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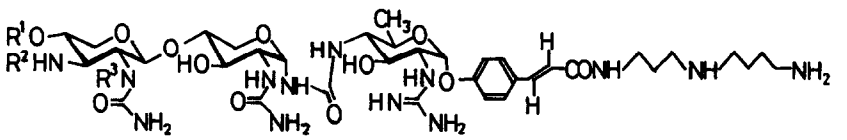
SYNTHETIC KEY INTERMEDIATES OF GLYCOCINNAMOYLSPERMIDINES ; DIAMINOHEXOSYLOXYCINNAMATE AND AMINOPENTOSE DISACCHARIDE MOIETIES

Koichi Araki, Ken-ichi Miyazawa, Hironobu Hashimoto*, and Juji Yoshimura
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

Summary: Two key intermediates for the total synthesis of glycocinnamoylspermidines were derived from the corresponding 2-azido sugars.

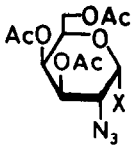
Glycocinnamoylspermidines, LL-BM 123β (1a), γ_1 (1b) and γ_2 (1c), are new broad-spectrum antibiotics whose structures were recently proposed.[1] These antibiotics are of special interest because of not only their bioligical activity against gram-negative organisms and their protective effects against infections produced in mice,[2] but also their unique structure including α-ureido linkage between amino sugar components. Here we would like to report the synthesis of two key intermediates for the components, i.e., ethyl p-[4-amino-2-t-(butoxycarbonyl)amino-2,4,6-trideoxy-α-D-glucopyranosyl]oxycinnamate (15) and methyl 4-O-(2-azido-2-deoxy-β-D-xylopyranosyl)-2-azido-2-deoxy-α-D-xylopyranoside derivative (31). Because of chemical stability and easy conversion into



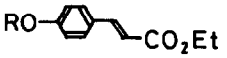
1a $R^1=R^2=R^3=H$
1b $R^1,R^2=CO$, $R^3=H$
1c $R^1=H$, $R^2,R^3=CO$

various modified amino functions, 2-azido sugars were chosen as starting compounds.

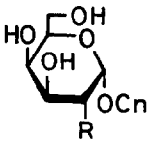
In order to convert 2-azido-2-deoxy-D-galactose into 15 the required synthetic operations are (A) glycosylation, (B) 4-amination and (C) 6-deoxygentation. Considering availability of starting 2-azido sugars and necessity of 2-azido group for the glycosylation, the sequence, A → B → C, seemed to be favorable. On glycosylation of ethyl p-hydroxycinnamate (4) with 3,4,6-tri-O-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl chloride[3] (2) the best result as to the ratio of α-anomer formed [α-(3*) : β-anomer = 5.5 : 1.0, yield 42%] was obtained in the presence of $AgClO_4$ (1.2 equiv.) and Ag_2CO_3 (2 equiv.) in dichloromethane at room temperature for 30 h. The yield was improved to 63% (α/β=5.5) by condensation of 2 with trimethylsilyl ether (5) of 4 under the same condition. This combination seems to be a new type of glycosidation of phenol derivatives[4] and proved to be very effective. The azido group of its de-O-acetylated product (6) was selectively hydrogenolyzed with 5% $Pd/BaSO_4$ (about one forth of substrate in weight)-quinoline (one drop/50 mg catalyst) in methanol for 15-24 h to give the 2-amino derivative (7), which was converted into N-(t-butoxycarbonyl) derivative (8) with 2-(t-butoxycarbonyl)thio-4,6-dimethylpyrimidine and Et_3N in dioxane-water. Benzoylation of 8 in acetone with BzCl (3 equiv.) in the presence of Et_3N at -10°C for 16 h gave



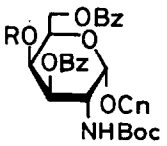
2 X=Cl
3 X=OCn



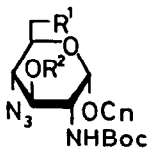
4 R=H(CnOH)
5 R=TMS



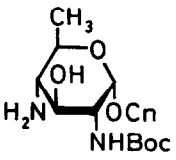
6 R=N_3
7 R=NH_2
8 R=NHBoc



9 R=H
10 R=Ms



11 R^1=OBz, R^2=Bz
12 R^1=OH, R^2=H
13 R^1=OTs, R^2=H
14 R^1=R^2=H



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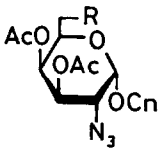
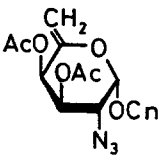


16 R=OTs
17 R=H



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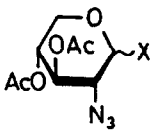
Ac=CH_3CO, Bz=C_6H_5CO
Boc=$(CH_3)_3COCO$, Ms =CH_3SO_2
Ts=p-$CH_3C_6H_4SO_2$, TMS=$(CH_3)_3Si$

