ELSEVIER

www.elsevier.com/locate/carres

Carbohydrate Research 334 (2001) 177–182

CARBOHYDRATE RESEARCH

Synthesis and evaluation of a *C*-glycosyl nucleoside as an inhibitor of chitin synthase

Juan Xie,[a,*] Annie Thellend,[b] Hubert Becker,[b] Anne Vidal-Cros[b]

[a]*Laboratoire de Chimie des Glucides, Université Pierre et Marie Curie, CNRS UMR 7613, 4 Place Jussieu, F-75005 Paris, France*

[b]*Laboratoire de Chimie Organique Biologique, Université Pierre et Marie Curie, CNRS UMR 7613, 4 Place Jussieu, F-75005 Paris, France*

Received 30 May 2001; accepted 5 July 2001

Abstract

As part of our ongoing program devoted to inhibit chitin synthases, we have prepared a novel *C*-glycosyl nucleoside as metabolically stable substrate analog of UDP-GlcNAc. The synthetic strategy relies on the consecutive coupling of nucleoside and amino *C*-glycosyl moieties with L-tartaric acid. However, this compound inhibited only weakly chitin synthase I, with an IC_{50} value of 20 mM.

Keywords: *C*-Glycosyl nucleoside; Amino *C*-glycosyl compound; Substrate analog; Chitin synthase inhibitor

1. Introduction

Complex oligosaccharides are involved in a wide variety of biological function and consequently show enormous potential as therapeutic agents for a number of cases ranging from infectious diseases to cancer therapies.[1–5] Inhibition of glycosyltransferases, which are responsible for the biosynthesis of oligosaccharides, represents a valuable target.[6–12]

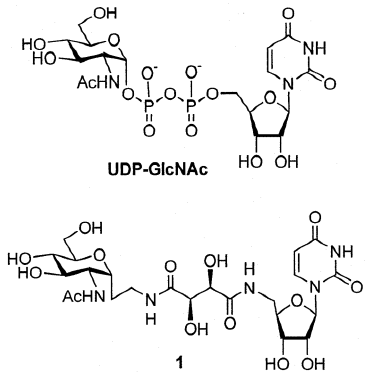
Chitin, the β-(1→4)-linked homopolymer of *N*-acetyl-D-glucosamine (GlcNAc), is the second most abundant biological polymer after cellulose and is found in a wide diversity of invertebrates and fungi. Since chitin is an essential structural component of the cell wall of most fungi and is absent in plants and mammals,[13] its biosynthesis seems to be an attractive target for novel fungicides lacking host toxicity. Chitin synthases (EC 2.4.1.16) are inverting, processive β-(1→4)-*N*-acetylaminoglucosaminyltransferases which catalyze the synthesis of chitin by transferring an *N*-acetyl-D-glucosamine (GlcNAc) residue from uridine-5′-diphosphoGlcNAc (UDP-GlcNAc) to a growing chain of β-(1→4)-linked GlcNAc residues.[14] The efficiency of chitin biosynthesis inhibition approach for antifungal therapeutics was exemplified by peptidyl nucleosides polyoxin D and nikkomycin Z. These natural nucleoside antibiotics have been demonstrated to be competitive inhibitors of chitin synthases and exhibit antifungal, insecticidal and acaricidal activities.[15,16]

As part of an ongoing program directed towards the design of potential chitin synthases inhibitors,[17] we have synthesized a novel *C*-glycosyl nucleoside **1** (Scheme 1) as a metabolically stable donor substrate analog. Since no data is still available concerning the

* Corresponding author. Tel.: +33-1-44275893; fax: +33-1-44275513.

E-mail address: xie@ccr.jussieu.fr (J. Xie).

