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Synthesis of tryptophan *N*-glucoside

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This work is dedicated to Prof. W. Steglich on the occasion of his 70th birthday

Abstract—The naturally occurring L-tryptophan *N*-glucoside was synthesized using 2-*O*-pivaloylated glucosyl trichloroacetimidate, which gave β-N^{In}-glucosides. From 2-*O*-acetylated donors only tryptophan-1-yl-ethylidene compounds (amide acetals) were obtained. The employment of α-azido L-tryptophan benzyl ester facilitated purification and deprotection and improved the yields of the glycosylation step.
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The amino acid tryptophan shows many biological functions. Tryptophan and its derivatives are of great interest due to their complex metabolism involving important metabolites and related diseases.[1] Besides the many examples of known tryptophan-containing natural products, a growing number of recently discovered C or N-linked tryptophan glycoconjugates has attracted interest. The *C*-mannosyl-L-tryptophan **1**[2a,b] was initially discovered in human RNase and several glycoproteins of the complement system.[2c] Fruits and other foods were found to be the source of *glyco*-tetrahydro-β-carboline-3-carboxylic acids and various L-tryptophan-*N*-glycosides with pentoses as the sugar part.[3] L-Tryptophan *N*-glucoside **2**[4a] (Fig. 1) was previously discovered as a novel tryptophan metabolite in fruits and foods formed by an enzymatic process.[4b] The *N*-acylated derivative **3** was isolated from the flowers of *Pueraria Lobata*, a drug used in traditional Chinese medicine.[5]

There are only a few examples of synthetic tryptophan *N*-glycosides. In 1985 an *N*-glucosylated N^{α}-acetyl-D,L-tryptophan was obtained from N^{α}-acetyl-L-tryptophan and glucose in low yield.[6] Herderich et al. found analytical amounts of *N*- and *C*-glycosylated tryptophan derivatives among *glyco*-tetrahydro-β-carbolines in acid-catalyzed condensations between pentoses[3] or hexoses[4a] and tryptophan. Cyclic peptides have been reported to react at the indole nitrogen of tryptophan using either a glycal[7a] or a galactosyl bromide.[7b] *N*-Glycosyl-indoles have been obtained via the glycosylation of substituted indoles[8a,b] or indolines followed by oxidation to the corresponding *N*-glycosyl-indole.[9]

We report a chemical synthesis for tryptophan *N*-glucoside **2** suitable for preparing the amounts required for biological studies. Initially, we envisioned the formation of the β-linked tryptophan-*N*-glucoside from tetra-acetyl-glucosylimidate **4** and Cbz–Trp–OBzl **5**.[10] The glycosylation was initiated with boron trifluoride etherate as an activator and led to the unexpected tryptophan amide acetal **7**, which can be viewed as an aza analogue of a glycosyl orthoester (Fig. 2). Only one stereoisomer was found, which was arbitrarily assigned. The isolation of stable indole-1-yl-ethylidene glycosides has been reported in the literature.[8] To determine if the formation of orthoester-like indolyl glycosides was related to the protecting groups of the amino acid moiety, the azido-protected tryptophan **6** was employed. This compound was synthesized from tryptophan benzyl ester[10a] in 68% yield following a procedure introduced by Vasella et al.[11] However, even in the presence of the strong activator TMSOTf the reaction of the azide **6** with donor **4** only gave amide acetal **8**,[12] suggesting a low tendency for this compound to rearrange to the desired *N*-glycoside.

To avoid the formation of the orthoester-like compounds, replacement of the 2-acetyl moiety of donor **4**

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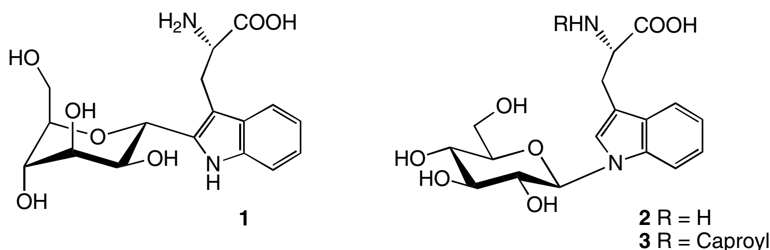

Figure 1. Structures of tryptophan *C*-mannoside **1** and tryptophan *N*-glucosides **2** and **3**.

