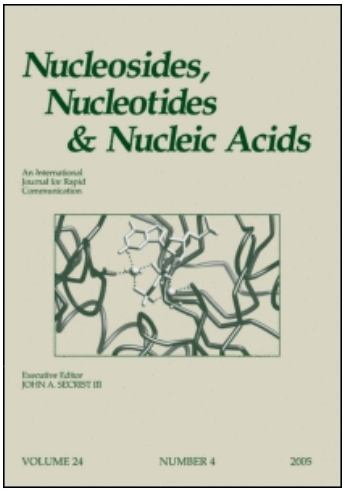

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Diastereoselective Synthesis of 2',3'-Dideoxy- β-*C*- Glucopyranosides as Intermediates for the Synthesis of 2',3'-Dideoxy-β-D-Glucopyranosyl-*C*-Nucleosides

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DIASTEREOSELECTIVE SYNTHESIS OF 2′,3′-DIDEOXY-β-*C*-GLUCOPYRANOSIDES AS INTERMEDIATES FOR THE SYNTHESIS OF 2′,3′-DIDEOXY-β-D-GLUCOPYRANOSYL-*C*-NUCLEOSIDES

Michael Löpfe and Jay S. Siegel □ *Institute of Organic Chemistry, University of Zurich, Zurich, Switzerland*

□ *An extension of the Vorbrüggen method of nucleotide synthesis for the synthesis of C-glucopyranosides, as intermediates for C-nucleosides, is described. It could be shown that the diastereoselectivity of the reaction can be tuned by a simple change of protecting groups.*

Keywords *C*-glycosides; *C*-nucleosides

INTRODUCTION

C-glycosides serve as glycomimetics,[1] as well as important intermediates for the synthesis of *C*-nucleosides.[2]

Most of the methods available for the synthesis of *C*-glycosides are more suited for the synthesis of α-*C*-glycosides than for β-*C*-glycosides.[3] Moreover, the diastereoselectivity of the typically used methods for the synthesis of β-*C*-glycosides are dependent on the influence of the neighbouring group at 2-*O*-position and are therefore ineffective for the diastereoselective prepartion of 2-*deoxy* sugar β-*C*-glycosides.[4] This limitation motivated the developement of methods to epimerize the α- to the β-anomer.[5] As part of our ongoing studies towards the synthesis of *C*-nucleosides, especially 2′,3′-dideoxy-β-D-glucopyranosyl-*C*-nucleosides (homo-DNA-*C*-nucleosides) **1**, we developped an extension of the Hilbert-Johnson method[6] of nucleoside synthesis, modified by Vorbrüggen et al.[7] to form *C*-glycosides **2–4** as a key-intermediates. This new method allowed us to tune the β/α ratio according to the protecting group at the OC(4) and OC(6) positions and, with the benzyl protecting group, gave direct access (without additional epimerisation) to the desired 2′, 3′-dideoxy-β-*C*-glycoside, which was used to synthesize **1**.

The Vorbrüggen method of nucleoside synthesis forms the glycosidic bond between the sugar and the persilylated heterocyclic base under Lewis

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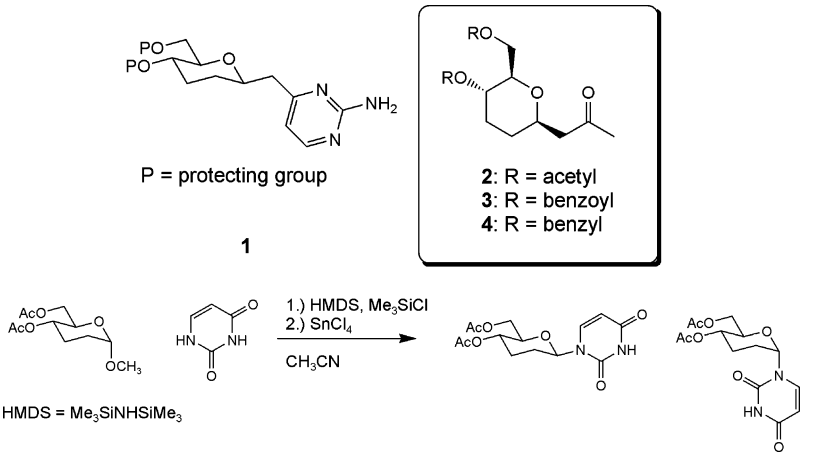


FIGURE 1 Homo-DNA-*C*-nucleoside (**1**), key intermediates (**2–4**) and typical example of a *Vorbrüggen*-coupling.