0008-6215/01/$ - see front matter
PII: S0008-6215(01)00191-4



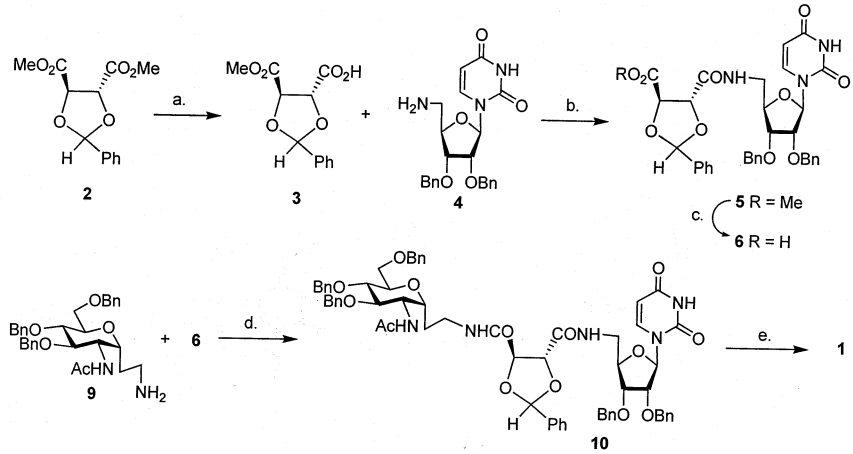
Scheme 1.

active site structure of any processive glycosyltransferase, the suitable spacer to be introduced between the *C*-linked *N*-acetyl-D-glucosamine residue and the uridine moiety to maximize interaction had to be found. A tartaric residue was introduced in the molecule to mimic the diphosphate moiety in the substrate for the chelating of divalent ion present at the active site of enzyme. Recently, an 1-*N*-iminosugar-based UDP-galactose analog bearing a vicinal diol linker has been shown to be a potent inhibitor of α-(1→3)-galactosyltransferase.[12] We report herein the synthesis of compound **1** and biological evaluation of this *C*-glycosyl nucleoside as inhibitor of chitin synthase.

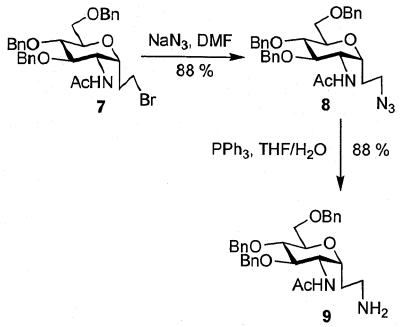
2. Results and discussion

The synthesis of compound **1** can be accomplished by successive coupling of protected L-tartaric acid **3** with the nucleoside **4** and the amino *C*-glycosyl compound **9** (Scheme 2).

The methyl hydrogen 2,3-*O*-benzylidene L-tartrate (**3**) was selected as the key building block so as to remove simultaneously all the protecting groups. Partial hydrolysis of the dimethyl 2,3-*O*-benzylidene L-tartrate (**2**) with potassium hydroxide at room temperature produced **3**[18], accompanied by some racemization product that can be easily eliminated by chromatography. The monoester **3** was obtained in 54% yield after purification. The asymmetry of the benzylidene group leads to each compound existing as an inseparable mixture of two diastereomers, complicating the ^{1}H and ^{13}C NMR spectra. For example, in the ^{1}H NMR spectrum of **3**, two methyl protons (δ 3.76, 3.82) and two benzylidene protons (δ 6.07, 6.09) were observed in quasi-equivalent proportions. Successful coupling of the acid **3** with 5′-amino-2′,3′-di-*O*-benzyl-5′-deoxyuridine (**4**)[17] was carried out with the DCC–HOBt method, affording **5** in 66% yield. The amide proton in the ^{1}H NMR spectrum of **5** resonated at δ 6.74, 7.04 (t, $J_{NH,5'}$ 6.0 Hz). Saponification of **5** with LiOH in MeOH yielded **6** in 91% yield. The amino *C*-glycosyl compound **9** was prepared from the bromo *C*-glycosyl derivative **7**[19] (Scheme 3). Treatment of **7** with an excess of NaN_3 in DMF afforded **8** in 88% yield. Selective reduction of the azido group is possible only with PPh_3–water, which gave **9** in 88% yield. Other reducing systems such as Raney Ni, Lindlar Pd or $HS(CH_2)_3SH$–$NaBH_4$ were unsuccess-



Scheme 2. (a) KOH. MeOH, THF, rt, 54%; (b) DCC, HOBt, CH_2Cl_2, THF, 0 °C to rt, 66%; (c) LiOH, MeOH, rt, 91%; (d) DCC, HOBt, CH_2Cl_2, THF, 0 °C to rt, 79%; (e) $Pd(OH)_2$, cyclohexene, MeOH, 90 °C, 100%.



