

HETEROCYCLES, Vol. 102, No. 9, 2021, pp. 1791 - 1796. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 11th May, 2021, Accepted, 11th June, 2021, Published online, 15th June, 2021
DOI: 10.3987/COM-21-14493

CONCISE SYNTHESIS OF EUTIGOSIDE C

Shiqiang Yan,^{1#} Yueyue Zhu,^{1#} Lisha Wu,² Liqun Chi,^{3*} and Wei Zhang^{1*}

¹ School of Pharmacy, Fudan University, Shanghai, 201203, China. ² Weihai Ocean Vocational College, Weihai, 264300, China. ³ Department of Pharmacy, Haidian Maternal & Child Health Hospital of Beijing, Beijing, 100080, China. E-mail addresses: chilikun@sohu.com (L. Chi); Zhangw416@fudan.edu.cn (W. Zhang)

[#]These authors contributed equally to this work

Abstract – Eutigoside C, a new glucoside with a variety of biological activities, was synthesized *via* regioselective Me₂SnCl₂-catalyzed *O*-6 acylation and mild oxidation strategy. Through this route, eutigoside C was obtained from inexpensive starting materials in a linear 5-step sequence with an overall yield of 35.2%.

Phenylethanoid glycosides (PhGs) are one group of water-soluble secondary metabolites widely distributed in several medicinal plant species and well known for their important biological activities, including antioxidant, neuroprotective, antibacterial, antiviral, antitumor, anti-inflammatory, analgesic, anti-radiation, anti-aging, anti-fatigue, cardioprotective activities and others.¹⁻⁴ Phenylethanoid glycosides are structurally characterized by 2-phenylethyl-β-D-glucoside core, which is attached to a cinnamoyl group, mainly at *O*-4 or *O*-6. More complex PhGs metabolites contain additional saccharide units. The diversity of glycosyl, hydroxyphenethyl and cinnamoyl moieties make the plentiful variation of PhGs.⁵

Given the outstanding pharmacological activities and complex structures of PhGs, they have been increasingly brought to researchers' attention in the past few decades. However, the development of PhGs has been severely limited by the fact that most of them can only be isolated in small amounts from natural sources.^{6,7} Besides, there are also some difficulties associated with total synthesis of PhGs because of the incompatibility of common hydroxyl protecting groups with the phenylpropenic ester group.⁸ For example, the removal of benzyl ether protecting groups by hydrogenolysis or acetyl protecting groups by hydrolysis would result in reduction or migration of the cinnamoyl moieties, respectively. So the efficient synthesis investigation is highly desired to facilitate further bioactivity studies of this class of compounds.

Eurya emarginata (Thumb) Makino (Theaceae) is narrowly distributed in coastal areas from southern China, along southern Korea and extending to central and southern Japan.⁹ The leaves of *E. emarginata* were used as traditional medicine in the coastal areas of Jeju Island to treat ulcers or as a diuretic.¹⁰

In 1992, a new glucoside, 6'-*O*-cinnamoyl-1'-*O*-[2-(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)ethyl]- β -D-glucopyranoside (eutigoside C) was isolated from the fresh leaves of *E. emarginata* by Sticher and co-workers.¹¹ Eutigoside C exerted the cytotoxicity against promyelocytic leukemia cells such as HL-60 via the down-regulation of Bcl-2 and the activation of caspase.¹² In addition, this compound exhibited significant anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines (interleukin-6, TNF- α , NO, and PGE2).⁹ Some researchers also revealed that these inhibitory effects involved suppression of the activation of NF- κ B and phosphorylation of MAP kinases (ERK1/2, JNK and p38).¹³ Moreover, eutigoside C could be a useful radioprotector capable of defending radiation-induced intestinal injury.¹⁰

In our continuous efforts towards the synthesis of bioactive natural glycoconjugates,¹⁴⁻¹⁸ herein we report a short and high-yield synthesis of eutigoside C without tedious protection-deprotection procedure.

