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Towards stable di-carba analogues of guanofosfocins

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ABSTRACT

Guanofosfocins are strong inhibitors of chitin synthases, but also very prone to hydrolytic cleavage. Two advanced intermediates **15** and **20** for the synthesis of stable di-carba-guanofosfocins were prepared via ester **11**. Acylation of the allylic C-glycoside **6** with riburonic acid chloride **10** afforded ester **11** in 79% yield. This ester was converted to **15** in four steps and in 54% yield and to **20** in eight steps and in 20% yield.

Guanofosfocins (Fig. 1) were isolated in 1996 by *Nippon Roche* from the fermentation broth of *Streptomyces* and *Trichoderma* spp.[1] They strongly inhibit chitin synthases from *Saccharomyces cerevisiae* and *Candida albicans* and β-glucan synthase from *C. albicans*. The investigation of their mode of action was hampered by their high instability. The structure of the guanofosfocins is characterised by a C(8) substituted guanosine moiety, a 1,3-di-O-substituted α-D-mannopyranosyl residue, an 11-membered ring, and a pyrophosphate substituent. We assume that the two activated *O,O*-acetal moieties of the guanofosfocins are responsible for their instability, and, for this reason, designed the C-glycoside analogue **1** (Fig. 1) as a synthetic target. An approach towards a different, carba-sugar type, analogue was reported by Sugimura and Hosogai.[2]

The main challenges in the synthesis of **1** may be characterised as follows: incorporation of a methylene group between the mannosyl and guanyl moieties, formation of an ether bond between the O–C(3) of the mannosyl moiety and C(5) of the ribosyl unit, and cyclisation to an 11-membered ring.

The problem of incorporating a methylene group between the mannosyl and guanyl moieties was solved earlier in our group.[3] The guanine ring was constructed by cyclising 4-acylamino-5-nitrosopyrimidines.[4] This strategy led to the acid **2** which, however, did not undergo the planned macrolactonisation. The mannopyranosyl-C-glycoside unit of **2** adopts a $^1C_4$ and the guanosine unit a *syn* conformation, favoured by an intramolecular hydrogen bond between COOH and N(3), both factors disfavouring the macrolactonisation. Looking for an alternative strategy to close the 11-membered ring, we opted for an intramolecular N-glycosylation, and report on the synthesis of intermediates suitable to explore this approach.

The allyl C-glycoside **6** (Scheme 1) was prepared from methyl α-D-mannopyranoside (**3**) that was selectively protected via the stannylene acetal and methoxybenzylated to form **4**. The remaining hydroxy groups were benzylated to obtain **5** in a yield of 49% from **3**.[5] Treating **5** with allylTMS (3.4 equiv) and TMSOTf (0.5 equiv) resulted both in allylation and deprotection of the PMB–OR group to yield 73% of **6**.[6] The cleavage of the PMB–OR group preceded allylation, as treating **5** with 1 equiv of allylTMS and 0.5 equiv of TMSOTf led selectively to **7**.

The known riburonic acid **9** (Scheme 2) was prepared by periodate cleavage of the C(5)–C(6) bond of the vicinal diol **8**,[7] and oxidation of the resulting aldehyde with sodium chlorite–hydrogen peroxide.[8] Diol **8** was prepared in five steps and in 21% overall yield from D-glucose.[9]

The common intermediate **11** was synthesised by acylating alcohol **6** (Scheme 2) with the acid chloride **10**, and then subjected to ozonolysis. Reductive workup with dimethyl sulfide and oxidation of the resulting aldehyde furnished the carboxylic acid **12** that was converted to the acyl chloride **13** using oxalyl chloride/DMF. The amide **14** was obtained upon treating **13** with 6-(benzyloxy)-5-nitrosopyrimidine-2,4-diamine in the presence of K_2CO_3. These conditions greatly facilitated the workup, merely filtration through Celite and evaporation being sufficient, and furnished very pure crude **14** that was used directly in the next step. This procedure is preferred to chromatography on silica gel that resulted in low yields of **14** contaminated with impurities, as shown by the ^{1}H NMR spectra. The formation of **14** proceeds presumably via the O-acylated (O-acyloximino) intermediate,[4] as indicated by an initial colour change from blue to green (in