Scheme 3.

ful; the starting material remained unchanged. Condensation of the acid **6** with the amino *C*-glycosyl compound **9** in the presence of DCC–HOBt afforded **10** in 79% yield. Finally, hydrogenolysis of **10** with $Pd(OH)_2$ in a mixture of cyclohexene and MeOH at 90 °C led to the target compound **1** in quantitative yield (Scheme 2).

Chitin synthase inhibition studies were performed using *Saccharomyces cerevisiae* microsomal preparations obtained as previously described.[20] Chitin synthase activity was assayed by measuring the rate of formation of ^{14}C-chitin from UDP-^{14}C-GlcNAc in the presence of the Mg^{2+} cation and trypsin. Activation of enzyme present as zymogen was performed by addition of trypsin in the assay. Using these conditions, ensuring a measure of mainly chitin synthase I activity, the K_m value for UDP-GlcNAc was 0.3 mM and the IC_{50} value for the compound **1** was 20 mM.

In summary, a new *C*-glycosyl nucleoside has been efficiently prepared, which appeared to be a very poor inhibitor of chitin synthase I.

3. Experimental

General procedures.—Melting points were measured with a Thomas–Hoover apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AGH-250 spectrometer unless noted in $CDCl_3$ solutions. Optical rotations were measured using a Perkin–Elmer 141 polarimeter and a 10-cm cell. Column chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H_2SO_4 and heating about 2 min at 300 °C. THF was distilled over Na and benzophenone prior to use. Dichloromethane was distilled over CaH_2. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie. High-resolution mass spectra (HRMS) were recorded using fast-atom bombardement (FAB) method at the Service de Spectromètrie de Masse de l'Ecole Normale Supérieure de Paris.

*(4*R*,5*R*)-2-Phenyl-[1,3]dioxolane-4,5-dicarboxylic acid monomethyl ester* (**3**)[18].—To a solution of KOH (231 mg, 4.135 mmol) in MeOH (2 mL), was added dropwise a solution of dimethyl 2,3-*O*-benzylidene-L-tartrate (**2**, 1 g, 3.759 mmol) in THF (10 mL) during 1 h. The solution was stirred at rt for 15 h. After concentration, the residue was dissolved in a mixture of 1:1 EtOAc–water (100 mL), neutralized with 10% HCl. The organic layer was washed with water (50 mL), dried ($MgSO_4$) and concentrated. The crude product was chromatographed (1:3 EtOAc–hexane to pure EtOAc) to give **3** as an oil (508 mg, 54%): R_f 0.41 (EtOAc); ^{1}H NMR: δ 7.51–7.34 (m, 5 H, Ph), 6.09 and 6.07 (2s, 1 H, H-2), 6.00 (s, 1 H, OH), 4.97 (d, 1 H, H-5), 4.84 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 3.82 and 3.76 (2s, 3 H, CH_3). Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.28; H, 4.71.

*(4*R*,5*R*)-5-[(3′,4′-di-O-benzyl-5′-deoxyuridin-5′-yl)-carbamoyl]-2-phenyl-[1,3]dioxolane-4-carboxylic acid methyl ester* (**5**).—To a solution of acid **3** (100 mg, 0.397 mmol) in THF (1 mL) at 0 °C, were added successively 5′-amino-2′,3′-di-*O*-benzyl-5′-deoxy-uridine (**4**)[17] (168 mg, 0.397 mmol) in CH_2Cl_2 (1 mL), HOBt (54 mg, 0.397 mmol) in THF (0.5 mL) and DCC (82 mg, 0.397 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at 0 °C for 1 h and at rt for 15 h. The precipitated DCU was then filtered and the solution was diluted in EtOAc (20 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The crude product was chromatographed with 3:2 EtOAc–hexane to give **5** as a white solid (172 mg, 66%): mp (dec) 74-75 °C, R_f 0.31 (2:1 EtOAc–hexane); ^{1}H NMR: δ 8.81 (s, 0.5 H, NH), 8.47 (s, 0.5 H,

