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TETRAHEDRON

Total Synthesis of α-Deamino-3-(β-D-glucopyranosyloxy)kynurenine

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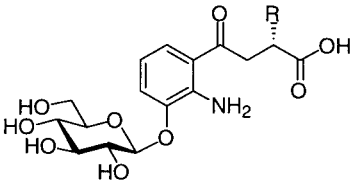
Abstract—α-Deamino-3-(β-D-glucopyranosyloxy)kynurenine, a yellow, fluorescent compound isolated from human lens, was synthesized in 8 steps (10% overall yield) from commercially available 3-methoxy-2-nitrobenzaldehyde. Key events included preparation and glucosylation of methyl 4-(3-hydroxy-2-nitrophenyl)-4-oxobutanoate followed by reduction of the nitro group and deprotection.

Introduction

α-Deamino-3-(β-D-glucopyranosyloxy)kynurenine (**1**) is the most recently identified member of a series of UV-filtering agents isolated from the protein-free extract of human eye lens.[1] Other known members of this class of compound are 3-(β-D-glucopyranosyloxy)-L-kynurenine (**2**),[2,3] kynurenine (**3**),[2,3] and 3-hydroxy-L-kynurenine (**4**).[4] A structurally related glucoside, 2-amino-3-(β-D-glucopyranosyloxy)acetophenone (**5**),[5] has been isolated from the insoluble protein fraction of human lens. The three glucosides are unusual both because glucoside formation in mammalian tissue is rare and because these compounds are found in the lenses of primates but not in the lenses of other animals.[2] Although compounds **1**–**5** may serve as photoprotective filters,[6] they limit the frequency range of visual perception by primates[7] and may contribute to cataract formation through photosensitization of molecular oxygen.[2,8] Access to these compounds in order to study their biological and photophysical properties is clearly desirable.



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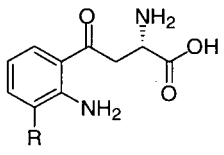

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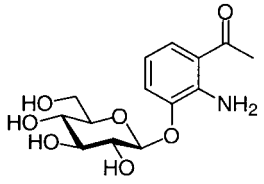

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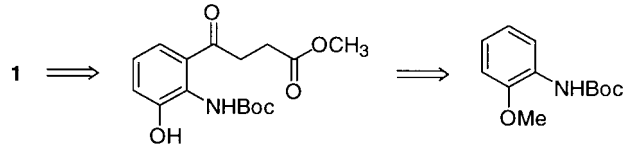
To provide material in a quantity suitable for further study, we have devised a practical synthesis of **1**. During the course of our work, another synthesis of **1** was also reported.[9]

Results and Discussion

We initially investigated *ortho*-metalation/acylation of a suitably protected 2-aminophenol, such as **7** (Scheme 1), as a route to assemble the aglycone portion of **1**. Although the dianion of **7** could be generated (3.0 equiv. of *t*BuLi in ether, −78 to −20°C) and successfully formylated or deuterated, reactions of the dilithium salt of **7** with active acyl derivatives (anhydride, acid chloride, and Weinreb amide[10]) of succinic acid led only to recovered **7** (Table 1). Apparently, the hard aryl anion prefers to deprotonate the acyl



6 **7**

Scheme 1.

Keywords: glycosidation; lithiation; natural products; NMR.

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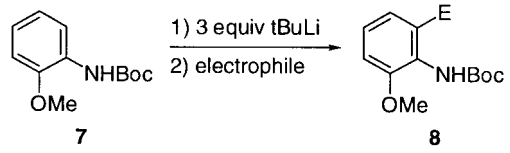
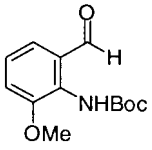
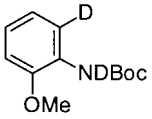
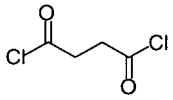
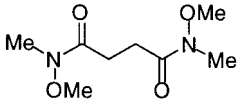
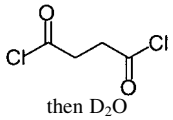
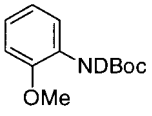
Table 1. *ortho*-Metalation reactions of **7**



Entry	Electrophile	Product	Yield (%)
1	DMF		85
2	D_2O		86
3		**7**	78
4		**7**	81
5	 then D_2O		75

donor. Treatment of the dilithium salt of **7** with 1 equiv. of succinyl chloride prevented deuterium incorporation in the aromatic ring upon subsequent quench and work-up with D_2O (Table 1, entries 2 and 5). This behavior stands in stark contrast to the usual tendency of organolithium reagents to add efficiently not only to acid chlorides but also to the ketones thus produced.[10–12] Also surprising is the apparent failure of succinyl chloride to undergo dehydrohalogenation and generate a ketene intermediate, which itself would be a highly reactive acylating agent.[13] Although a softer aryl anion, such as a magnesium, manganese, zinc, or copper salt, would probably undergo succinylation satisfactorily,[14] we also found that protected aminophenol **10** was not readily glycosylated by tetra-*O*-acetylglucopyranosyl bromide (**9**) in the presence of silver imidazolate[15] (Scheme 2). We therefore turned to an aglycone intermediate in which a nitro group served as the precursor to the amino group.