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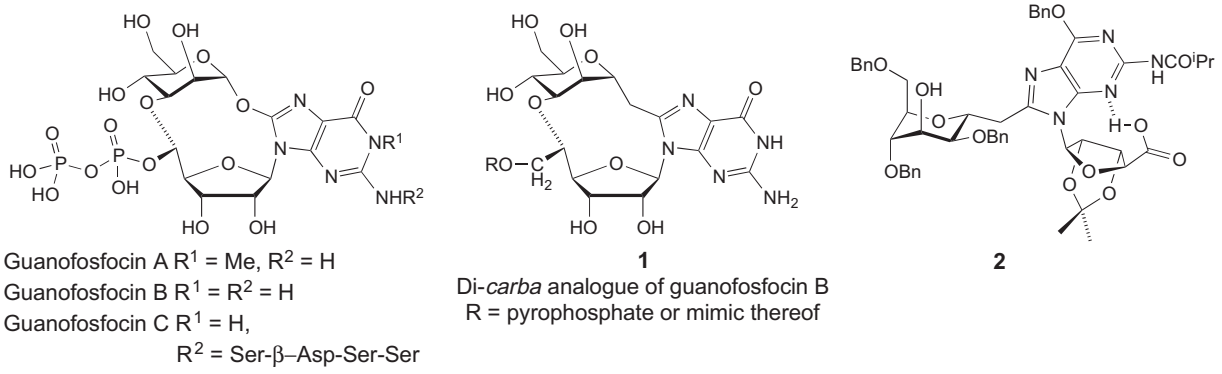
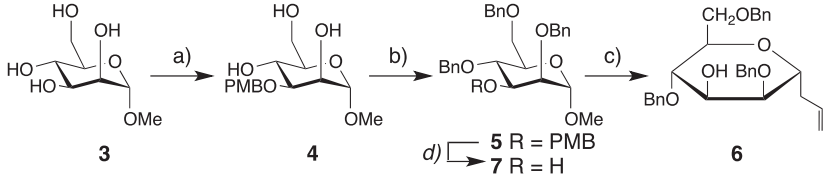
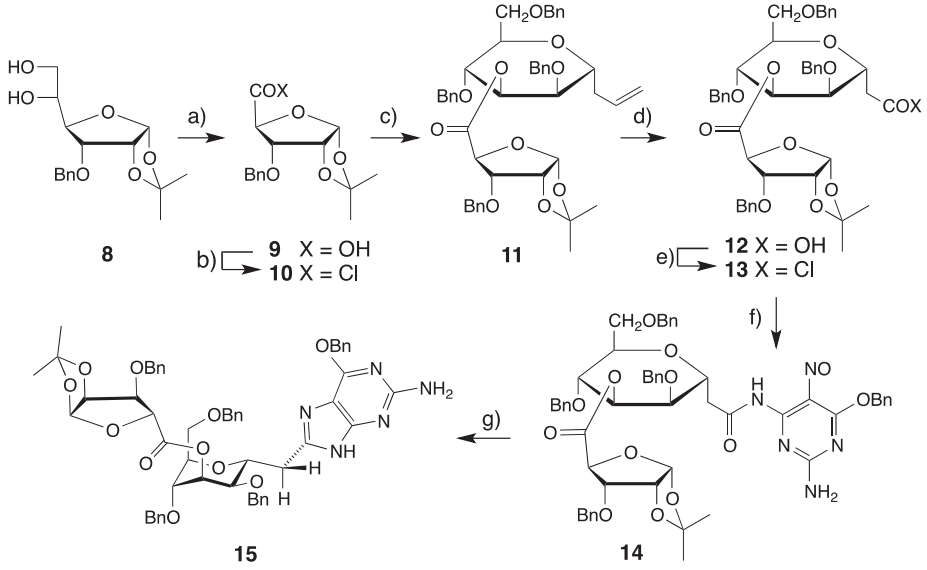


Figure 1. Structure of guanofosfocins, analogues, and an advanced intermediate **2**.



Scheme 1. Reagents and conditions: (a) (1) Bu_2SnO, MeOH, reflux; (2) PMBCl, CsF, DMF; (b) BnBr, NaH, TBAI, DMF; 49% from **3**; (c) allylTMS (3.4 equiv), TMSOTf (0.5 equiv), MeCN, −10°→25°; 73%; (d) allylTMS (1 equiv), TMSOTf (0.5 equiv), MeCN, −15°→5°; 73%.

