Indian Journal of Heterocyclic Chemistry
Vol. 33 - Number 02 (Apr-Jun 2023) 209-214
https://connectjournals.com/01951.2023.33.209
https://doi.org/10.59467/IJHC.2023.33.209

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

Total Synthesis of Three Natural Phenolic Glycosides

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ABSTRACT Phenolic glycosides are substances widely occurring in nature, especially those with phenolic hydroxyl, ester, or methoxy groups at benzene rings. Such compounds are known to possess anti-diabetic, anti-inflammatory, and neuroprotective effects. However, some of them are not inherently abundant. Therefore, the synthesis of such molecules is desirable. In this study, natural phenol glycosides 1-3 were synthesized from readily accessible materials with overall yields of 45.4~48.7%.

KEYWORDS: Total synthesis, Natural products, Phenolic glycosides.

How to cite this article: Cao, N., Cao, S., Tang, K., Lu, D., Zhang, J., Ye, Z., Zhuang, Z., Ye, M., Lu, J., Hu, L., Song, Y., and Ye, X. Total Synthesis of Three Natural Phenolic Glycosides, *Indian J. Heterocycl. Chem.*, **2023**, *33*, 209–214. (https://doi.org/10.59467/IJHC.2023.33.209)

INTRODUCTION

Phenol glycoside with phenolic hydroxyl, ester, or methoxy function at benzene rings is substances widely occurring in nature. The most famous compound among this kind of biological products is *cuculigoside*, which is isolated from *Curculigo orchioides Gaertn*.[1,2] It's rhizome, named "Xian Mao" in traditional Chinese medicine, has been applied in the treatment for impotence, limb limpness, arthritis of the lumbar and knee joints, and watery diarrhea.

As shown in **Figure 1**, phenol glycosides 1 (curculigoside A) [2-hydroxy-5-(((2*S*,3*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2yl) oxy) benzyl 2,6-dimethoxybenzoate], phenol glycosides 2 (curculigosideB) [2-hydroxy-5-(((2*S*,3*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy) benzyl 2-hydroxy-6-methoxybenzoate], and phenol glycosides 3 (curculigoside **C**) [2-hydroxy-5-(((2*S*,3*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl)oxy)benzyl 3-hydroxy-2,6-dimethoxybenzoate]. These compounds have attracted scientific attention as a consequence of their diverse biological activities,[2,4,5] which include anti-diabetic, anti-inflammatory, and neuroprotective effect. However, all of these compounds have been isolated in poor yields from natural sources and synthesis of them are seldom recorded.[4,6,9] So far, detailed pharmacological study of these compounds has been minimal. Hence, efficient synthetic paths for these potentially useful natural products are required. We herein report the first total synthesis of phenol glycosides 1-3 involving new synthetic methods to obtain key-intermediates 10b and 10c from inexpensive materials.

RESULTS AND DISCUSSION

As displayed in **Scheme 1**, the synthesis of compounds **1-3** began with commercially accessible methyl 2,5-dihydroxybenzoate (**4**). The reported benzyl-protection method was used to protect the aromatic hydroxy group of **4** to yield compound **5** in 60% of yield. Compound **5** was reduced with $LiAlH_4$ (3 equiv.) to afford the corresponding alcohol **6** in 90% yield. Then, compounds **7a-c** were obtained by Steglich Esterification[5,10,11] with **10a-c**.

On the other hand, 2,3,4,6-tetra-O-benzyl-1-bromo-α-*D*-glucopyranose (**20**) was prepared from *D*-glucose in three steps according to a literature[4,6] method

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(s, 1H), 7.38 (t, *J*=8.8 Hz, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 6.98 (d, *J*=8.8 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J*=3.0 Hz, 1H), 6.78 (d, *J*=8.5 Hz, 1H), 6.73 (d, *J*=8.5 Hz, 1H), 6.64 (dd, *J*=3.0, 8.8 Hz, 1H), 5.32 (s, 2H), 4.61 (d, *J*=7.4 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.46 (dd, *J*=5.5, 11.4 Hz, 1H), 3.23 (m, 3H), 3.16 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 165.9, 157.1 (2C), 152.8, 147.9, 131.7, 127.7, 117.7, 115.2, 114.9, 113.2 (2C), 104.8, 103.1, 77.5, 77.0, 73.8, 70.3, 61.8, 61.4, 56.3(2C).

Synthesis of 2-hydroxy-5-(((2S,3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl) oxy)benzyl 2-hydroxy-6-methoxybenzoate (2)

The procedure was the same as compound 1 in Section 3.2.18 from compound 9b to afford a colorless solid 2 in 91% yield. m.p. 209.6~211.1°C. HR-MS (ESI) calced for $C_{21}H_{24}O_{11}Na[M+Na]^+$ 475.1319 found 475.1316. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.01 (s, 1H), 9.05 (s, 1H), 7.23 (t, *J*=8.3 Hz, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 6.98 (d, *J*=8.8 Hz, 1H),6.93 (s, 1H), 6.85 (d, *J*=2.8 Hz, 1H), 6.64 (dd, *J*=2.8, 8.8 Hz, 1H), 6.57 (d, *J*=8.3 Hz, 1H), 6.53 (d, *J*=8.3 Hz, 1H) 5.31 (s, 2H), 4.62 (d, *J*=6.9 Hz, 1H), 3.76 (s, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.46 (dd, *J*=5.5, 11.4 Hz, 1H), 3.23 (m, 3H), 3.16 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 166.6, 157.9, 156.1, 152.8, 148.0, 131.7, 127.4, 117.8, 115.2, 114.9, 111.4, 102.7, 103.1, 77.4, 76.9, 73.8, 70.3, 61.7 (2C), 61.3, 56.3.

Synthesis of2-hydroxy-5-(((2S,3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl 3-hydroxy-2,6-dimethoxybenzoate (3)

The procedure was the same as compound 1 in Section 3.2.18 from compound 9c to afford a colorless solid 3 in 91% yield. m.p. 107.3~108.1°C. HR-MS (ESI) calced for $C_{22}H_{26}O_{12}Na[M+Na]^+$ 505.1424 found 475.1319. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.19 (s, 1H), 9.06 (s, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 6.99 (d, *J*=8.8 Hz, 1H), 6.88 (d, *J*=8.9 Hz, 1H), 6.82 (d, *J*=2.3 Hz, 1H), 6.67 (d, *J*=8.9Hz, 1H), 6.65 (dd, *J*=2.3, 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (d, *J*=6.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.57 (s, 1H), 3.51 (s, 1H), 3.46 (dd, *J*=5.5, 11.4 Hz, 1H), 3.23 (m, 3H), 3.16 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 165.3, 152.3, 148.5, 147.6, 144.6, 126.5, 118.7, 117.6, 117.2, 114.9, 114.6, 107.3, 102.5, 77.0, 76.5, 73.3, 70.0, 61.5 (2C), 60.8, 60.5, 56.1.

ACKNOWLEDGMENT

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Received: 15 Jan 2023; Accepted: 14 May 2023