NH), 7.25–7.17 (m, 15 H, Ph), 7.04 (t, 0.5 H, $J_{NH,5'}$ 6.0 Hz, NH), 7.01 (d, 0.5 H, *J* 8.0 Hz, CH=), 6.85 (d, 0.5 H, *J* 8.0 Hz, CH=), 6.74 (t, 0.5 H, $J_{NH,5'}$ 6.0 Hz, NH), 6.04 (s, 0.5 H, H-2), 5.77 (s, 0.5 H, H-2), 5.56 (d, 0.5 H, $J_{1',2'}$ 3.0 Hz, H-1′), 5.48 (d, 0.5 H, CH=), 5.47 (d, 0.5 H, CH=), 5.34 (d, 0.5 H, $J_{1',2'}$ 3.3 Hz, H-1′), 4.90 (d, 0.5 H, $J_{4,5}$ 4.6 Hz, H-4), 4.80 (d, 0.5 H, $J_{4,5}$ 3.8 Hz, H-4), 4.74 (d, 0.5 H, H-5), 4.64 (d, 0.5 H, H-5), 4.63–4.35 (m, 4 H, 2 × OCH_2), 4.22–3.66 (m, 3 H, H-2′,3′,4′), 3.77 and 3.70 (2s, 3 H, CH_3), 3.48–3.45 (m, 2 H, H-5′). ^{13}C NMR: δ 169.3, 168.7, 168.6, 162.6, 162.5, 149.0 (CO); 141.0, 139.8 (C=); 136.2, 136.0, 134.4, 134.2 (C_{ipso}); 129.2, 129.1, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.1, 125.8 (CH–Ph); 105.1, 105.0 (C-2); 101.4 (C=), 92.4, 90.5 (C-1′); 79.4, 79.3, 77.3, 77.2, 77.0, 76.9 (CH); 71.8, 71.6, 71.5, 71.4 (CH_2), 51.8 (CH_3), 39.9, 39.6 (C-5′). Anal. Calcd for $C_{35}H_{35}N_3O_{10}$: C, 63.92; H, 5.36; N, 6.39. Found: C, 63.78; H, 5.32; N, 6.47.

*(4*R,*5*R*)-5-[(3′,4′-di-*O*-benzyl-5′-deoxyuridin-5′-yl)-carbamoyl]-2-phenyl-[1,3]dioxolane-4-carboxylic acid* (**6**).—To a solution of ester **5** (100 mg, 0.152 mmol) in MeOH (1 mL), was added $LiOH·H_2O$ (10 mg, 0.228 mmol). The reaction was allowed to continue 15 h at rt. After concentration, EtOAc (20 mL) and water (10 mL) were added. The mixture was neutralized with HCl 10%. The resulting organic layer was washed with water (20 mL), dried ($MgSO_4$) and concentrated to give the title compound as white solid (89 mg, 91%): mp (dec) 86–88 °C, R_f 0.22 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR: δ 9.60 and 9.48 (2s, 1 H, NH), 7.46–7.15 (m, 15 H, Ph), 6.97 and 6.84 (2d, 1 H, *J* 8.0 Hz, CH=), 6.00 and 5.85 (2s, 1 H, H-2), 5.50 (d, 1 H, CH=), 5.42 and 5.25 (2d, 1 H, $J_{1',2'}$ 3.0 Hz, H-1′), 4.83–4.31 (m, 6 H, H-4,5, 2 × OCH_2), 4.13–3.44 (m, 5 H, H-2′,3′,4′,5′).

