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An amide orthoesterification route to *N*-(1′-alkylthioglucopyranosyl)indoles

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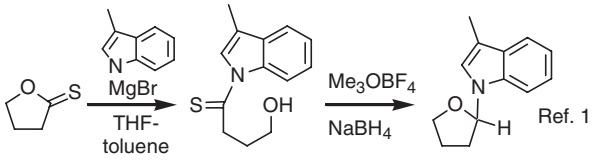
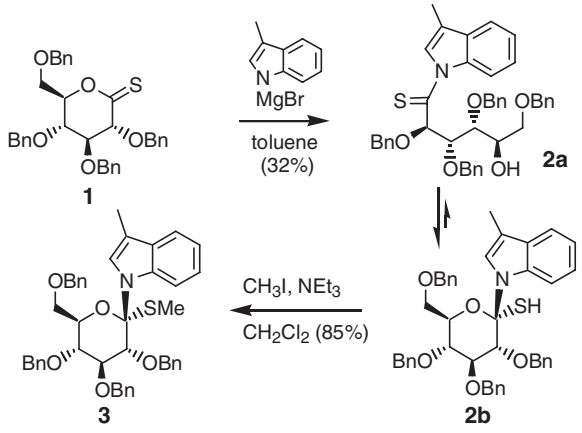
Abstract—The addition of 3-methylindolylmagnesium bromide to tetra-*O*-benzyl-α-D-gluconothionolactone yields the expected indole *N*-gluconothioamide as its hemiorthothioamide tautomer. The thiol function is alkylated to yield the corresponding orthothioamide, a 1′-alkylthio-substituted *N*-glycoside. Alternatively, the 1′-alkylthio-*N*-glycoside can be accessed from the corresponding indole *N*-gluconamide via a boron trifluoride-etherate mediated orthoesterification with ethanethiol. Radical reduction of the orthothioamide yields the *N*-glycosides in 2:1 stereoselectivity in favor of the β-*N*-glycoside, while reduction via the oxonium ion leads to an improved 6:1 selectivity.

We recently reported a reductive strategy toward *N*-glycosides from thionolactones (Scheme 1),[1] which is extended here to the carbohydrate series. The chemical behavior is quite distinct from that observed for the simple thionolactones, and we report herein two routes to a family of novel 1′-alkylthio-substituted *N*-glycosides.[2,3] These compounds may be interesting *N*-glycoside analogs, as well as polyvalent intermediates for the synthesis of other classes of analogs.[2,4,5]

The acylation conditions were applied to the known tetra-*O*-benzyl-α-D-gluconothionolactone **1**[6] (Scheme 2). Treatment of a solution of 3-methylindolylmagnesium bromide in toluene with thionolactone **1** in THF yields *N*-[1′-sulfhydryl-α-D-glucopyranosyl]-3-methylindole **2b** in a modest 32% yield. It is nonetheless noteworthy that,



Scheme 1. Reductive *N*-glycosylation.[1]



Scheme 2. Synthesis of hemiorthothioamide **2b** and orthothioamide **3**.

in contrast to the model thionobutyrolactone system, the expected thioamide **2a** exists preferentially as the cyclic hemiorthothioamide tautomer **2b**.[7,8]

The hemiorthothioamide structure is assigned based on the ^{13}C NMR chemical shift of the C1′ carbon, at 104.0 ppm versus 208.3 ppm for the open form indole *N*-thioamide reported previously.[1] The coupling constants around the pyranose ring ($J_{4',5'} = 9.7$, $J_{4',3'} = 8.8$ Hz) are consistent with a cyclic form.[9] Alkylation of hemiorthothioamide **2b** with iodomethane and triethylamine yields the corresponding orthothioamide **3**.[10]