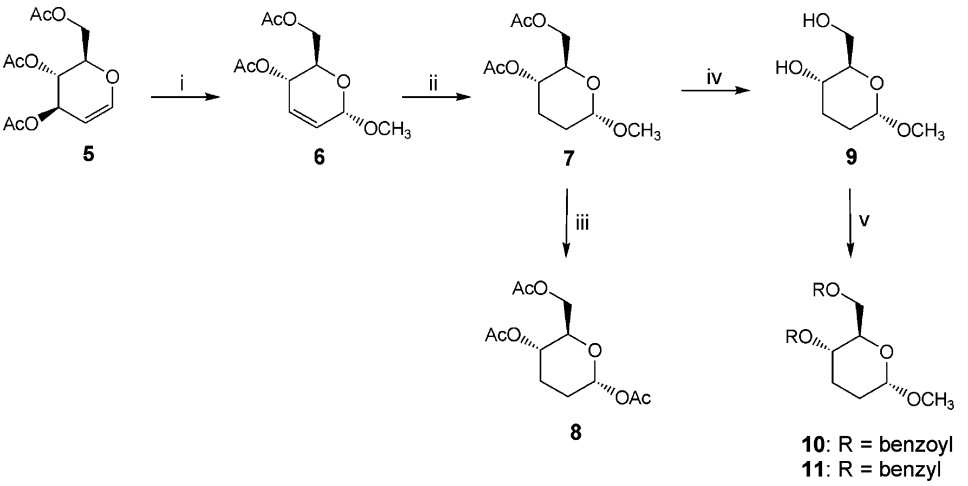
acid catalysis. This method possesses two advantages: First, no activation of C(1) in the sugar is necessary and second, the persilylated heterocyclic base is produced *in situ* in the reaction mixture and does not need to be isolated (Figure 1). The first advantage is critical for the synthesis of *C*-glycosides, the *in situ* generation of the silylenolether (versus the isolation of the silylenolether) offers preparatively no benefits.

RESULTS AND DISCUSSION

Commercially available 3,4,6-tri-*O*-acetyl-D-glucal **5** was converted, according to a procedure by Ferrier and Prasad,[8] to methyl-4,6-di-*O*-acetyl-β-D-erythro-hex-2-enopyranoside (**6**) (**6**α/**6**β = 8:1). The following hydrogenation resulted in pyranoside **7**. C(1) activation of pyranoside **7** under strongly acidic conditions gave access to 1,4,6-tri-*O*-acetyl-pyranoside **8** in 76% yield and with a diastereomeric ratio α/β 5:1 (Scheme 1).

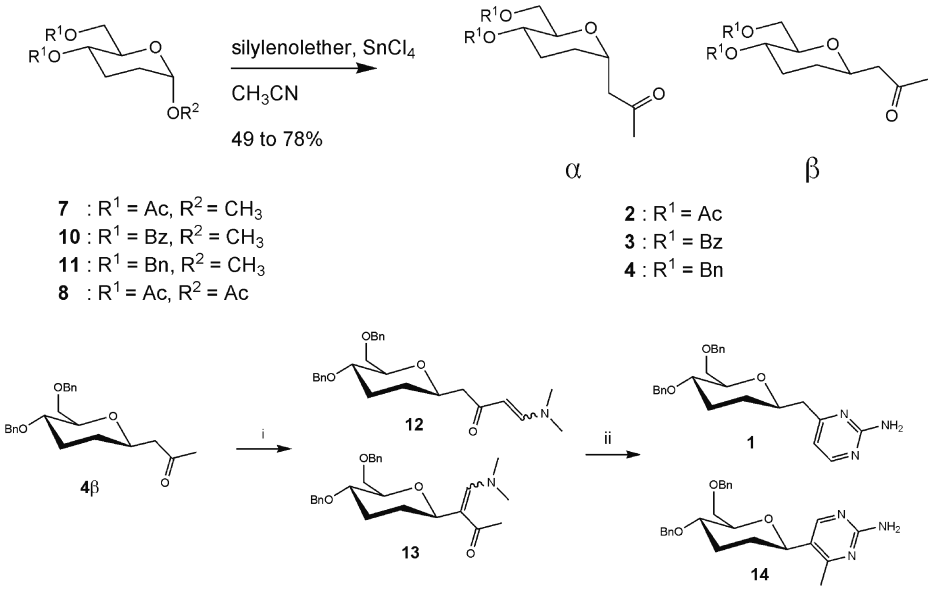
Eschenmoser et al.[9] reported that, for the product distributions and the yields of the classical Vorbrüggen coupling, the configuration at the anomeric center of the starting material had no influence. Under the coupling conditions for *C*-glycoside **2**, a diastereomeric mixture (**2**α/**2**β 66:34) was obtained. Although a separation of the two diastereomers **2**α/**2**β was possible on preparative column chromatography, the unfavourable α/β ratio was a synthetic challenge. Inspired by the Vorbrüggen method for the synthesis of nucleosides, the coupling also was carried out without C(1) activation, resulting in a diastereomeric ratio **2**α/**2**β 47:53 with a yield of 49% (Scheme 2).

