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An expeditious chemo-enzymatic synthesis of dihydronorcapsaicin β-D-glucopyranoside

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Abstract

A seven-step and scalable synthesis of dihydronorcapsaicin β-D-glucopyranoside, non-pungent and adrenal secretion enhancement activity (diet effect), was accomplished from vanillin. A simple and inexpensive glucosyl donor, acetobromoglucose, was reacted with phenolic hydroxyl group of α-iodovanillin nitrile under basic conditions. Another key step was the lipase-catalyzed coupling reaction of primary amine, which was resulted from the reduction of the glucosylated product, with methyl nonanoate.

Keywords: Capsaicin; Glucoside; Lipase; Aminolysis; Vanillin

1. Introduction

Capsaicin has biological activities such as adrenal catecholamine secretion, which enhances energy metabolism, and is expected for 'diet effect' [1]. Its strongly pungent taste, which has very well been known as a spice for a long time, is an obstacle for intake in a large quantity. Towards the development of non-pungent, but biologically active materials, Watanabe, Kobata and co-workers have extensively studied, and capsiate (an ester) was elaborated [2]. As another approach to non-pungent, water-soluble, and biodegradable derivative, Hamada and co-workers enzymatically glycosylated capsaicins, by applying cultured plant cell of *Phytolacca americana* [3]. For example, the glucoside **2** was obtained in 46% yield from **1** (dihydronorcapsaicin, a synthetic analog of natural form). They also prepared **2** by way of a Lewis-acid catalyzed glycosylation of **1** with a glycosyl fluoride in 78% yield of this particular step [4]. In both cases, the syntheses were completed by the glycosylation at the final stage on dihydronorcapsaicin **1** itself, which had been synthesized separately in a chemical manner. Herein we describe a chemo-enzymatic, short-step total synthesis of **2** from vanillin **3a**, a synthetic flavor produced in large quantities, as shown in Scheme 1. In contrast to Hamada's syntheses, the glycosylation locates in an earlier stage, and the glycosyl donor is a very simple acetobromoglucose, which can be prepared from glucose in one-pot reaction. Another feature is chemo- and regioselective introduction of fatty acid on the primary amine, by an enzyme-catalyzed aminolysis of ester.

2. Experimental section

All melting points were uncorrected. IR spectra were measured as thin films for oils or KBr disks of solid on a JASCO FT/IR-410 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured at 270 MHz on a JEOL JNM EX-270 or at 400 MHz on a JEOL JNM GX-400 spectrometer. Fast atom bombardment (FAB) mass spectra were recorded on a Jeol JMS-700 spectrometer. Optical rotation values were recorded on a Jasco DIP 360 polarimeter. Silica gel 60 (spherical, 100–210 μm, 37558-79) of Kanto Chemical Co. was used for column chromatography. Preparative TLC was performed with E. Merck silica gel 60 F_{256} plates (0.5 mm thickness, No. 5744).

2.1. 4-Hydroxy-3-iodo-5-methoxybenzaldehyde (3b)

A solution of vanillin **3a** (2.5 g, 16.4 mmol) and iodine (4.99 g, 19.3 mmol) in aqueous ammonia (28% solution, 11 mL) and THF (16.4 mL) was stirred at room temperature for 1.5 h. The dark solution became colorless at the end of the reaction. The reaction was quenched with saturated $Na_2S_2O_3$ solution. Then concentrated hydrochloric acid was added until

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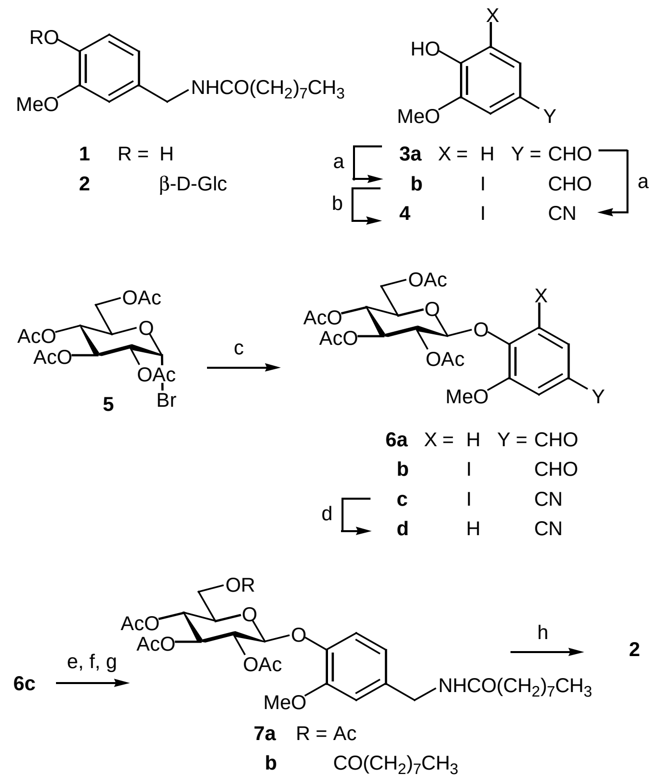

Scheme 1. Reagents and conditions: (a) NH_3 aq., I_2 (58%); (b) $NH_2OH{\cdot}HCl$, NaI, CH_3CN (85%); (c) *i*-Pr_2NEt, CH_3CN (71% for **6c**); (d) H_2, Pd–C, MeOH, K_2HPO_4 aq. (62%); (e) $NaBH_4$, $NiCl_2$, EtOH; (f) *Candida antarctica* lipase (Chirazyme L-2), $CH_3(CH_2)_7CO_2CH_3$, $(CH_3CH_2)_2C(OH)CH_3$, 70 °C, 150 Torr; (g) Ac_2O, pyridine (3 steps 66% for **7a**, 13% for **7b**); (h) Et_3N, MeOH (quant).