Keywords: Indole *N*-thioamide; Hemiorthothioamide; Orthothioamide; *N*-Glycoside; Glycosylated bis(indolyl)maleimides.
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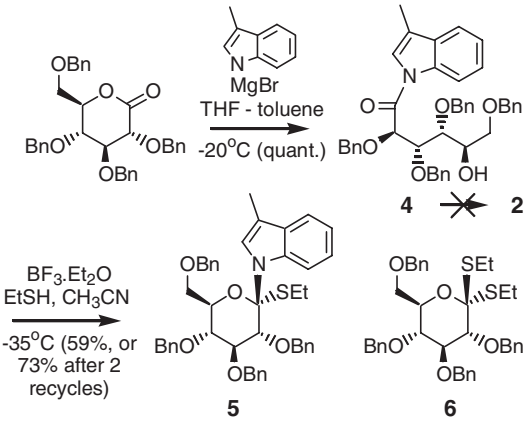
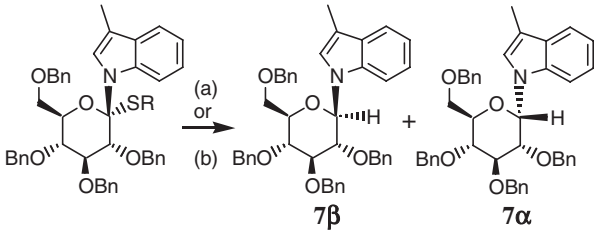


Scheme 3. Synthesis of orthothioamides via amides.

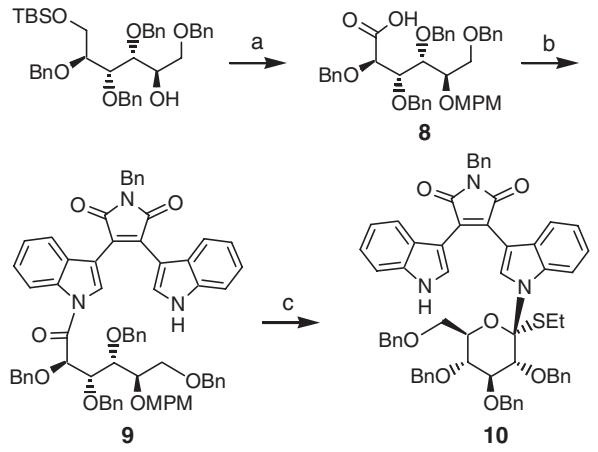
This compound is related to the 1′-thiophenyl nucleosides synthesized by Kumamoto et al. by an alternative route.[2] The orthothioamide structure was further established based on the analogy of the ^{1}H and ^{13}C NMR spectra to those of the corresponding bisindolylmaleimide 1′-ethylthio-*N*-glycoside **10** described below.

A more efficient route was sought to the 1′-thio-substituted *N*-glycoside compounds such as **2b** or **3**. An alternative would be to convert the indole *N*-amide to the corresponding thioamide. Treatment of 2,3,4,6-tetra-*O*-benzylgluconolactone[11] with 3-methylindolylmagnesium bromide at −20 °C in toluene/THF yielded amide **4** (Scheme 3). As in our previous study, however, treatment of amide **4** with either Lawesson's reagent[12] or Belleau's reagent[13] under standard conditions failed to give even traces of thioamide **2a** or **2b**. Nonetheless, treatment of amide **4** with ethanethiol and BF_3-etherate at −35 °C in acetonitrile for 3 h was found to yield orthothioamide **5** in a respectable 59% yield.[14] While such a conversion is well established for *C*-glycosides (ketone to monothioketal equilibrium), it is unusual at the higher oxidation state corresponding to the indolyl *N*-amide (amide to orthothioamide equilibrium).[8] Pushing the reaction to higher conversion, via higher temperatures or longer reaction times, led to the formation of dithioorthoester **6**. Running the reaction to low conversion and recycling the recovered starting material led to a slight improvement, to a 73% yield after two recycles.

Kahne et al.[5] and Kumamoto et al.[2] have shown that 1′-thioalkyl-substituted glycosides are useful intermediates for radical-mediated substitution chemistry. The reduction of the sulfur group was thus investigated in order to determine the stereoselectivity of the reaction (Scheme 4). In the event, radical reduction of orthothioamide **5** yielded the corresponding alpha- and beta-glucopyranosylindoles **7β** and **7α** as a 2:1 ratio of stereoisomers. The stereoselectivity is thus considerably lower than that observed by Kahne in the corresponding *O*-glycoside series.[5] The oxonium-mediated reduction conditions developed in our previous study were therefore applied to this case. Treatment of hemiorthothioamide **2b** with trimethyloxonium tetrafluoroborate (Meerwein's reagent) gives the corresponding oxonium ion, which is treated



Scheme 4. Stereoselectivity of the reduction of orthothioamides. Reagents and conditions: (a) R = Et; Bu_3SnH, AIBN, toluene, reflux. **7β**:**7α** = 2:1; (b) R = H; Me_3OBF_4, CH_3CN, −20 °C, then $NaBH_4$, −20 °C–rt. **7β**:**7α** = 6:1.