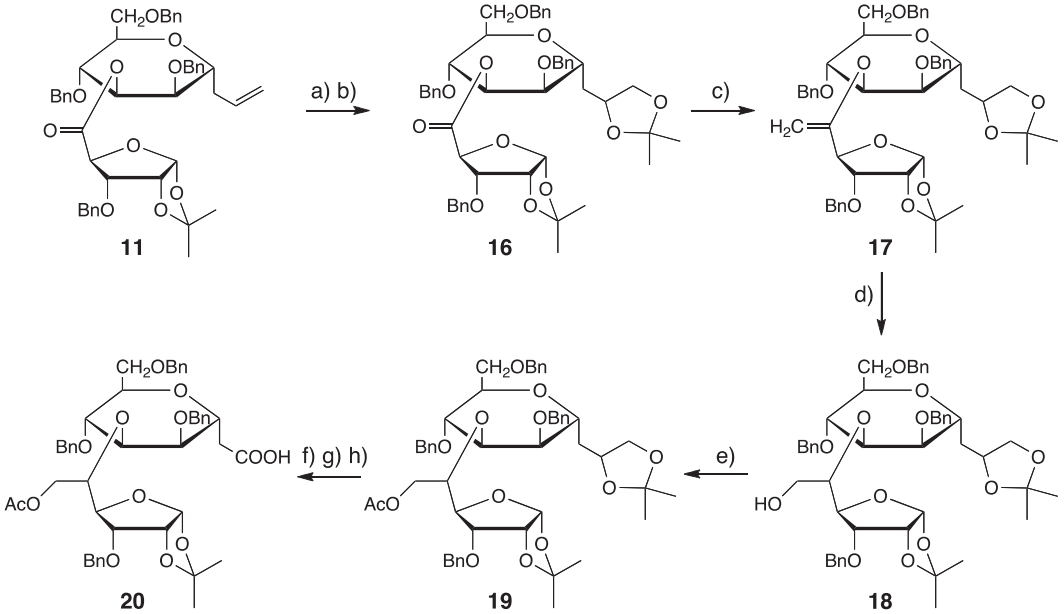


Scheme 2. Reagents and conditions: (a) (1) $NaIO_4$, MeOH, H_2O; (2) H_2O_2, $NaClO_2$, NaH_2PO_4, CH_3CN, H_2O; 73%; (b) $(COCl)_2$, DMF, CH_2Cl_2; (c) **6+10**, py, DMAP, CH_2Cl_2; 79%; (d) (1) O_3, CH_2Cl_2, *n*-pentane, −90°; (2) Me_2S; (3) 2-methyl-2-butene, *t*-BuOH, $NaClO_2$, NaH_2PO_4, H_2O; 85%; (e) (1) $(COCl)_2$, DMF, CH_2Cl_2; (f) **13**, 2,4-diamino-6-(benzyloxy)-5-nitrosopyrimidine, K_2CO_3, THF, −60°→25°; (g) DPPE, *p*-xylene, reflux; 63% from **12**.

THF) in the course of the reaction. The isolated amide **14** is blue oil. It was treated with 1,2-bis(diphenylphosphino)ethane (DPPE) in boiling *p*-xylene to provide guanine **15** in a yield of 63% from **12**. The transformation of the nitroso group in the course of the reaction was accompanied by a typical colour change from blue-green to brown.

The second intermediate was synthesized as shown in Scheme 3. The double bond of **11** was dihydroxylated, and the resulting diol protected as isopropylidene acetal **16** that was obtained in a yield of 79% as a mixture of two diastereoisomers. The carbonyl group of **16** was methylenated with Petasis' reagent to yield 68% of **17**. Hydroboration (BH_3·THF) and workup with H_2O_2/NaOH provided **18** that was acetylated to afford **19** as a mixture of four diastereoisomers which were not separated. Selective hydrolysis with aqueous acetic acid of the more labile dioxolane ring of **19**, periodate cleavage of the resulting diol, and oxidation of the resulting aldehyde led to the desired carboxylic acid **20** that was obtained as ca. 1:1 mixture of two diastereoisomers in a yield of 20% from **11**.

In conclusion, we have prepared two advanced intermediates for the synthesis of analogues of guanofosfocins.[10] Both intermediates derive from ester **11** which was readily obtained in gram quantities. This divergent route allows selecting the order of the final key steps in our projected synthesis of di-carba guanofosfocins (formation of the guanine ring, N-glycosylation, and methylenation of the ester group).



Scheme 3. Reagents and conditions: (a) OsO_4, NMO, acetone, H_2O; 93%; (b) 2,2-dimethoxypropane, *p*-TsOH, acetone; 85%; (c) Cp_2TiMe_2, toluene, reflux; 68%; (d) (1) BH_3·THF, $CHCl_3$; (2) H_2O_2, NaOH, H_2O, 0°; 60%; (e) Ac_2O, DMAP, Et_3N, CH_2Cl_2; 98%; (f) AcOH, H_2O; (g) $NaIO_4$, MeOH, H_2O; (h) H_2O_2, $NaClO_2$, NaH_2PO_4, CH_3CN, H_2O; 62% from **19**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.102.