In a model study, glucosylation of 2-nitrophenol (**12**) proceeded smoothly to give aryl glucoside **13** in 76% yield. Apparently, this glycosylation requires the phenoxide anion as the nucleophile, and silver imidazolate is able to deprotonate **12** but not **10**.

Toward synthesizing the actual aglycone, we set about to allylate 3-methoxy-2-nitrobenzaldehyde (**14**). Although allylmagnesium bromide failed to give the desired product in reasonable yield, reaction of **14** with allyltrimethylsilane[16] in the presence of $TiCl_4$ gave **15** in 90% yield (Scheme 3). While hydroboration of **15** as the free alcohol[17] using BH_3·THF or 2 mol equivalents of dicyclohexylborane generated in situ[18] failed to generate **16** satisfactorily,[19] exposure of **15** to a slight excess of borane (previously treated with a substoichiometric amount of cyclohexene) followed by basic H_2O_2 produced diol **16** in good yield and high regioselectivity. Oxidation of **16** with Jones reagent gave the desired ketoacid in modest yield. Demethylation of **17** with LiCl in DMF at reflux[20] followed by esterification of the reaction residue by BF_3·OEt_2 in methanol at reflux produced the desired aglycone **18**.

Coupling of **18** and **9** proceeded efficiently in the presence of silver imidazolate and zinc chloride to afford glucoside **19** as a single diastereomer (Scheme 4). Catalytic reduction of **19** over Pd-C gave **20**, which was deacetylated in methanol that had not been previously dried to give the free acid, **1**, directly.

The identity of **1** was established by agreement of its NMR data with the partial ^1H and ^{13}C spectra reported.[1] The structure of **1** was further confirmed and its ^1H and ^{13}C resonances were assigned by NOE difference, COSY, HMQC, and HMBC experiments.

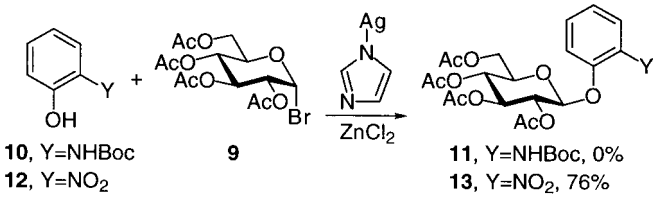
Conclusion

In conclusion, we have developed a practical synthesis of fluorescent glucoside **1**, confirmed its structure, and made full assignment of its ^1H and ^{13}C NMR spectra. Further study is required to determine the role of **1** and related glucosides as UV filters in human lens and as possible causative agents in the aging of human lens, particularly in the generation of cataracts.

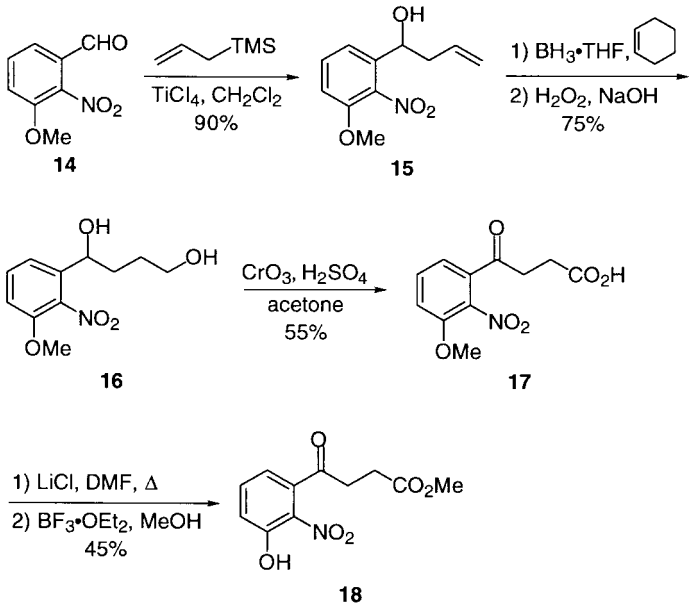
Experimental

General procedures

Methylene chloride and THF were purified by distillation under nitrogen from CaH_2 or sodium/benzophenone, respectively. All reactions were conducted under nitrogen in flame or oven-dried glassware with magnetic stirring, unless noted



Scheme 2.