Recent results from Woerpel et al.,[10] studying systematically the *C*-glycolsylation reactions of mannose and other pyranoses, have shown that the alkoxy groups at C-2, C-3, and C-4 exert powerful influences on the



SCHEME 1 Synthesis of intermediates **8–11**. i) MeOH, BF_3*OEt_2, toluene; ii) Pd(C), H_2, MeOH/AcOH 100:1; iii) H_2SO_4, AcOH, Ac_2O; iv) 2N NaOH, THF/MeOH/H_2O 5:4:1 resp. amberlite IRA 400, MeOH; v) BzCl, pyridine resp. NaH, BnBr, Bu_4NI, THF.

diastereoselectivity. This effect led us to investigate the influence of the protecting groups at OC(4) and OC(6) on the diastereoselectivity of the *C*-glycolsylation. The benzoyl-protected derivative **10** was prepared from pyranoside **7** by a deprotection with the strongly basic anion exchange resin amberlite IRA 400, followed by an esterification with benzoyl-chloride. The benzyl-protected pyranoside **11** was accessible from the 4,6-dihydroxy-pyranoside **9** by an ether formation with benzyl bromide.



SCHEME 2 *Vorbrüggen*-coupling reactions and synthesis of *β-C*-nucleosides **1**, **14** from **4** i) *t*BuOCH$(NMe_2)_2$, toluene; ii) guanidine-sulfate, NaOEt, EtOH.