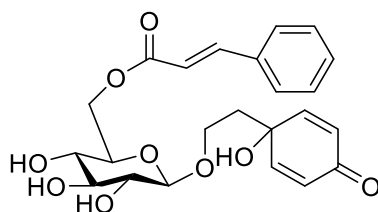
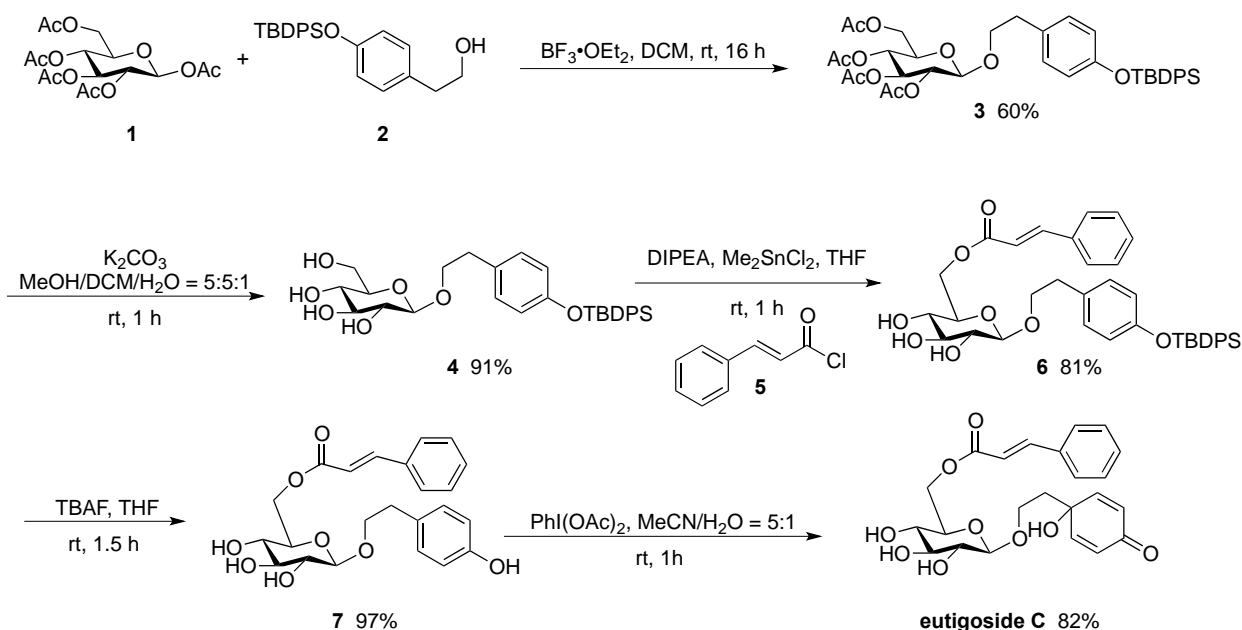


Figure 1. Chemical structure of eutigoside C

Our synthetic route for eutigoside C was outlined in **Scheme 1**. Coupling of 1,2-*trans*- β -glycosylation of peracetate D-glucose (**1**) with 2-phenylethanol (**2**) through a neighboring group participation mechanism afforded 2-phenylethyl- β -D-glucoside (**3**).



Scheme 1. Synthesis of eutigoside C

The next step is the removal of the acetyl groups in compound **3**. To our delight, treatment of compound **3** with K_2CO_3 in MeOH/DCM/ H_2O (5:5:1) provided β -D-glucopyranoside **4** in 91% yield after purification by column chromatography.^{17,18} Then the acylated glucoside **6** was prepared in 81% yield by a directly regioselective *O*-6 acylation of unprotected 2-phenylethyl- β -D-glucoside **4** in the presence of 1.5 equiv. cinnamoyl chlorides **5** as acylating reagent and Me_2SnCl_2 as catalyst.^{17,18} Deprotection of the TBDPS group of acylated glucoside **6** produced compound **7** in 97% yield.¹⁹ Finally, the target product was achieved in 82% yield after treatment of **7** with (diacetoxyiodo)benzene in aqueous acetonitrile.²⁰ The structure of the synthesized eutigoside C was confirmed by 1H NMR, ^{13}C NMR, and HRMS, and the data matched well with that of natural product. To the best of our knowledge, this is the first total synthesis of eutigoside C so far.

In conclusion, eutigoside C was synthesized in five linear steps in 35.2% overall yield for the first time. No migration and/or hydrolysis of the cinnamoyl moieties were observed at any stage. The remarkable strategy in this synthesis involves a regioselective Me_2SnCl_2 -catalyzed *O*-6 acylation of an unprotected glucose core, which has general applicability for the synthesis of phenylpropanoid glycosides acylated at *O*-6.

EXPERIMENTAL

General information

Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz or 600 MHz spectrometer as indicated in the data list. The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet, respectively.