*1-Azido-2-(2′-*N*-acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-*D*-glucopyranosyl) ethane* (**8**).—A mixture of bromide **7**[19] (600 mg, 1.033 mmol) and NaN_3 (1.342 g, 20.654 mmol) in anhyd DMF (5 mL) was heated at 70 °C for 15 h. Water (50 mL) was then added before extraction with EtOAc (3 × 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated to give **8** as white solid (497 mg, 88%): mp 100 °C, $[\alpha]_D$ +11.1 (*c* 1, CH_2Cl_2), R_f 0.47 (1:1 EtOAc–hexane); ^{1}H NMR: δ 7.47–7.35 (m, 15 H, Ph), 6.76 (d, 1 H, $J_{NH,2'}$ 9.5 Hz, NH), 4.77–4.53 (m, 6 H, 3 × OCH_2), 4.37 (m, 1 H, H-5′), 4.31–4.28 (m, 1 H, H-2′), 4.20–4.15 (m, 1 H, H-1′), 4.00 (dd, 1 H, $J_{5',6'a}$ 7.3, J_{gem} 9.8 Hz, H-6′a), 3.87 (dd, 1 H, $J_{5',6'b}$ 6.8 Hz, H-6′b), 3.82–3.80 (m, 1 H, H-4′), 3.71–3.70 (m, 1 H, H-3′), 3.51–3.49 (m, 2 H, H-1), 2.01 (s, 3 H, CH_3), 1.87–1.78 (m, 2 H, H-2). ^{13}C NMR: δ 170.3 (CO), 138.5, 137.9, 137.7 (C_{ipso}); 129.0, 128.9, 128.6, 128.4, 128.2, 128.1, 128.0 (CH–Ph), 75.4, 74.6, 73.5 (C-3′,4′,5′); 73.7, 72.5, 72.3 (OCH_2); 68.1 (C-6′), 65.5 (C-1′), 48.3 (C-1), 48.0 (C-2′), 31.3 (C-2), 23.7 (CH_3). Anal. Calcd for $C_{31}H_{36}N_4O_5$: C, 68.35; H, 6.66; N, 10.29. Found: C, 68.58; H, 6.72; N, 10.20.

*1-Amino-2-(2′-*N*-acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-*D*-glucopyranosyl) ethane* (**9**).—To a solution of **8** (370 mg, 0.680 mmol) and PPh_3 (196 mg, 0.748 mmol) in THF (3.4 mL), was added water (136 μL, 0.755 mmol). The reaction was allowed to continue at rt for 4 days. After concentration, the crude product was chromatographed (4:1 then 3:2 CH_2Cl_2–MeOH) to give the title compound as a white solid (310 mg, 88%): mp 139–140 °C, $[\alpha]_D$ +12.2 (*c* 1, CH_2Cl_2), R_f 0.40 (4:1 CH_2Cl_2–MeOH); ^{1}H NMR: δ 7.45–7.30 (m, 15 H, Ph), 6.70 (d, 1 H, $J_{NH,2'}$ 9.8 Hz, NH), 4.73–4.31 (m, 6 H, 3 × OCH_2), 4.28 (m, 1 H, H-5′), 4.20 (m, 1 H, H-2′), 4.10 (m, 1 H, H-1′), 4.01 (dd, 1 H, $J_{5',6'a}$ 8.0, J_{gem} 10.0 Hz, H-6′a), 3.76–3.67 (m, 2 H, H-4′,6′b), 3.57 (m, 1 H, H-3′), 2.85 (t, 2 H, $J_{1,2}$ 6.5 Hz, H-1), 2.15 (s, 3 H, CH_3), 1.91 (s, 2 H, NH_2), 1.80–1.48 (m, 2 H, H-2). ^{13}C NMR: δ 170.4 (CO), 138.4, 138.0, 137.7 (C ipso); 128.9, 128.8, 128.5, 128.3, 128.2, 128.0 (CH–Ph); 75.1 (C-5′), 74.8 (C-4′), 73.7 (C-3′), 73.6, 72.6, 72.3 (OCH_2); 67.8 (C-6′), 66.8 (C-1′), 48.5 (C-2′), 39.3 (C-2); 34.8 (C-1), 23.7 (CH_3). Anal. Calcd for $C_{31}H_{38}N_2O_5$: C, 71.79; H, 7.38; N, 5.40. Found: C, 71.66; H, 7.42; N, 5.44.