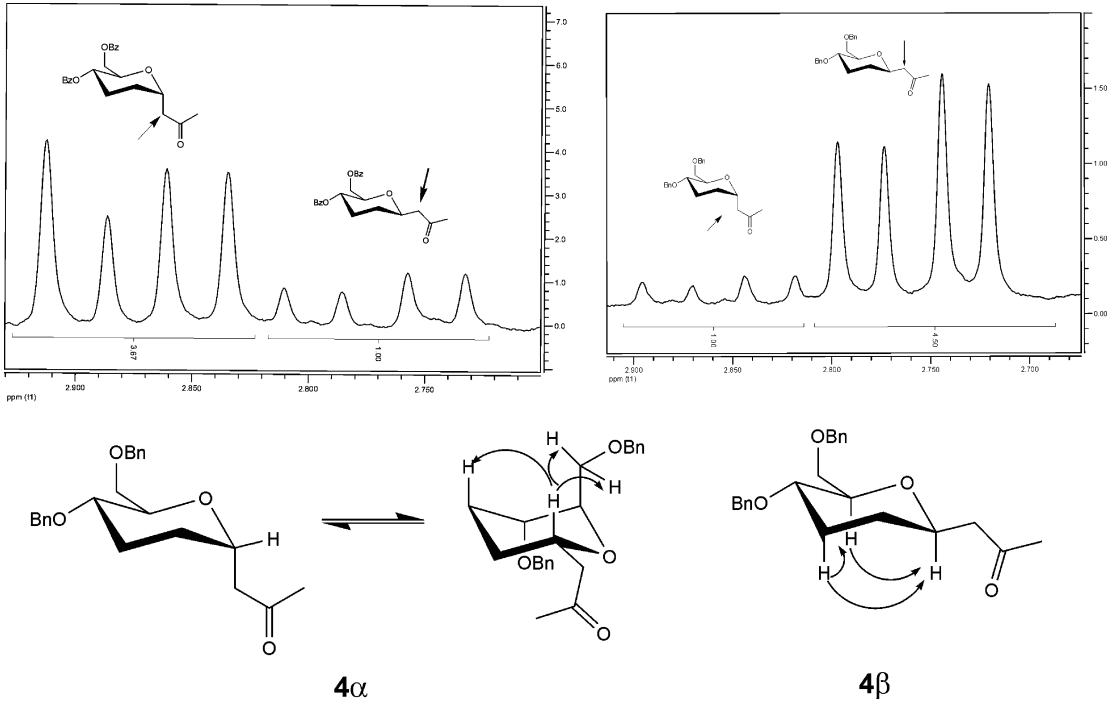


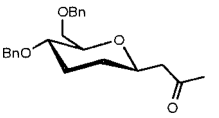
FIGURE 2 Determination of the diastereoselectivity of the coupling for **3** and **4**/observed NOES for α and β.

The diastereomeric ratio of the reaction product was inverted by a protecting group change from benzoyl (**10**) to benzyl (**11**). Under the coupling conditions (25°C, 6 hours for **7**, **10**, **11**, respectively −78°C, 1.5 hours for **8**), the following effect was observed: the benzoyl-protected derivative **10** resulted in a diastereomeric ratio **3**α/**3**β 77:23, compared to a diastereomeric ratio **4**α/**4**β 18:82 with 4,6-*O*-benzyl-pyranoside **11**. A reduction of the reaction time with **11** (2 hours) resulted in a ratio **4**α/**4**β 43:57 during an increase of the reaction time to 2 hours gave a **4**α/**4**β 8:92 ratio, indicating a rearrangement from **4**α to the thermodynamically more stabile **4**β (Figure 2). The diastereoselectivity can be explained by a complexation of the Sn^{IV} with the ester protecting groups in **7**, **8**, and **10** protecting these compounds from the rearrangement. The two diastereomers **4**α/**4**β were separable on preperative column chromatography. With this synthetic strategy, the desired diastereomer **4**β was accessible and was converted with *Bredereck*'s reagent to the regioisomeric enaminoketones **12** and **13**. Condensation under basic conditions with guanidine-sulfate resulted in a 3:1 mixture (**1**:**14**) of the *C*-nucleosides **1**, **14** which were separated on column chromatography (cf. Scheme 2).

CONCLUSION

It was shown that 2′,3′-dideoxy-β-*C*-glucopyranosides, as intermediates for the synthesis of homo-DNA-*C*-nucleosides, can be synthesised based on an extension of the Vorbrüggen method for the synthesis of nucleosides, particularly without C(1) activation of the sugar in acceptable yields (44–56%) and that the diastereoselectivity of the reaction can be varied by a simple change of protecting groups.

EXPERIMENTAL DATA OF FINAL COMPOUNDS



4β

R_f (SiO_2; Et_2O/hexane 2:1) 0.22 ($Ce(SO_4)_2$).

IR (film): 3410*w*, 3087*w*, 3062*m*, 3030*m*, 2934*s*, 2864*vs*, 1954*w*, 1876*w*, 1812*w*, 1714*vs* (CO), 1605*w* 1586*w*, 1496*m*, 1453*s*, 1437*m*, 1418*m*, 1367*s*, 1330*m*, 1315*m*, 1285*m*, 1206*m*, 1161*s*, 1091br. *vs*, 1028*s*, 999*s*, 931*w*, 908*m*, 874*w*, 818*w*, 846*w*, 737*vs*, 698*vs*, 649*w*, 609*w*, 566*w*, 466*w*.

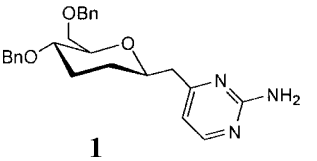
^{1}H-NMR (600 MHz, $CDCl_3$): 7.34–7.21 (*m*, arom. H); 4.63–4.39 (*m*, benz. H); 3.78 (*dddd*, J = 12.9, 7.4, 5.6, 2.0, HC(1)); 3.71 (*dd*, J = 10.7, 1.2, 1H from $H_2C(6)$); 3.67 (*dd*, J = 10.7, 4.4, 1H from $H_2C(6)$); 3.42–3.39 (*m*, HC(4), HC(5)); 2.75 (*dd*, J = 15.9, 7.1, 1H from C(1)CH_2CO); 2.46

(*dd*, J= 15.9, 5.6, 1H from C(1)CH_2CO); 2.29–2.23 (*m*, HC(3)$_{eq}$); 1.83–1.76 (*m*, HC(2)$_{eq}$); 1.56–1.43 (*m*, HC(3)$_{ax}$); 1.35 (*dddd*, J= 17.3, 13.4, 11.2, 3.9, HC(2)$_{ax}$).