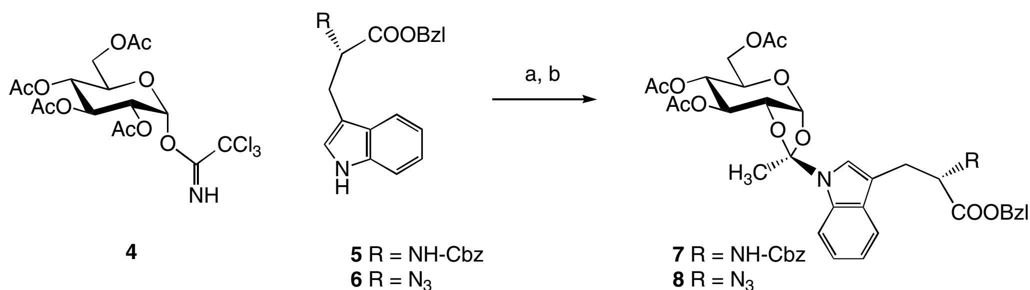

Figure 2. Reagents and conditions: (a) **4** + **5**, 0.14 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 42%; (b) **4+6**, 0.1 equiv TMSOTf, CH_2Cl_2, −10 °C, 26%.

with the bulky 2-pivaloyl residue as introduced by Kunz and Harreus[13] was planned. This protecting group has been described as giving *N*-glycosylated indoles.[8b]

The required trichloroacetimidate building block **11** (Fig. 3) was synthesized from tetra-acetyl-glucose **9**.[14] After pivaloylation of OH-2 the anomeric acetate was cleaved with hydrazine acetate and the intermediate hemiacetal was converted to the imidate **11** in a DBU-catalyzed reaction with trichloroacetonitrile,[15] giving an overall yield of 78% over the two steps.

The glycosylation of tryptophan derivative **5** with the pivaloylated donor **11** activated by boron trifluoride etherate gave the desired tryptophanyl-*N*-glucoside **12** in 17% yield (Fig. 3). Using TMSOTf as an activator gave better yields (27%) but in both cases the product **12** could not be purified completely by flash chromatography. Thus, the α-azido-tryptophan-benzyl ester **6** was examined as an acceptor. The reaction of azide **6**, glycosyl donor **11** and boron trifluoride etherate as an activator furnished the *N*-glucosylated tryptophan **13**,[16] which could easily be purified by flash chromatography (23% yield). When TMSOTf was used for activation the yield could be raised to 43%.

The deprotection of tryptophan *N*-glucoside **13** was accomplished via a two step procedure. Catalytic