*(4*R,*5*R*)-2-Phenyl-[1,3]dioxolane-4,5-dicarboxylic acid 4-{[2-(2′-*N*-acetylamino-4′,5′,6′-tri-*O*-benzyl-2′-deoxy-α-*D*-glucopyranosyl)-ethyl]-amide}-5-[(3′,4′-di-*O*-benzyl-5′-deoxyuridin-5′-yl)-amide]* (**10**).—To a solution of

acid **6** (84 mg, 0.131 mmol) in THF (1 mL) at 0 °C, were added successively amine **9** (68 mg, 0.131 mmol) in CH_2Cl_2 (1 mL), HOBt (18 mg, 0.131 mmol) in THF (0.5 mL) and DCC (27 mg, 0.131 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at 0 °C for 1 h and at rt for 15 h. The precipitated DCU was then filtered and the crude product was purified by preparative TLC with 15:1 CH_2Cl_2–MeOH as eluent to give **10** as a white solid (117 mg, 79%): mp 90–92 °C; R_f 0.51 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR: δ 9.15 (s, 1 H, NH), 7.98–7.91 (m, 1 H, NH), 7.76–7.31 (m, 31 H, NH and 6 × Ph), 7.21 and 7.16 (2d, 1 H, J 7.3 Hz, CH=), 6.86 and 6.84 (2d, 1 H, $J_{NH,2'}$ 9.6 Hz, NHAc), 6.18 and 6.08 (2s, 1 H, H-2), 5.74 and 5.71 (2d, 1 H, J 7.3 Hz, CH=), 5.67 and 5.59 (2d, 1 H, $J_{1',2'}$ 3.8 Hz, H-1′ uridine), 4.93–4.31 (m, 14 H), 4.20–3.25 (m, 10 H), 2.15 (s, 3 H, CH_3), 2.03–1.92 (m, 2 H, CH_2 ethylene). ^{13}C NMR: δ 170.6, 170.5, 169.7, 169.4, 163.7, 150.3 (CO); 142.2, 141.6 (C= uridine), 138.3, 138.0, 137.7, 136.0 (C_{ipso}); 130.4, 129.0, 128.7, 128.6, 128.4, 128.2, 128.0, 127.3 (CH–Ph); 106.1, 105.5 (C-2); 102.9 (C= uridine), 93.3, 92.4 (C-1′ uridine); 81.3, 80.9, 78.7, 78.5, 75.0, 74.4 (CH); 73.4, 73.2, 72.9, 72.6, 72.2 (OCH_2); 68.1, 67.9 (CH); 67.5, 66.8 (OCH_2); 48.5 (CH–N), 40.6, 38.0, 37.7, 30.9 (CH_2); 23.7 (CH_3). Anal. Calcd for $C_{65}H_{69}N_5O_{14}$: C, 68.23; H, 6.08; N, 6.12. Found: C, 68.01; H, 6.17; N, 6.23. FAB-HRMS Calcd for $C_{65}H_{70}N_5O_{14}$ $[M+H]^+$ 1144.4919. Found 1144.4908.

*(2*R*,3*R*)*-N-*[2-(2′*-N-*Acetylamino-2′-deoxy-α-*D*-glucopyranosyl)-ethyl]*-N′-*(5′-deoxyuridin-5′-yl)-2,3-dihydroxysuccinamide* (**1**).—To a solution of **10** (50 mg, 0.044 mmol) in MeOH (3 mL), were added cyclohexene (7 mL) and 20% $Pd(OH)_2$ (48 mg). The suspension was heated at 90 °C for 17 h. After filtration and concentration, the title compound was obtained as a white solid (27 mg, 100%): mp 200–203 °C, $[\alpha]_D$ + 78 (*c* 0.5, water), R_f 0.28 (3:2 CH_2Cl_2–MeOH); ^{1}H NMR (CD_3OD): δ 7.62 (d, 1 H, J 8.0 Hz, CH=), 5.71 (d, 1 H, $J_{1',2'}$ 5.0 Hz, H-1′ uridine), 5.67 (d, 1 H, CH=), 4.49 (m, 2 H), 4.23 (t, 1 H, $J_{1',2'} = J_{2',3'} = 5.0$ Hz, H-2′ uridine), 4.20–3.90 (m, 4 H), 3.85 (dd, 1 H, $J_{5',6'}$ 2.0, J_{gem} 11.5 Hz, H-6′), 3.76–3.49 (m, 6 H), 3.32–3.25 (m, 2 H, CH_2N ethylene), 1.83 (s, 3 H, CH_3), 1.82–1.50 (m, 2 H, CH_2 ethylene). ^{13}C NMR (CD_3OD): δ 175.5, 175.0, 174.0, 166.6, 152.8 (CO); 143.8, 103.7 (C= uridine); 92.2 (C-1′ uridine), 84.3, 75.6, 75.1, 74.6, 73.3, 73.0, 72.7, 72.3 (CH), 63.7 (C-6′), 55.2, 50.2 (CH), 41.6, 37.6, 26.8 (CH_2); 23.1 (CH_3). FAB-HRMS Calcd for $C_{23}H_{35}N_5O_{14}Na$ $[M+Na]^+$ 628.2078. Found 628.2092.