Scheme 5. Synthesis of orthothioamide **10**. Reagents and conditions: (a) (i) *p*-methoxybenzyl chloride, NaH, THF–DMF (70%); (ii) TBAF, THF (93%); (iii) TEMPO, NaOCl, KBr, Bu_4NCl, $NaHCO_3$, THF–H_2O (72%). (b) (i) 1-Dimethylamino-1-chloro-2-methylpropene, CH_2Cl_2 (Ghosez's reagent); (ii) *N*-benzyl-2,3-bis(indolyl) maleimide, Cs_2CO_3, THF–DMF (50% for two steps). (c) BF_3·etherate, ethanethiol, CH_3CN, −20 °C (75%).

in situ with sodium borohydride to yield the glucopyranosyl indoles **7β** and **7α** in a 6:1 ratio, in favor of axial hydride addition, along with orthothioamide **3**.

In connection with our initial interests,[1] we applied this methodology to *N*-benzyl-2,3-bis(1*H*-indol-3-yl)maleimide (Scheme 5). The acid chloride was prepared from the differentially protected carboxylic acid **8** by treatment with Ghosez's reagent.[15,16] Monoacylation of the protected bis(indolyl)maleimide gave monoamide **9** in 50% yield for the two steps from the acid, along with the expected bisamide and recovered starting material. Treatment of the amide with boron trifluoride-etherate and ethanethiol at −20 °C, without the need for prior removal of the *p*-methoxybenzyl protecting group, gave orthothioamide **10** in 75% yield.[17]

Crystals of compound **10** were obtained of sufficient quality to obtain a partial X-ray crystal structure in which the C4 benzyl protecting group carbons were not located precisely. The structure in Figure 1 confirms the orthothioamide, 1′-thioethyl-substituted *N*-glycoside structure, as well as the β-(equatorial) stereochemistry of the indole ring. The S1-C28-N3-C21 (S-C1′-N-C2) dihedral angle is near 0°, indicating minimal overlap between

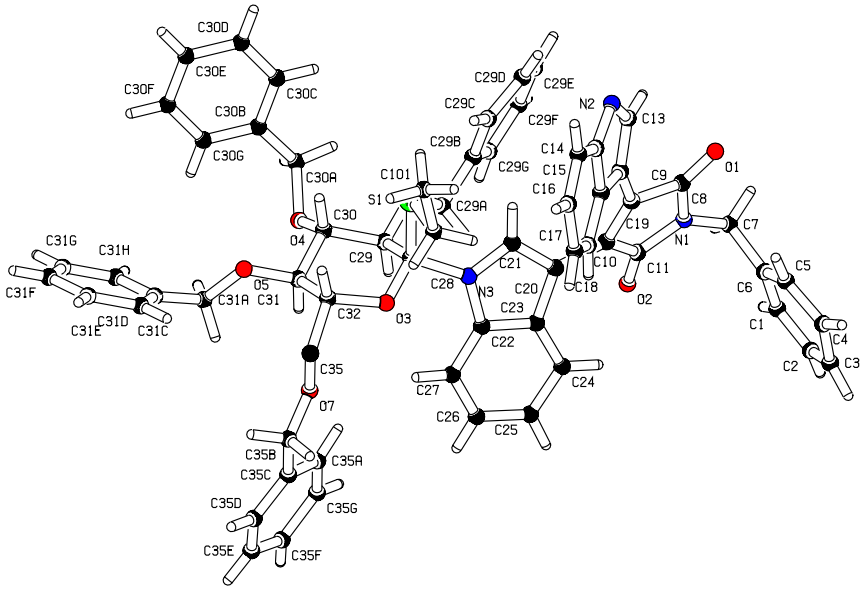


Figure 1. Partial X-ray structure of **10**.