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10. All compounds gave satisfactory analytical data (^{1}H NMR, ^{13}C NMR, IR, and elemental analysis or HR-MS). Data of key compounds follow. Compound **11**: Colourless oil; R_f (cyclohexane/AcOEt 5:1) 0.17; $[\alpha]_D^{25}$ +30.2 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3088 (w), 3067 (w), 3033 (w), 3010 (m), 2937 (w), 2871 (w), 1951 (w), 1873 (w), 1810 (w), 1752 (m), 1642 (w), 1606 (w), 1586 (w), 1496 (w), 1454 (m), 1384 (m), 1375 (m), 1219 (m), 1163 (m), 1094 (s), 1029 (s), 917 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz; assignments based on a DQFCOSY spectrum): δ 7.34–7.16 (m, 20 arom. H), 5.88–5.72 (m, overlapped with d of H–C(1'), $CH_2CH{=}CH_2$), 5.75 (d, *J* = 3.7 Hz, H–C(1')), 5.51 (dd, *J* = 5.6, 3.1 Hz, H–C(4)), 5.16–5.04 (m, $CH_2CH{=}CH_2$), 4.67–4.42 (m, 8PhCH, H–C(4')), 4.27 (br t, *J* = 3.7 Hz, H–C(2')), 3.98–3.88 (m, irrad. at 2.39→change, H–C(2)), H–C(6)), 3.85 (br t, *J* = 5.6 Hz, irrad. 5.51→d, *J* = 5.0 Hz, irrad. at 3.93→change, H–C(3)), 3.79–3.73 (m, H–C(5), H–C(3')), 3.72 (dd, *J* = 10.6 Hz, 5.6, H_a–C(1)), 3.67 (dd, *J* = 10.6, 5.0 Hz, H_b–C(1)), 2.42 (br dd, *J* ≈ 14.8, 6.8 Hz, $CH_aCH{=}CH_2$), 2.36 (br dd, *J* ≈ 14.9, 7.5 Hz, $CH_bCH{=}CH_2$), 1.57, 1.32 (2s, Me_2C); ^{13}C NMR ($CDCl_3$, 75 MHz; assignments based on a HSQC spectrum): δ 169.68 (s, C=O), 138.40, 137.97, 137.90, 137.53 (4s), 134.30 (d, $CH_2CH{=}CH_2$), 128.59–127.69 (several d, arom. CH), 117.56 (t, $CH_2CH{=}CH_2$), 113.67 (s, Me_2C), 104.93 (d, C(1')), 80.66 (d, C(3')), 78.16 (d, C(2')), 77.60 (d, C(4')), 75.21 (d, C(5)), 74.37 (d, C(3)), 73.79 (d, C(2)), 73.44, 73.26, 72.80, 71.98 (4t, 4 $PhCH_2$), 71.39 (d, C(6)), 71.06 (d, C(4)), 68.61 (t, C(1)), 35.16 (t, $CH_2CH{=}CH_2$), 27.15, 26.76 (2q, Me_2C). HR-MALDI-MS: 789.3059 (73, [M+K]$^+$, $C_{45}H_{50}KO_{10}^+$; calcd 789.3041), 773.3284 (100, [M+Na]$^+$, $C_{45}H_{50}NaO_{10}^+$; calcd 773.3302). Anal. calcd for $C_{45}H_{50}O_{10}$ (750.87): C, 71.98; H, 6.71. Found: C, 71.95; H, 6.78. Compound **15**: Yellowish oil; R_f ($CHCl_3$/AcOEt 1:4) 0.22; IR ($CHCl_3$): ν_{max} 3527 (w), 3421 (w), 3362 (w), 3257 (w), 3090 (w), 3067 (w), 3034 (w), 3008 (w), 2994 (w), 2938 (w), 2872 (w), 1951 (w), 1877 (w), 1809 (w), 1758 (m), 1625 (s), 1591 (s), 1524 (w), 1496 (w), 1466 (m), 1455 (m), 1409 (m), 1385 (m), 1376 (m), 1356 (m), 1324 (m), 1268 (m), 1219 (m), 1163 (m), 1147 (m), 1091 (s), 1038 (m), 1029 (m), 991 (m), 912 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz; assignments