^{13}C-NMR: (75 MHz, $CDCl_3$): 207.0 (*s*, CO); 138.4, 138.3 (2*s*, arom. C$_{quart.}$); 128.23, 128.19, 127.7, 127.6, 127.5, 127.4 (6*d*, arom. C); 80.5, 73.8, 72.9 (3*d*, C(1), C(4), C(5)); 73.3, 70.9, 69.6 (3*t*, 2 OCH_2-arom., C(6)); 49.4 (*t*, C(1)CH_2CO); 30.9 (*q*, Me); 30.5, 29.1 (2*t*, C(2), C(3)).

CI-MS: 386 (100, $[M+NH_4]^+$), 369 (15, $[M+H]^+$), 277 (9, $[M-C_7H_7]^+$), 206 (7), 189 (5), 91 (6, $[C_7H_7]^+$).

Anal. calc. for $C_{23}H_{28}O_4$ (368.47) : C 74.97, H 7.66; found C 74.95, H 7.62.



1

R_f (Al_2O_3; EtOAc/hexane 2:1) 0.25 (UV_{254}, $Ce(SO_4)_2$).

IR (film): 3337*vs* (br.), 3063*m*, 3030*m*, 2935*m*, 2863*m*, 2079*w*, 1955*w*, 1812*w*, 1631*vs*, 1578*vs*, 1495*m*, 1459*s*, 1369*m*, 1341*m*, 1315*w*, 1265*w*, 1205*m*, 1100*s*, 1027*m*, 1001*w*, 907*w*, 880*w*, 800*w*, 781*w*, 736*s*, 698*s*, 646*w*, 607*w*.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.11 (*d*, 1H, J= 5.1 Hz, NC$H_{arom.}$), 7.33–7.21 (*m*, 10H, arom. H), 6.64 (*d*, J= 5.1 Hz, NCHCH_{arom}), 5.29 (br. *s*, NH_2), 4.63–4.40 (*m*, 4H, benz. H), 3.76–3.71 (*m*, 1H from H_2C(6), HC(1)), 3.66 (*dd*, J = 10.8, 4.8 Hz, 1H from H_2C(6)), 3.44–3.39 (*m*, *H*C(4), *H*C(5)), 2.88 (*dd*, J= 14.0, 7.6 Hz, 1H from HC(1)CH_2-arom.), 2.68 (*dd*, J= 14.0, 5.1 Hz, 1H from HC(1)CH_2-arom.), 2.29–2.26 (*m*, *H*C(3)$_{eq.}$), 1.79–1.76 (*m*, *H*C(2)$_{eq.}$), 1.50–1.40 (*m*, *H*C(3)$_{ax}$).

^{13}C-NMR ($CDCl_3$, 150 MHz): 169.1 (*s*, C(1)CH_2C_{arom}); 162.1 (*s*, H_2NC_{arom}); 157.3 (*d*, NCH_{arom}); 138.5, 138.4 (2*s*, 2 OCH_2C_{arom}); 128.4, 128.3, 127.7, 127.6, 127.5 (5*d*, 5 C$_{arom}$); 111.9 (*d*, NCHCH_{arom}); 80.7 (*d*, *C*(5)); 76.3 (*d*, *C*(1)); 73.3 (*t*, 1 OCH_2-arom); 73.1 (*d*, *C*(4)); 71.0 (*t*, 1 OCH_2-arom); 69.8 (*t*, *C*(6)); 43.8 (*t*, C(1)CH_2-arom); 30.6 (*t*, *C*(2)); 29.2 (*t*, C(3)).

ESI-MS: 458.1 (5, $[M+K]^+$), 442.2 (6, $[M+Na]^+$), 420.3 (100, $[M+H]^+$).

HR-ESI-MS: calc. for $C_{25}H_{30}N_3O_3$ ($[m+H]^+$) 420.2287; found 420.2287.

Anal. calc. for $C_{25}H_{29}N_3O_3$ (419.52) C 71.57 H 6.97; found C 71.62 H 6.94.

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