the indole ring π system and the σ* orbital of the axial C–S bond. The thioethyl group is oriented in the expected *exo*-anomeric conformation, and the conformation of the bis(indolyl)maleimide moiety is similar to that observed in the crystal structure of the parent bis(indolyl)maleimide.[18]

In conclusion, two routes have been developed to pyranose orthothioamide functions, which can be accessed conveniently via indole *N*-amides or *N*-thioamides. The unusual reactivity of the latter compounds reflects both the fulvenoid character of the indole *N*-amides, as well as the particular steric and electronic environment of the pyranose ring. The synthesis is complementary to that of Kumamoto et al.,[2] giving access to the pyranose series bearing substitutents in the C2 position. These compounds are interesting *N*-glycoside analogs, as well as potential intermediates for the preparation of other *N*-glycoside analogs. The scope of this reaction, as well as the substitution chemistry of this functional group are currently under investigation.

Acknowledgements

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9. Compound **2b**: ^{1}H NMR ($CDCl_3$): δ 7.95 ppm (1H, d, $J = 8.5$ Hz); 7.80 (1H, m, $J = 0.9$ Hz); 7.50 (1H, d, $J = 7.8$ Hz); 7.40–7.05 (19H, m); 7.02–6.90 (3H, m); 4.92 (1H, d, $J = 10.9$ Hz); 4.87 (1H, d, $J = 10.9$ Hz); 4.82 (1H, d, $J = 10.9$ Hz); 4.70 (1H, d, $J = 10.7$ Hz); 4.62 (1H, d, $J = 11.7$ Hz); 4.50 (1H, d, $J = 11.7$ Hz); 4.41 (1H, ddd, $J = 9.8$, 1.9, 1.9 Hz); 4.20 (1H, dd, $J = 9.7$, 8.8 Hz); 4.10–3.95 (4H, m); 3.79 (1H, dd, $J = 10.7$, 1.7 Hz); 3.36 (1H, d, $J = 10.4$ Hz); 2.82 (1H, s); 2.29 (3H, d, $J = 0.9$ Hz). ^{13}C NMR ($CDCl_3$): δ 138.3 ppm (s), 138.2 (s), 138.1 (s), 137.3 (s); 135.2 (s), 131.6 (s), 128.5 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.6 (d), 127.6 (d), 126.3 (d), 122.0 (d), 120.1 (d), 119.0 (d), 115.0 (d), 110.7 (s) 104.0 (s) 82.7 (d); 80.9 (d); 80.6 (d); 76.8 (d); 75.7 (t), 75.3 (t), 74.9 (t), 73.4 (t), 68.2 (t), 9.6 (q). IR (neat): 2550 cm^{-1} (weak).
10. Compound **3**: ^{1}H NMR ($CDCl_3$): δ 7.99 ppm (1H, d, $J = 8.3$ Hz); 7.72 (1H, d, $J = 1.0$ Hz); 7.50 (1H, d, $J = 8.1$ Hz); 7.45–7.10 (18H, m); 7.10 (1H, dd, $J = 8.1$, 7.2 Hz); 7.03 (2H, m); 7.00 (1H, dd, $J = 8.4$, 7.2 Hz); 4.92 (1H, d, $J = 11.0$ Hz); 4.86 (1H, d, $J = 10.9$ Hz); 4.80 (1H, d, $J = 10.7$ Hz); 4.68 (1H, d, $J = 10.9$ Hz); 4.62 (1H, d, $J = 11.8$ Hz); 4.52 (1H, d, $J = 11.7$ Hz); 4.20–4.08 (3H, m); 4.03–3.94 (3H, m); 3.80 (1H, dd, $J = 10.7$, 0.7 Hz); 3.44 (1H, d, $J = 10.5$ Hz); 2.27 (3H, d, $J = 1.0$ Hz); 1.97 (3H, s). ^{13}C