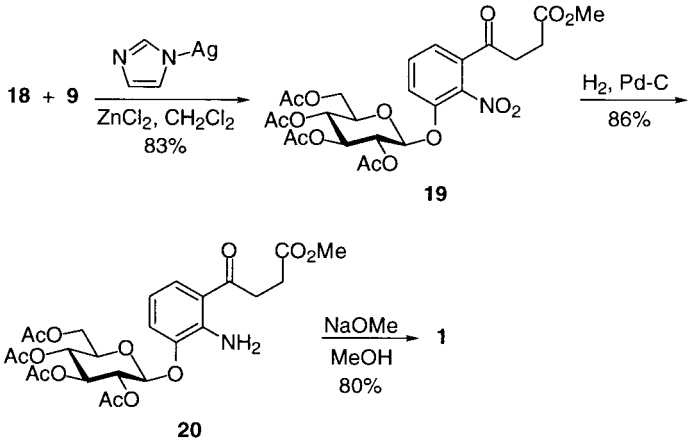
Scheme 3.

otherwise. TLC was performed on 2.5×10 cm plates coated with 250 μm-thick silica gel GF. Column chromatography was performed on flash-grade silica gel (60 Å, 230–400 mesh).

Unless specified otherwise, ^{1}H NMR and ^{13}C NMR spectra (400 and 101 MHz, respectively) were recorded using $CDCl_3$ as the solvent. A JVERT pulse sequence differentiated ^{13}C nuclei bearing an even number of hydrogen atoms from those bearing an odd number. IR spectra were obtained of samples as neat oils or KBr pellets. Liquid secondary ion mass spectra (LSIMS) were obtained using Cs^{+} (15 eV) as the ionizing beam and either glycerol or *p*-nitrobenzyl alcohol as the matrix. In some cases, NaI was added to the matrix to enhance the relative intensity of the quasi-molecular ion. Elemental analysis was performed by Micro-Analysis, Inc.

1-(3-Methoxy-2-nitrophenyl)-3-buten-1-ol (15). To a solution of 3-methoxy-2-nitrobenzaldehyde (3.62 g, 20 mmol) in 20 mL of CH_2Cl_2 was added $TiCl_4$ (10 mL of a 1 M solution in CH_2Cl_2) over 15 min. After 10 min at rt, 4.8 mL of allyltrimethylsilane (3.45 g, 30 mmol) was added all at once. After 10 more min, the reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation of the residual brown oil (5 Torr, bath temperature=160°C) gave **15** as a pale yellow oil (4.10 g, 92%). R_f (1:2 EtOAc–hexanes) 0.65. ^{1}H NMR δ 2.19 (d, J=3.2 Hz, 1H), 2.47 (m, 1H), 2.59 (m, 1H), 3.89 (s, 3H), 4.73 (m, 1H), 5.15 (m, 2H), 5.78 (m, 1H), 6.96 (d, J=8.3 Hz, 1H), 7.17 (d, J=7.7 Hz, 1H), 7.44 (dd, J=7.7, 8.3 Hz, 1H). ^{13}C NMR (even) δ 43.3, 115.0, 119.8, 137.2, 150.9; (odd) δ 56.9, 69.0, 111.9, 118.9, 131.6, 133.9. IR (neat) 3418, 1852, 1609, 1531, 1438 cm^{-1}. HRLSIMS calcd for $C_{11}H_{14}NO_4$ ($M+H^{+}$) 224.0923, found 224.0910.

1-(3-Methoxy-2-nitrophenyl)-1,4-butanediol (16). Cyclohexene (1.28 g, 16 mmol) and 15 mL of THF were combined in a 250-mL round-bottomed flask. The flask was cooled in an ice-water bath and BH_3·THF (24 mL of a 1 M solution in THF) was added. After 10 min, **15** (4.55 g,



Scheme 4.