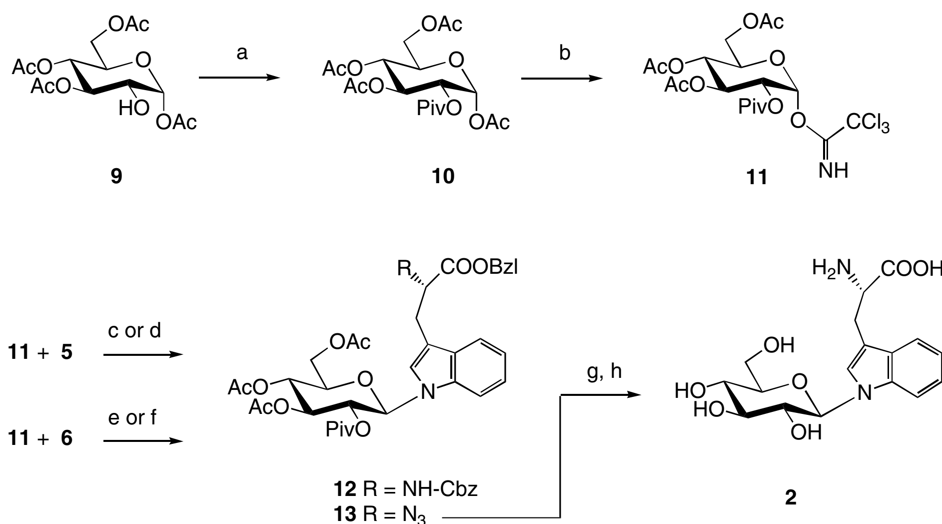

Figure 3. Reagents and conditions: (a) 5 equiv PivCl, py, $CHCl_3$, rt, 91%; (b) (i) 1.5 equiv $H_2N{-}NH_3OAc$, DMF, rt; (ii) 0.1 equiv DBU, 5 equiv CCl_3CN, 0 °C, 78% (over two steps); (c) 1.2 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C, 17%; (d) 0.1 equiv TMSOTf, CH_2Cl_2, −10 °C, 27%; (e) 0.6 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C, 23%; (f) 0.1 equiv TMSOTf, CH_2Cl_2, −15 °C, 43%; (g) PdO–H_2O, H_2, MeOH, rt, 42%; (h) $MeNH_2$ 40% in H_2O, rt, 77%.

hydrogenation over palladium oxide-hydrate removed the benzyl ester and reduced the azido group simultaneously. Subsequently, complete deacetylation was carried out with 40% aqueous methylamine.[17] After purification using size exclusion chromatography (Superdex 30) the target molecule **2** was obtained in 77% yield. NMR spectra were recorded in the same solvent as reported in the literature and showed excellent accordance.[4a,18] In conjunction with the optical rotation the structural assignment of the isolated compound was confirmed by total synthesis.

In conclusion we have developed a strategy to obtain the natural product *N*-glucosyl-tryptophan **2** by chemical synthesis. Key steps involve the introduction of a 2-pivaloyl moiety to suppress the formation of the tryptophan-1-yl amide acetals and the use of an α-azido tryptophan derivative for improved yields. This chemical synthesis can provide sufficient amounts of *N*-glucosyl-tryptophan to conduct biological studies.

