-phase C18, MeOH:water, ~9:1), and the pure major diastereomer was isolated in good yield.

Table 1
Galactosylation-induced asymmetric Mannich reaction of aldimines **7** with *O*-silyl ketene acetals **8** (Scheme 3)

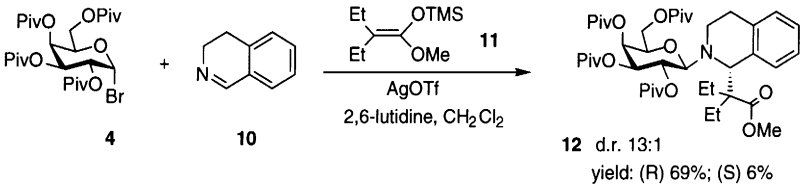
Product	R^1	R^2	R^3	R^4	Yield (%)[a] (R)	(S)	d. r.[b]
9 a	Et	Ph	Et	Me	68	18	4:1
9b	Et	Ph	Me	Me	48	17	3:1
9c	Et	Ph	$-(CH_2)_5-$	Et	63	23	3:1
9d	Et	4-NO_2-Ph	Et	Me	53	7	8:1
9e	Et	3,4$(MeO)_2$Ph	Et	Me	68	24	3:1
9f	Ph	Ph	Et	Me	88[c]		3:1
9g	All	Ph	Et	Me	70	18	4:1
9h	Bn	Ph	Et	Mer	37	30	5:4

a) Pure diastereomers with correct elemental analysis isolated by preparative HPLC; b) Ratio of diastereomers determined from crude product by analytical HPLC; c) Mixture of diastereomers.

The relative configuration within the major diastereomers **9** was confirmed by X-ray structure analysis of the major diastereomer of **9d** [mp 74°C; $[\alpha]=-5.42$ (*c* 1, $CHCl_3$)].[10]

This stereochemical outcome suggested that *N*-glycosylation not only activates the imines but is also accompanied by a prevailing *E*- to *Z*-isomerization at the C=N double bond of **7** prior to the reaction of the imium intermediate with the nucleophiles **8**. Large *N*-substituents **9h** obviously oppose this isomerization to form the *E*-iminium compounds (corresponding to the *Z*-imine) which results in low diastereoselectivity of the Mannich reaction.

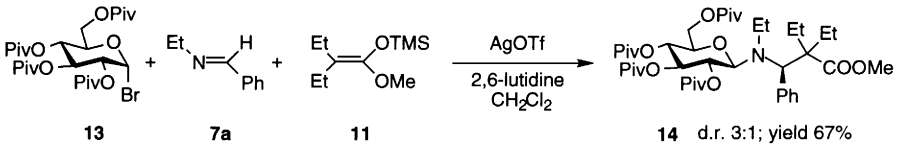
In agreement with this rationalization, the 3,4-dihydroquinoline[11] **10** reacted with silyl ketene acetal **11** after activation by *N*-galactosylation to give the β-amino acid ester **12** with high diastereoselectivity according to analytical HPLC of the crude product (Scheme 4).



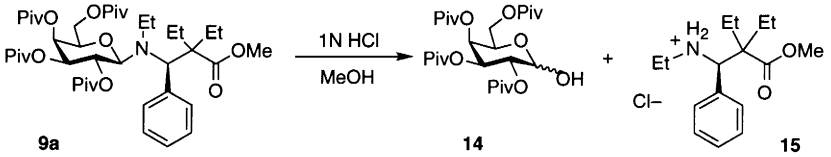
Scheme 4.

The pure (*R*)-diastereomer of **12** was isolated by preparative HPLC [acetonitrile:water, 93:7, Kromasil C18; mp 68–70°C; $[\alpha]_D^{22}$=+1.24 (*c* 1, $CHCl_3$)] in good yield.

It should be mentioned that tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide[8] **13** also induced the Mannich reaction of imines, e.g. **7a**, with silyl ketene acetals **11** (Scheme 5). The corresponding β-amino acid derivative **14** was obtained with slightly lower yield and diastereoselectivity compared to **9a** (Scheme 6).



Scheme 5.



Scheme 6.

In comparison to Mannich reactions of glycosyl imines[6,7] **1** and other chiral imines, the stereodifferentiation at the C=N double bond of the *N*-glycosyl iminium intermediates cannot be supported by coordination to $ZnCl_2$[4,6,7] or other Lewis acids.[4e,5] In addition, the *exo*-anomeric effect in these iminium intermediates was weaker than in glycosyl imines[6,7] **1** or than the π-delocalization in intermediary chiral *N*-amino acyl iminium salts.[4g] Therefore, the diastereoselectivity in the *N*-galactosylation-induced Mannich reactions was lower than that in the aforementioned syntheses of β-amino acids. However, the method reported here has the following advantageous features: (a) the *O*-pivaloyl-protected glycosyl bromides are readily accessible in two steps; (b) the major diastereomers are obtained by chromatography in pure form; and (c) the removal of the stereodifferentiating galactosyl (or other glycosyl) moiety does not need a long-winded multi-step process. The *N*-galactoside bond was mildly cleaved by treatment with dilute hydrogen chloride in methanol as has already been demonstrated for β-amino acid derivatives[6,7] and for *N*-glycosylated alkaloids.[12]

From the pure diastereomers of **9a** the pure enantiomers of **15** were obtained essentially quantitatively by treatment with 1N HCl in methanol: (*R*)-**15**: yield 98%, $[\alpha]_D^{22}$=+8.75 (*c* 1, 1N aq. HCl); (*S*)-**15**: yield 93%, $[\alpha]_D^{22}$=−8.45 (*c* 1, 1N aq. HCl).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. We thank Dr. Dieter Schollmeyer, Universität Mainz, for performing X-ray crystal structure analyses.

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