the solution reached to pH 1. The reaction mixture was extracted with AcOEt three times. The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was recrystallized from (hexane–AcOEt = 2/5), afforded **3b** (2.64 g, 58%) as colorless solid; mp 176 °C (lit. [5] 179–180 °C); IR (KBr, cm^{-1}) 3176, 2846, 2243, 1666, 1574, 1490, 1417, 1296, 1165, 1039, 785, 671; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.98 (s, 3H, OMe), 6.67 (s, 1H, OH) 7.38 (d, $J = 1.6$ Hz, 1H, H-6), 7.82 (d, $J = 1.6$ Hz, 1H, H-2), 9.78 (s, 1H, CHO). The IR and NMR spectra were identical with those reported previously [5].

2.2. 4-Hydroxy-3-iodo-5-methoxybenzonitrile (4)

A solution of the aldehyde **3b** (1.0 g, 3.60 mmol), $NH_2OH{\cdot}HCl$ (0.33 g, 4.78 mmol) and NaI (0.27 g, 1.80 mmol) in CH_3CN (14.4 mL) was degassed to remove any trace of oxygen by applying ultrasonic (70–80 W) under evacuation, three times for each 1 s. The mixture was stirred under reflux for 19 h. Then, 10% aqueous $Na_2S_2O_3$ (12.6 mL) was added to the mixture, and the stirring was further continued until the red-brown color disappeared. The solvent, CH_3CN was then removed in vacuo, and the residue was extracted with AcOEt three times. The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (22 g). Elution with hexane–AcOEt (2/1) afforded nitrile **4** (840 mg, 85%) as colorless solid, mp 131–133 °C; IR (KBr, cm^{-1}) 3313, 3010, 2231, 1595, 1573, 1491, 1411, 1284, 1180, 1041, 856, 821, 615; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.94 (s, 3H, OMe), 6.57 (s, 1H, OH), 7.06 (d, $J = 1.6$ Hz, 1H, H-6), 7.64 (d, $J = 1.6$ Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.6, 80.9, 105.1, 113.4, 117.6, 135.2, 145.7, 150.0. Anal. calcd for $C_8H_6NO_2I$: C 34.94, H 2.20, N 5.09; found: C 35.02, H 2.23, N, 5.05.

2.3. Vanillyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (6a)

Acetobromoglucose **5** (252.7 mg, 0.615 mmol) was added to a solution of **3a** (926.4 mg, 6.09 mmol) and diisopropylethylamine (0.8 mL, 4.86 mmol) in CH_3CN (13.8 mL), and the mixture was stirred at room temperature for 21 h. Then the mixture was concentrated in vacuo and any trace of solvent and diisopropylethylamine were removed azeotropically with toluene twice. The residue was purified by silica gel column chromatography (39 g). Elution with hexane–AcOEt (1/1) gave the glycoside **6a** (215.7 mg, 73%); mp 142–143 °C (lit. [6] 144–145 °C); $[\alpha]_D^{21}$ −47.5° (*c* 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ: 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.08 (s, 3H, OAc), 3.85 (m, 1H, H-5), 3.89 (s, 3H, OMe), 4.19 (dd, $J = 2.6$, 12.6 Hz, 1H, H-6a), 4.28 (dd, $J = 2.6$, 12.6 Hz, 1H, H-6b), 5.22 (m, 3H, H-2, H-3, H-4), 5.35 (d, $J = 7.4$ Hz, 1H, H-1), 7.21 (d, $J = 8.4$ Hz, 1H, H-3′), 7.41 (dd, $J = 1.8$, 8.4 Hz, 1H, H-2′), 7.43 (d, $J = 1.8$ Hz, 1H, H-6′), 9.89 (s, 1H, CHO).

2.4. 4-Formyl-2-iodo-6-methoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (6b)

The glycoside **6b** was obtained according to the procedure as above with acetobromoglucose **5** (13.3 mg, 32.3 μmol), aldehyde **3b** (18.0 mg, 64.6 μmol), diisopropylethylamine (9.6 μL, 55.4 μmol) and in acetonitrile (1 mL) for 20 h. The mixture was stirred further under reflux for 2 h. The workup and purification provide **6b** (14.3 mg, 73%). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.01 (s, 3H, OAc), 2.02 (s, 6H, OAc), 2.06 (s, 3H, OAc), 3.67 (m, 1H, H-5), 3.90 (s, 3H, OMe), 4.09 (dd, $J = 2.2$, 12.1 Hz, 1H, H-6a), 4.16 (dd, $J = 4.6$, 12.1 Hz, 1H, H-6b), 5.27 (m, 3H, H-2, H-3, H-4), 5.46 (d, $J = 7.4$ Hz, 1H, H-1), 7.40 (d, $J = 1.6$ Hz, 1H, H-6′), 7.84 (d, $J = 1.6$ Hz, 1H, H-2′), 9.81 (s, 1H, CHO). Its structure was confirmed by the conversion to **6c**, in a similar manner as described for the preparation of **4**.

2.5. 4-Cyano-2-iodo-6-methoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (6c)

Acetobromoglucose **5** (205.8 mg, 0.50 mmol), nitrile **4** (172.8 mg, 0.628 mmol), and diisopropylethylamine (96 μL, 0.55 mmol) were reacted in CH_3CN (4.5 mL) under reflux for 2.5 h. The workup and purification provided **6c** (220 mg,