20 mmol) in 15 mL of THF was added. The ice bath was removed and the reaction was stirred for 30 min while warming to rt. With caution, 10 mL of 3.0 M NaOH followed by 3.42 mL of 30% aqueous H_2O_2 were added over 10 min. The reaction was stirred vigorously for 5 min, diluted with ether, and washed sequentially with saturated aqueous NH_4Cl, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography of the residue gave **16** as a pale yellow solid (3.69 g, 75%), mp 103°C. R_f (1:3 EtOAc–hexanes) 0.15. ^{1}H NMR δ 1.69 (m, 2H), 1.86 (m, 2H), 3.67 (m, 2H), 3.89 (s, 3H), 4.70 (m, 1H), 6.95 (d, J=8.3 Hz, 1H), 7.20 (d, J=7.8 Hz, 1H), 7.43 (dd, J=7.8, 8.3 Hz, 1H). ^{13}C NMR (even) δ 29.5, 36.2, 63.0, 138.2, 140.2, 150.8; (odd) δ 56.9, 69.9, 111.7, 118.9, 131.6. IR (KBr) 3320, 1527, 1372, 1280, 1058, 1019 cm^{-1}. HRLSIMS calcd for $C_{11}H_{16}NO_5$ ($M+H^+$) 242.1028, found 242.1027. Anal. calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.91; H, 6.42; N, 5.80.

4-(3-Methoxy-2-nitrophenyl)-4-oxobutanoic acid (17). A solution of 0.10 g of CrO_3 in 2 mL of 80% aqueous H_2SO_4 was added dropwise over 5 min to a solution of **16** (360 mg, 1.49 mmol) in 15 mL of acetone. After 30 min, 5 g of silica gel was added, and the mixture was evaporated to dryness. The residue was placed on a column of silica gel and eluted to give **17** (208 mg, 55%) as pale brown needles, mp 139°C. R_f (1:9 acetone/CH_2Cl_2) 0.30. ^{1}H NMR (250 MHz) δ 2.80 (t, J=6.5 Hz, 2H), 3.23 (t, J=6.5 Hz, 2H), 3.93 (s, 3H), 7.25 (d, J=8.2 Hz, 1H), 7.42 (d, J=7.9 Hz, 1H), 7.55 (dd, J=7.9, 8.2 Hz, 1H). ^{13}C NMR (DMSO-d_6) (even) δ 28.4, 40.0, 131.8, 140.2, 152.4, 174.0, 197.9; (odd) δ 57.8, 118.8, 122.2, 132.8. IR (KBr) 1698, 1695, 750, 668 cm^{-1}. HRLSIMS calcd for $C_{11}H_{12}NO_6$ ($M+H^+$) 254.0664, found 254.0653. Anal. calcd for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.51; H, 4.41; N 5.59.

Methyl 4-(3-hydroxy-2-nitrophenyl)-4-oxobutanoate (18). A solution of LiCl (80 mg, 1.89 mmol) and **17** (130 mg, 0.51 mmol) in 10 mL of 95% aqueous DMF was heated at reflux for 4 h. The reaction mixture was diluted with ethyl acetate, washed sequentially with 5% aqueous HCl, water, and brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in 20 mL of dry methanol and 0.5 mL of $BF_3{\cdot}OEt_2$ was added. The reaction was heated at reflux for 1 h, and then concentrated. The residue was chromatographed to give **18** (59 mg, 45%) as a yellow oil. R_f (1:3 EtOAc–hexanes) 0.32. ^{1}H NMR δ 2.83 (t, J=6.6 Hz, 2H), 3.09 (t, J=6.6 Hz, 2H), 3.73 (s, 3H), 6.94 (dd, J=1.1, 7.3 Hz, 1H), 7.23 (dd, J=1.1, 8.5 Hz, 1H), 7.61 (dd, J=7.3, 8.5 Hz, 1H), 10.51 (br s, 1H) ^{13}C NMR (even) δ 28.4, 38.1, 115.0, 140.3, 155.6, 173.4, 200.7; (odd) δ 52.4, 119.0, 121.6, 137.4. IR (KBr) 1734, 1699 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{11}NO_6$ 253.0586, found 253.0577.

3-(4-Methoxy-4-oxobutanoyl)-2-nitrophenyl tetra-*O*-acetyl-β-D-glucopyranoside (19). To a mixture of **18** (32 mg, 0.126 mmol) and **9** (156 mg, 0.380 mmol) dissolved in 6 mL of CH_2Cl_2 was added silver imidazolate (66 mg, 0.377 mmol) followed by 0.38 mL of 1.0 M $ZnCl_2$ in ether. After stirring 16 h at rt in the dark, the reaction mixture was filtered, and the filtrate was concentrated. Chromatography of the residue gave recovered **18** (12 mg) followed by **19** as a yellow foam (38 mg, 83% based on starting material consumed). R_f (1:1 EtOAc–hexanes) 0.28. ^{1}H NMR δ 2.05 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.17 (s, 3H), 2.67–2.84 (m, 2H), 3.12–3.33 (m, 2H), 3.69 (s, 3H), 3.79–3.94 (m, 1H), 4.24–4.29, (m, 2H), 4.99–5.35 (m, 4H), 7.52–7.58 (m, 2H), 7.62–7.67 (m, 1H) ^{13}C NMR (even) δ 27.7, 34.9, 61.6, 131.3, 140.8, 148.2, 169.2, 169.2, 170.1, 170.4, 172.7, 195.8; (odd) δ 20.4, 20.5, 20.7, 21.0, 51.9, 67.9, 70.2, 72.0, 72.3, 100.5, 123.6, 123.8, 131.1 IR (KBr) 1743, 1699 cm^{-1}. HRLSIMS calcd for $C_{25}H_{29}NO_{15}Na$ ($M+Na^+$) 606.1462, found 606.1449.