based on a DQFCOSY spectrum): δ 11.35 (br s, exchange with CD_3OD, H–N(9'')); 7.54–6.94 (m, 25 arom. H); 5.77 (d, *J* = 3.5 Hz, H–C(1')); 5.68 (br t, *J* ≈ 2.5 Hz, H–C(4)); 5.54 (br s, $PhCH_2$); 4.84 (br s, exchange with CD_3OD, NH_2); 4.65–4.28 (m, 7 PhCH, H–C(4')); 4.25 (br t, *J* = 4.0 Hz, H–C(2')); 4.19–4.13 (m, PhCH, H–C(2)); 4.08 (br t, *J* = 9.3 Hz, H–C(6)); 3.74–3.64 (m, H_a–C(1), H–C(5), H–C(3')); 3.53 (br s, H–C(3)); 3.39 (br d, *J* ≈ 14.6 Hz, H_b–C(1), H_a–C(7)); 2.96 (dd, *J* = 15.6, 9.8 Hz, H_b–C(7)); 1.57, 1.30 (2s, Me_2C). ^{13}C NMR ($CDCl_3$, 100 MHz; assignments based on a HSQC spectrum): δ 169.48 (s, C=O), 160.30, 158.87, 155.70 (3s, C(2''), C(4''), C(6'')); 148.38 (s, C(8'')); 137.68, 137.33, 137.28, 137.19, 136.89 (5s); 130–127 (several d); 114.89 (s, C(5'')); 113.65 (s, Me_2C); 105.15 (d, C(1')); 80.68 (d, C(3')); 77.77 (d, C(2')); 77.23 (d, C(4')); 74.81 (d, C(3)); 74.42 (d, C(2)); 74.34 (d, C(5)); 73.16, 72.68, 72.47, 72.07 (4t, 4 $PhCH_2$); 68.25 (d, C(6)); 67.93 (t, $PhCH_2$); 67.26 (d, C(4)); 66.64 (t, C(1)); 31.49 (t, C(7)); 27.17, 26.78 (2q, Me_2C). HR-MALDI-MS: 1024.363 (4, [M−H+K+Na]$^+$, $C_{55}H_{56}KN_5NaO_{11}^+$; calcd 1024.3511), 1008.386 (24, [M−H+2Na]$^+$, $C_{55}H_{56}N_5Na_2O_{11}^+$; calcd 1008.3772), 1002.378 (21, [M+K]$^+$, $C_{55}H_{57}KN_5O_{11}^+$; calcd 1002.3692), 986.3976 (73, [M+Na]$^+$, $C_{55}H_{57}N_5NaO_{11}^+$; calcd 986.3952); 964.4109 (100, [M+H]$^+$, $C_{55}H_{58}N_5O_{11}^+$; calcd 964.4133). Compound **20** (mixture of 2 diastereoisomers): Colourless gum; IR ($CHCl_3$): ν_{max} 2962 (w), 1740 (m), 1494 (m), 1454 (w), 1371 (m), 1259 (s), 1092 (s), 1026 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.12 (m, arom. H), 5.76 (d, *J* = 3.7 Hz), 5.62 (dd, *J* = 3.4, 3.8 Hz), 5.57 (d, *J* = 3.6 Hz), 5.22 (d, *J* = 3.7 Hz), 4.70–4.41 (m), 4.32–3.99 (m), 3.92–3.60 (m,), 3.51 (dd, *J* = 3.9, 10.6 Hz), 2.77–2.50 (m), 1.93 (s), 1.80 (s), 1.59 (s,), 1.55 (s), 1.33 (s), 1.21 (s); ^{13}C NMR ($CDCl_3$, 75 M) δ 171.02, 170.44, 169.48, 137.79, 137.51, 137.30, 129.09, 128.57, 128.55, 128.51, 128.46, 128.41, 128.38, 128.36, 128.22, 128.20, 128.16, 128.13, 127.94, 127.92, 127.88, 127.82, 127.78, 127.70, 127.03, 113.00, 112.61, 104.09, 77.54, 77.41, 77.12, 76.95, 76.86, 76.69, 76.26, 75.97, 73.30, 71.85, 71.46, 67.85, 63.95, 63.57, 36.61, 27.07, 26.87, 26.67, 26.19, 21.51, 20.91, 20.71; HR-MALDI-MS: 849.3475 ([M+Na]$^+$, $C_{47}H_{54}NaO_{13}^+$; calcd 849.3462); 871.3288 [M−H+2Na]$^+$, $C_{47}H_{53}Na_2O_{13}^+$; calcd 871.3282).