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References and Notes

1. Sainio, E. L.; Pulkki, K.; Young, S. N. *Amino Acids* **1996**, *10*, 21–47.
2. (a) Hofsteenge, J.; Müller, D. R.; de Beer, T.; Löffler, A.; Richter, W. J.; Vliegenthart, J. F. G. *Biochemistry* **1994**, *33*, 13524–13530; (b) Gäde, G.; Kellner, R.; Rinehart, K. L.; Proefke, M. L. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 1303–1309; (c) Hofsteenge, J.; Blommers, M.; Hess, D.; Furmanek, A.; Miroshnichenko, O. *J. Biol. Chem.* **1999**, *274*, 32786–32794.
3. Diem, S.; Albert, J.; Herderich, M. *Eur. Food Res. Technol.* **2001**, *213*, 439–447.
4. (a) Gutsche, B.; Grun, C.; Scheutzow, D.; Herderich, M. *Biochem. J.* **1999**, *343*, 11–19; (b) Diem, S.; Bergmann, J.; Herderich, M. *J. Agric. Food Chem.* **2000**, *48*, 4913–4917.
5. Kinjo, J.-E.; Takeshita, T.; Nohara, T. *Chem. Pharm. Bull.* **1988**, *36*, 4171–4173.
6. Nyhammar, T.; Pernemalm, P.-A. *Food Chem.* **1985**, *17*, 289–296.
7. (a) Kessler, H.; Michael, K.; Kottenhahn, M. *Liebigs Ann. Chem.* **1994**, 811–816; (b) Itazaki, H.; Fujiwara, T.; Sato, A.; Kawamaru, Y.; Matsumoto, K. 1995, JP7109299; *Chem. Abstr.* **1995**, 701969.
8. (a) Sokolova, T. N.; Shevchenko, V. E.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1980**, *83*, 249–261; (b) Buchanan, J. G.; Stoddart, J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1417–1426.
9. Preobrazhenskaya, M. N.; Vigdorchik, M. M.; Suvorov, N. N. *Tetrahedron* **1967**, *23*, 4653–4660, and references cited therein.
10. (a) Arai, J.; Muramatsu, J. *J. Org. Chem.* **1983**, *48*, 121–123; (b) Guillaume, H. A.; Perich, J. W.; Johns, R. B.; Tregear, G. W. *J. Org. Chem.* **1989**, *54*, 1664–1668.
11. Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073–2077.
12. Compound **8**: ESI-MS: $C_{32}H_{34}N_4O_{11}$ M_r (calcd) 650.22, *M* (found) 673.18 ($M+Na^+$); $[\alpha]_D^{21}$ −1.1 (*c* 1.0, dichloromethane); ^1H NMR (360 MHz, [d_6]-DMSO): δ 7.65 (d, $J_{6,7}$ = 8.2 Hz, 1H, H-7), 7.54 (d, $J_{4,5}$ = 7.8 Hz, 1H, H-4), 7.33–7.18 (m, 7H, Ph, H-2, H-6), 7.09 (dd, $J_{4,5}$ = 7.8 Hz, $J_{5,6}$ = 7.3 Hz, 1H, H-5), 5.78 (d, $J_{1',2'}$ = 5.7 Hz, 1H, H-1′), 5.14–5.10 (m, 3H, CH_2–Ph, H-3′), 4.84–4.81 (m, 1H, H-4′), 4.63–4.59 (m, 1H, H-α), 4.21–4.08 (m, 4H, H-2′, H-5′, H-6′), 3.18 (dd, J_{gem} = 14.8 Hz, J_{vic} = 5.7 Hz, 1H, H-βa), 3.13 (dd, J_{gem} = 14.8 Hz, J_{vic} = 7.6 Hz, 1H, H-βb), 2.10, 2.05, 1.97, 1.84 (4s, 12H, CH_3); ^{13}C NMR (90 MHz, [d_6]-DMSO): δ 170.2, 169.8, 169.5, 168.9 (4C=O), 135.3 (Cq, Ph), 134.0 (C-7a), 129.1 (C-3a), 128.6–127.9 (CH, Ph), 124.1 (C-2), 122.3 (C-6), 119.9 (C-5), 118.7 (C-4), 112.4 (C″), 112.3 (C-7), 110.0 (C-3), 96.8 (C-1′, $J_{C,H}$ = 186.7 Hz), 72.2 (C-2′), 68.9 (C-3′), 67.7 (C-4′), 66.8 (CH_2–Ph), 66.5 (C-5′), 62.8 (C-6′), 61.3 (C-α), 26.9 (C-β), 23.8 (CH_3), 20.7, 20.6, 20.5 (CH_3, OAc).
13. Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41–48.
14. Helferich, B.; Zirner, J. *Chem. Ber.* **1962**, *95*, 2604–2611.
15. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
16. Compound **13**: ESI-MS: $C_{35}H_{40}N_4O_{11}$ M_r (calcd) 692.27, *M* (found) 715.31 ($M+Na^+$); $[\alpha]_D^{24}$ −20.0 (*c* 0.4, dichloromethane); IR (KBr) ν = 2108.6 cm^{-1} azide; ^1H NMR (360 MHz, [d_6]-DMSO): δ 7.63 (d, $J_{6,7}$ = 8.4 Hz, 1H, H-7), 7.53 (d, $J_{4,5}$ = 7.7 Hz, 1H, H-4), 7.40–7.32 (m, 5H, Ph), 7.27 (s, 1H, H-2), 7.19 (dd, $J_{6,7}$ = 8.4 Hz, $J_{5,6}$ = 7.6 Hz, 1H, H-6), 7.06 (dd, $J_{4,5}$ = 7.7 Hz, $J_{5,6}$ = 7.6 Hz, 1H, H-5), 6.22 (d, $J_{1,2}$ = 8.6 Hz, 1H, H-1′), 5.59–5.48 (m, 2H, H-2′, H-3′), 5.25–5.15 (m, 3H, CH_2–Ph, H-4′), 4.54–4.50 (m, 1H, H-α), 4.33–4.29 (m, 1H, H-5′), 4.15–4.02 (m, 2H, H-6a′, H-6b′), 3.18 (dd, J_{gem} = 14.9 Hz, J_{vic} = 5.2 Hz, 1H, H-βa), 3.07 (dd, J_{gem} = 14.9 Hz, J_{vic} = 8.0 Hz, 1H, H-βb), 2.04, 1.96, 1.93, (3×s, total 9H, Ac), 0.67 (s, 9H, Piv); ^{13}C NMR (90 MHz, [d_6]-DMSO): δ 175.5 (COOBzl), 170.1, 169.7, 169.5, 169.4 (4CO), 136.3 (C-7a), 135.4 (C_q, Ph), 128.5, 128.2, 128.1 (CH, Ph), 127.7 (C-3a), 124.2 (C-2), 122.1 (C-6), 120.0 (C-5), 118.7 (C-4), 110.8 (C-3), 110.4 (C-7), 81.1 (C-1′), 73.0 (C-5′), 72.5 (C-3′), 69.7 (C-2′), 68.0 (C-4′), 66.9 (CH_2–Ph), 62.2 (C-6′), 61.5 (C-α), 37.9 (C_q, Piv), 26.6 (C-β), 26.1 (CH_3, Piv), 20.5, 20.4, 20.1 (CH_3, Ac).
17. Griffin, B. E.; Jarman, M.; Reese, C. B. *Tetrahedron* **1968**, *24*, 639–662.
18. Compound **2**: ESI-MS: $C_{17}H_{22}N_2O_7$ M_r (calcd) 366.1427, *M* (found) 367.1507 $(M+H)^+$; $[\alpha]_D^{21}$ −19.0 (*c* 0.2, water); lit.[4b]: $[\alpha]_D^{25}$ −20.3 (*c* 0.2, water); ^1H NMR (360 MHz, [d_4]-MeOH+1% TFA): δ 7.62 (d, $J_{4,5}$ = 7.8 Hz, 1H, H-4), 7.58 (d, $J_{6,7}$ = 8.2 Hz, 1H, H-7), 7.36 (s, 1H, H-2), 7.23 (dd, $J_{6,7}$ = 8.2 Hz, $J_{5,6}$ = 7.1 Hz, 1H, H-6), 7.14 (dd, $J_{4,5}$ = 7.8 Hz, $J_{5,6}$ = 7.1 Hz, 1H, H-5), 5.51 (d, $J_{1',2'}$ = 9.1 Hz, 1H, H-1′), 4.28 (dd, $J_{8a,9}$ = 8.6 Hz, $J_{8b,9}$ = 4.5 Hz, 1H, H-9), 3.92–3.85 (m, 2H, H-2′, H-6a′), 3.67–3.46 (m, 5H, H-3′, H-4′, H-5′, H-6b′, H-8a), 3.33–3.27 under MeOD signal (m, 1H, H-8b); ^{13}C NMR (90 MHz, [d_4]-MeOH + 1% TFA): δ 171.5 (COOH), 138.8 (C-7a), 129.1 (C-3a), 125.7 (C-2), 123.6 (C-6), 121.3 (C-5), 119.3 (C-4), 111.1 (C-7), 109.6 (C-3), 86.4 (C-1′), 80.3 (C-5′), 78.6 (C-3′), 74.0 (C-2′), 71.2 (C-4′), 62.3 (C-6′), 54.1 (C-9), 27.3 (C-8).