NMR ($CDCl_3$): δ 138.4 ppm (s), 138.1 (s), 137.5 (s), 135.1 (s), 131.5 (s); 129.0 (d); 128.4 (d); 128.4 (d); 128.3 (d); 128.1 (d); 128.0 (d); 127.9 (d); 127.8 (d); 127.7 (d); 127.6 (d); 127.5 (d); 127.5 (d); 125.9 (d); 125.2 (d); 121.9 (d), 119.9 (d), 118.8 (d), 115.0 (d); 110.9 (s), 103.4 (s); 83.4 (d); 83.2 (d); 77.2 (d); 75.6 (t), 75.2 (t); 74.8 (t); 73.9 (d); 73.3 (t); 68.5 (t); 9.6 (q); 9.3 (q).
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14. Compound **5**: ^{1}H NMR ($CDCl_3$): δ 8.00 ppm (1H, d, $J = 8.3$ Hz); 7.74 (1H, s); 7.50 (1H, d, $J = 7.8$ Hz); 7.45–7.15 (18H, m); 7.10 (1H, dd, $J = 8.1$, 7.2 Hz); 7.01 (2H, m); 6.95 (1H, dd, $J = 8.4$, 7.2 Hz); 4.92 (1H, d, $J = 10.7$ Hz); 4.86 (1H, d, $J = 10.8$ Hz); 4.80 (1H, d, $J = 10.8$ Hz); 4.68 (1H, d, $J = 10.7$ Hz); 4.64 (1H, d, $J = 11.7$ Hz); 4.52 (1H, d, $J = 11.7$ Hz); 4.24 (1H, m); 4.17–4.09 (2H, m); 4.01 (1H, d, $J = 10.5$ Hz); 4.00–3.94 (2H, m); 3.80 (1H, dd, $J = 10.4$, 0.7 Hz); 3.42 (1H, d, $J = 10.5$ Hz); 2.55 (2H, q, $J = 7.5$ Hz); 2.28 (3H, s); 1.23 (3H, t, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 138.5 ppm (s), 138.2 (s), 137.5 (s), 135.3 (s), 131.5 (s); 128.5 (d); 128.4 (d); 128.3 (d); 128.2 (d); 128.1 (d); 128.0 (d); 128.0 (d); 127.8 (d); 127.8 (d); 127.6 (d); 127.5 (d); 126.3 (d); 121.9 (d), 119.8 (d), 118.8 (d), 115.1 (d); 110.7 (s), 104.1 (s); 83.5 (d); 83.4 (d); 77.2 (d); 75.7 (t), 75.3 (t); 74.9 (t); 74.09 (d); 73.4 (t); 68.5 (t); 21.0 (t); 13.6 (q); 9.6 (q).
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17. Compound **10**: ^{1}H NMR ($CDCl_3$): δ 8.44 ppm (2H, s); 8.00 (1H, d, $J = 8.5$ Hz); 7.67 (1H, d, $J = 2.6$ Hz); 7.48 (2H, d, $J = 6.8$ Hz); 7.40–7.15 (19H, m); 7.10–6.90 (8H, m); 6.87–6.76 (2H, m); 6.61 (1H, dd, $J = 7.2$, 8.1 Hz); 4.92 (1H, d, $J = 10.8$ Hz); 4.85–4.77 (4H, m); 4.66 (1H, d, $J = 10.9$ Hz); 4.62 (1H, d, $J = 11.9$ Hz); 4.50 (1H, d, $J = 11.7$ Hz); 4.21–4.05 (5H, m); 3.95 (1H, dd, $J = 0.8$, 10.5 Hz); 3.78 (1H, d_{app}, $J = 10.5$ Hz); 3.72 (1H, d, $J = 10.7$ Hz); 2.39–2.32 (1H, m); 2.17–2.11 (1H, m); 1.06 (3H, t, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 171.9 ppm (s); 171.8 (s); 139.2 (s), 139.1 (s), 138.7 (s), 137.9 (s), 136.1 (s), 135.8 (s), 129.9 (s); 129.2 (d), 129.0 ($2 \times$ d); 128.9 (s); 128.7 (d); 127.9 (s); 127.9 (d) 127.3 (s), 125.8 (s); 123.0 (d), 122.6 (d), 122.5 (d), 121.6 (d), 120.7 (d), 116.0 (d), 111.4 (d); 107.5 (s), 107.4 (s), 105.5 (s); 83.9 (d), 77.7 (d); 75.6 (t), 75.6 (t); 75.3 (d), 73.5 (d); 75.0 (t), 68.6 (t); 42.1 (t); 21.2 (t); 13.7 (q).
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