3-(4-Methoxy-4-oxobutanoyl)-2-aminophenyl tetra-*O*-acetyl-β-D-glucopyranoside (20). A solution of **6** (32 mg, 0.055 mmol) in 5 mL of methanol was stirred with 8 mg of 5% Pd-C under an atmosphere of H_2 at rt for 3 h. The reaction mixture was filtered and concentrated. Chromatography of the residue (1:3 EtOAc–hexane with 1% Et_3N) afforded **7** (26 mg, 86%) as a pale yellow foam. R_f (1:1 EtOAc–hexanes) 0.48. ^{1}H NMR δ 2.04 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.20 (s, 3H), 2.71 (m, 2H), 3.30 (t, J=6.6 Hz, 2H), 3.71 (s, 3H), 3.86 (ddd, J=2.4, 5.1, 9.9 Hz, 1H), 4.18 (dd, J=2.4, 12.3 Hz, 1H), 4.31 (dd, J=5.1, 12.3 Hz, 1H), 4.96 (m, 1H), 5.16 (m, 1H), 5.29–5.34 (m, 2H), 6.51 (br s, 2H), 6.55 (dd, J=7.8, 8.2 Hz, 1H), 7.04 (dd, J=1.0, 7.8 Hz, 1H), 7.53 (dd, J=1.0, 8.2 Hz, 1H). ^{13}C NMR (even) δ 28.8, 34.1, 61.8, 117.8, 142.2, 144.6, 169.4, 169.9, 170.1, 170.5, 173.6, 199.7; (odd) δ 20.5, 20.6, 20.7, 20.8, 51.8, 68.2, 71.1, 72.1, 72.2, 100.3, 113.9, 118.9, 125.5. IR (KBr) 1748, 1689, 1640 cm^{-1} HRLSIMS calcd for $C_{25}H_{31}NO_{13}Na$ ($M+Na^+$) 576.1693, found 576.1711.

α-Deamino-3-(β-D-glucopyranosyloxy)kynurenine (1). To a solution of **7** (26 mg, 0.047 mmol) in 5 mL of methanol was added 0.20 mL of 0.025 M NaOMe in methanol. After 14 h at rt, the reaction mixture was concentrated. The residue was chromatographed on reverse-phase silica gel (Analtech, C_{18}-bonded) with water to give **8** (14 mg, 80% yield) as a yellow crystalline solid. R_f (1:5:94 AcOH-EtOH-EtOAc) 0.22. ^{1}H NMR (D_2O) δ 2.49 (t, J=6.8 Hz, 2H, Hα), 3.23 (t, J=6.8 Hz, 2H, Hβ), 3.48 (m, 1H, H4′), 3.55 (m, 1H, H5′), 3.58 (m, 1H, H3′), 3.60 (m, 1H, H2′), 3.74 (dd, J=5.5, 12.5 Hz, 1H, H6′a), 3.89 (dd, J=2.0, 12.5 Hz, 1H, H6′b), 4.99 (d, J=7.1 Hz, 1H, H1′), 6.75 (dd, J=7.9, 8.3 Hz, 1H, H5), 7.28 (dd, J=1.1, 7.9 Hz, 1H, H4), 7.67 (dd, J=1.1, 8.3 Hz, 1H, H6). ^{13}C NMR (D_2O) δ 32.2 (Cα), 36.2 (Cβ), 60.8 (C6′), 69.7 (C4′), 73.2 (C3′), 75.8 (C2′), 76.5 (C5′), 101.9 (C1′), 116.2 (C5), 119.6 (C1), 120.7 (C4), 126.4 (C6), 141.4 (C2), 145.2 (C3), 182.3 (CO_2H), 204.7 (C=O). HRLSIMS ($M+Na^+$) calcd for $C_{16}H_{21}NO_9Na$ 394.1114, found 394.1118.

Acknowledgements

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