Chitin synthase assay.—Chitin synthase assays were performed in a standard 50 μL volume containing 50 mM Tris–HCl pH 7.4, 1 mM UDP-GlcNAc, 0.01 mCi UDP[U-^{14}C]-GlcNAc, 40 mM GlcNAc, 0.2% digitonine, 5 mM $Mg(OAc)_2$, 1 mg trypsin and 200 mg protein. Incubations were performed at 30 °C for 20 min and terminated by adding 1 mL of 10% trichloroacetic acid. After filtration through a glass fiber filter (GF/C Whatman) and washing with 3:7 AcOH–EtOH, discs were dried and radioactivity measured in a liquid scintillation counter.

Acknowledgements

The authors thank the undergraduate students Sébastian Bareyt, François Durrat and Claire Ferret-Courtel for the assistance in the synthetic work. We are grateful to CNRS (Centre National de Recherche Scientifique) for financial support (PCV program).

References

1. Hart, G. W. *Curr. Opin. Cell Biol.* **1992**, *4*, 1017–1023.
2. Sears, P; Wong, C. H. *Cell. Mol. Life Sci.* **1998**, *54*, 223–252.
3. Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317–11362.
4. Wong, C. H. *Acc. Chem. Res.* **1999**, *32*, 376–385.
5. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215–3237.
6. Palcic, M. M.; Heerze, L. D.; Srivastava, O. P.; Hindsgaul, O. *J. Biol. Chem.* **1989**, *264*, 17174–17181.
7. Schmidt, R. R.; Frische, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1747–1750.
8. Lu, P. P.; Hindsgaul, O.; Campston, C. A.; Palcic, M. M. *Bioorg. Med. Chem.* **1996**, *4*, 2011–2022.
9. Hashimoto, H.; Endo, T.; Kajihara, Y. *J. Org. Chem.* **1997**, *62*, 1914–1915.
10. Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007–3018.
11. Takayama, S.; Chung, S. J.; Igarashi, Y.; Ichigawa, Y.; Sepp, A.; Lechler, R. I.; Wu, J.; Hayashi, T.; Siuzdak, G.; Wong, C. H. *Bioorg. Med. Chem.* **1999**, *7*, 401–409.
12. Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Am. Chem. Soc.* **1999**, *121*, 5829–5830.

13. Groll, A. H.; De Lucca, A. J.; Walsh, T. J. *Trends Microbiol*. **1998**, *6*, 117–124.
14. Bulawa, C. E. *Annu. Rev. Microbiol*. **1993**, *47*, 505–534.
15. Calib, E. *Antimicrob. Agents Chemother*. **1991**, *35*, 170–173.
16. Isono, K.; Nagatsu, J.; Kobinata, K.; Kasai, K.; Suzuki, S. *Agric. Biol. Chem*. **1967**, *31*, 190–199.
17. Grugier, J.; Xie, J.; Duarte, I.; Valéry, J. M. *J. Org. Chem*. **2000**, *65*, 979–984.
18. Roush, W. R.; Ratz, A. M.; Jablonowski, J. A. *J. Org. Chem*. **1992**, *57*, 2047–2052.
19. Gaurat, O.; Xie, J.; Valéry, J. M. *Tetrahedron Lett*. **2000**, *41*, 1187–1189.
20. Orlean, P. *J. Biol. Chem*. **1987**, *262*, 5732–5739.