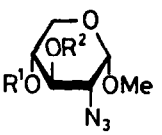
3,6-dibenzoate (9) in 75% yield from 6. Its 4-mesylate (10) was treated with NaN_3 (2 equiv.) in hexamethylphosphoric triamide (HMPT) at 80°C for 10 h to afford the corresponding 4-azide (11*) in 77% yield. Tosylation of its debenzoylated derivative (12) with TsCl (2 equiv.) in pyridine at room temperature for 20 h to give 6-tosylate (13) in 95% yield. Highly selective reduction of 6-tosyloxy group of 13, without reduction of CC double bond, was successfully carried out by $NaBH_3CN$ (7.5 mol) in the presence of NaI[5] (4 equiv.) in HMPT at 70-75°C for 15 h to yield the corresponding 6-deoxy derivative (14) in 79% yield. Finally, similar selective hydrogenolysis used for 6 gave ethyl p-[4-amino-2-(t-butoxycarbonyl)amino-2,4,6-trideoxy-α-D-glucopyranosyl]oxycinnamate (15*) in 75% yield.

In the course of above-mentioned transformation attempted 6-deoxygenation in advance of 4-amination, i.e., the operation sequence A → C → B, failed presumablly due to the effect of axially oriented acyloxy group on C-4.[6] For example, reduction of ethyl [3,4-di-O-acetyl-2-azido-2-deoxy-6-O-(p-tolylsylfonyl)-α-D-galactopyranosyl]oxycinnamate (16), which was derived from 6 by partial tosylation and successive acetylation in 64% yield, with $NaBH_3CN$ in the presence of NaI in HMPT at 70°C for 70 h gave the desired 6-deoxygenated product (17) only in 20% yield together with 5-enopyranoside (18) in 10% yield.

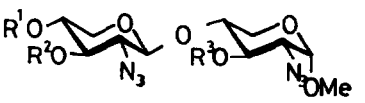
On the other hand, the disaccharides (29 and 30) were chosen as feasible candidates of synthetic intermediate for aminopentose disaccharide moiety. Azidonitration[3] of D-xylal diacetate followed by acetolysis gave peracetylated 2-azido-2-deoxy-D-xylopyranose (19) in 58% yield regio- and stereoselectively. Treatment of 19 with $TiCl_4$ or $TiBr_4$ in dichloromethane at room temperature gave the glycosyl chloride (20*) or bromide (21) in 77 and 63% yields, respectively. Furthermore, direct addition of methanol to the reaction mixture of azidonitration gave methyl 3,4-di-O-acetyl-2-azido-2-deoxy-α-D-xylopyranoside (22) in 84% yield. Deacetylation of 22 followed by benzoylation with BzCl and Et_3N (each 2 equiv.) in acetone gave 4-benzoate (23) in 75% yield together with 3,4-dibenzoate (20%). Then, treatment of 23 with BnBr and Ag_2O in benzene and with 2,3-dihydro-4H-pyran and pyridinium p-toluenesulfonate in dichloromethane gave, respectively, 3-O-benzyl derivative (24) in 74% yield and 3-O-tetrahydropyranyl derivative (25) quantitatively. Treatment of 24 and 25 with sodium methoxide in methanol yielded de-O-benzoylated derivatives (26 and 27, respectively).



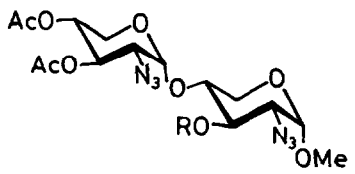
19 X=OAc
20 X=Cl(α)
21 X=Br(α)



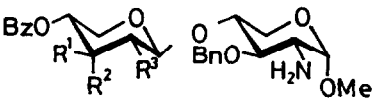
22 R^1=R^2=Ac
23 R^1=Bz, R^2=H
24 R^1=Bz, R^2=Bn
25 R^1=Bz, R^2=THP
26 R^1=H, R^2=Bn
27 R^1=H, R^2=THP



28 R^1=R^2=Ac, R^3=Bn
29 R^1=R^2=Ac, R^3=THP
30 R^1=R^2=H, R^3=Bn
31 R^1=Bz, R^2=Ms, R^3=Bn



32 R=Bn
33 R=THP



34 R^1=OMs, R^2=H, R^3=NH_2
35 R^1=H, R^2, R^3=NH
36 R^1=N_3, R^2=H, R^3=NH_2

Bn=$C_6H_5CH_2$, THP= 

Several glycosylation methods[8-11] reported to favor 1,2-trans glycoside (β-glycoside in this case) formation were tried using 20 or 21 as donors and 26 and 27 as acceptors. The best result was obtained by coupling between 20 and 26 with a ratio of 1:3 in the presence of $AgClO_4$ and 2,4,6-trimethylpyridine (each 1.2 equiv.) in nitromethane[11] at -10°C for 60 h. The β-(28*) and α-disaccharide (32) was obtained in 73% yield with a ratio of 1.2:1.0. However, condensation of 20 with 27 under the same conditions afforded the β-(29) and α-disaccharide (33) in 47% yield with a ratio of 1.0:7.5 presumably due to decrease of reactivity of the acceptor because of the balky tetrahydropyranyl group. On the other hand, trimethylsilyl trifluoromethanesulfonate (TMSOTf) was recently introduced as a new effective Lewis acid for glycosylation.[12] This reagent seems to be also promising in our case, giving almost equal stereoselectivity and yield with those obtained by $AgClO_4$. Even equimolar condensation of 19 and 26 in the presence of TMSOTf (1.2 equiv.) and molecular sieve 4A in dichloromethane at 0°C for 24 h gave 28 and 32 in 36% and 16% yields, respectively. The above metioned results concerning both yield and stereoselectivity are not competely sufficient, but may be accepted as reasonable condidering that peracetylated 2-azido sugars has in general very low reactivity as shown in the case of the corresponding aldohexose analogs.[8]

Moreover, on the synthesis of glycocinnamoylspermidines via the trisaccharides obtained by the coupling of diaminopentose moiety such as 28 with 15 the conversion of the non-reducing end into the corresponding 2,3-diamino-D-xylose derivative is necessary. Therefore, this conversion was examined with 28. Its 4-O-benzoyl-3-O-mesyl derivative (31*) obtained by partial benzoylation followed by mesylation was hydrogendyzed in the presence of PtO_2 to give 2,2'-diamino derivative (34). Treatment of 34 with NaOAc in N,N-dimethylformamide at 80°C for 3 h afforded quantitatively the epimino derivative (35), which could be converted into the desired precursor (36*) of 2',3'-diamino derivative by azidolysis with NaN_3 in 2-methoxyethanol at 110°C for 3 h in 63% yield with high regioselectivity.

The structures of all new compounds were confirmed by their spectroscopic data and elemental analyses. Physical properties and spectral data of some key compounds (the number with asterisk) are given in the end of this paper.[13]

References and Notes

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13) 5: mp 95-97°C, $[\alpha]_D$ +164.9°; IR ν_{max}^{KBr} 2125, 1755, 1740, 1715, and 1630 cm^{-1}; NMR δ 5.65 (d, $J_{1,2}$ 3.8 Hz, H-1), 1.94, 2.10, and 2.17 (each s, 9 H, Ac), 1.33 (t) and 4.24 (q) (J 7.2 Hz, Et), 6.30 and 7.61 (each d, J 16.2 Hz, olefinic), and 7.07 and 7.45 (each d, 4 H, J 9.0 Hz, aromatic).
11: $[\alpha]_D$ +160.9°; IR ν_{max}^{NaCl} 2130 cm^{-1}; NMR δ 3.92 (t, $J_{3,4}=J_{4,5}$ 10.5 Hz, H-4).
15: mp 167-170°C, $[\alpha]_D$ +191.0°; IR ν_{max}^{KBr} 3450, 1710, 1680, 1630, 1600, 1520, and 1505 cm^{-1}; NMR δ 5.56 (d, $J_{1,2}$ 3.0 Hz, H-1), 2.63 (t, $J_{3,4}=J_{4,5}$ 9.3 Hz, H-4), 1.23 (d, 3 H, $J_{5,6}$ 7.0 Hz, H-6), 5.20 (d, $J_{NH,2}$ 8.3 Hz), 1.44 (s, 9 H, Boc) and signals for the cinnamate portion like 3.
20: mp 71-72°C, $[\alpha]_D$ +149.4°; NMR δ 6.10 (d, $J_{1,2}$ 3.3 Hz, H-1), and 3.78 (dd, $J_{2,3}$ 9.9 Hz, H-2).
28: $[\alpha]_D$ +10.2°; IR ν_{max}^{NaCl} 2100, 1745, and 1605 cm^{-1}; NMR δ 4.67 (d, $J_{1,2}$ 3.0 Hz, H-1), 4.35 (d, $J_{1',2'}$ 7.8 Hz, H'-1), 3.44 (s, 3 H, OMe), 2.04 and 2.12 (each s, 6 H, Ac).
31: mp 128-130°C, $[\alpha]_D$ -32.3°; NMR δ 4.73 (dd, $J_{2',3'}$ 9.8 Hz, H-3') and 5.20 (dt, $J_{3',4'}=J_{4',5'a}$ 9.0 Hz, $J_{4',5'e}$ 5.1 Hz, H-4').
36: $[\alpha]_D$ -7.7°; IR ν_{max}^{NaCl} 3370, 3300, 2100, and 1725 cm^{-1}; NMR δ 4.56 (d, $J_{1,2}$ 1.5 Hz, H-1), 4.31 (d, $J_{1',2'}$ 7.5 Hz, H-1'), 2.75 (dd, $J_{2',3'}$ 10.2 Hz, H-2'), 3.39 (s, 3 H. OMe).
Optical rotations and NMR spectra at 100 MHz were recorded in $CHCl_3$ and $CDCl_3$, respectively.

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