Experimental section

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-((*tert*-butyldiphenylsilyl)oxy)phenethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**3**). To a solution of **2** (3.76 g, 10.00 mmol), peracetate D-glucose **1** (7.80 g, 20.00 mmol) in dry CH_2Cl_2 (90 mL), $BF_3 \cdot OEt_2$ (3.60 mL, 15.00 mmol) was added dropwise at room temperature under N_2 atmosphere. The mixture was stirred for 16 h. After completion (TLC), the solution was diluted with water and then extracted with CH_2Cl_2 (2 \times 80 mL). The combined organic layer was washed with saturated brine (80 mL), dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain **3** (4.25 g, 60%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.7$ Hz, 4H), 7.47–7.28 (m, 6H), 6.90 (d, $J = 7.9$ Hz, 2H), 6.66 (d, $J = 8.2$ Hz, 2H), 5.16 (t, $J = 9.5$ Hz, 1H), 5.07 (t, $J = 9.6$ Hz, 1H), 4.97 (t, $J = 8.9$ Hz, 1H), 4.44 (d, $J = 7.9$ Hz, 1H), 4.25 (dd, $J = 12.1, 4.3$ Hz, 1H), 4.12 (dd, $J = 13.7, 6.9$ Hz, 1H), 4.04 (dd, $J = 15.6, 6.5$ Hz, 1H), 3.65 (d, $J = 9.9$ Hz, 1H), 3.57 (dd, $J = 16.3, 7.9$ Hz, 1H), 2.74 (d, $J = 6.9$ Hz, 2H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.71, 170.32, 169.41, 169.31, 154.06, 135.51, 133.00, 130.73, 129.87, 129.62, 127.75, 119.45, 100.73, 72.81, 71.78, 71.13, 70.84, 68.44, 61.93, 35.03, 26.51, 20.75, 20.61, 20.55, 19.44; HRESIMS calcd for $\text{C}_{38}\text{H}_{46}\text{O}_{11}\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 729.2702, found 729.2702.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-((*tert*-Butyldiphenylsilyl)oxy)phenethoxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**4**). To a solution of **3** (3.53 g, 5.00 mmol) in MeOH/DCM/ H_2O (25/25/5 mL) was added anhydrous potassium carbonate (1.38 g, 10.00 mmol). The solution was stirred for 1 h. After the completion of the reaction, the mixture was quenched with 1 M HCl and then concentrated. The residue was purified by silica gel column chromatography to obtain the desired compound **4** (2.69 g, 91%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 6.4$ Hz, 4H), 7.39–7.20 (m, 6H), 6.80 (d, $J = 7.5$ Hz, 2H), 6.61 (d, $J = 7.4$ Hz, 2H), 4.23 (d, $J = 7.2$ Hz, 1H), 3.87 (d, $J = 6.7$ Hz, 1H), 3.71 (d, $J = 13.1$ Hz, 2H), 3.53 (d, $J = 9.4$ Hz, 2H), 3.42 (t, $J = 8.6$ Hz, 1H), 3.29 (d, $J = 7.9$ Hz, 1H), 3.18 (s, 1H), 2.70 (s, 2H), 1.05 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 154.09, 135.47, 132.92, 130.14, 129.86, 129.61, 127.75, 119.59, 102.75, 76.23, 75.48, 73.31, 71.20, 69.20, 61.24, 35.11, 26.51, 19.43; HRESIMS calcd for $\text{C}_{30}\text{H}_{38}\text{O}_7\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 561.2279, found 561.2277.

((2*R*,3*S*,4*S*,5*R*,6*R*)-6-(4-((*tert*-Butyldiphenylsilyl)oxy)phenethoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-yl)methyl cinnamate (**6**). To a solution of **4** (0.81 g, 1.50 mmol) in dry THF (20.0 mL) at room temperature were added Me_2SnCl_2 (33.0 mg, 0.15 mmol) and DIPEA (530 μL , 3.0 mmol) under vigorous stirring. 15 min later, the mixture was treated with cinnamoyl chloride **5** (0.38 g, 2.25 mmol). After stirred for additional 1 h (TLC), the mixture was added MeOH and concentrated under reduced pressure. The residue was then extracted with EtOAc (50 mL), washed with 1 M HCl (20 mL) and saturated brine (20 mL), respectively. The combined organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and purified by silica gel column chromatography to obtain **6** (810 mg, 81%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.6$ Hz, 4H), 7.53–7.47 (m, 2H), 7.45–7.31 (m, 9H), 6.92 (d, $J = 8.3$ Hz, 2H), 6.67 (d, $J = 8.2$ Hz, 2H), 6.49 (d, $J = 16.0$ Hz, 1H), 4.69 (dd, $J = 12.4, 3.4$ Hz, 1H), 4.35 (d, $J = 12.2$ Hz, 1H), 4.26 (d, $J = 7.7$ Hz, 1H), 4.08 (dd, $J = 16.1, 7.3$ Hz, 1H), 3.68–3.31 (m, 6H), 3.15 (s, 1H), 2.81 (t, $J = 7.2$ Hz, 2H), 2.54 (s, 1H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.95, 154.15, 146.21, 135.51, 134.11, 132.94, 130.61, 130.43, 129.86, 129.59, 128.95, 128.25, 127.75, 119.64, 117.16, 102.95,

75.66, 74.31, 73.59, 71.16, 69.68, 63.16, 35.23, 26.50, 19.43; HRESIMS calcd for $C_{39}H_{44}O_8SiNa$ $[M+Na]^+$ 691.2698, found 691.2694.

((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-(4-hydroxyphenethoxy)tetrahydro-2*H*-pyran-2-yl)methyl cinnamate (**7**). To a solution of glucopyranoside **6** (0.76 g, 1.13 mmol) in THF (15 mL), TBAF·3H₂O (1.07 g, 3.40 mmol) was added. The reaction mixture was stirred for 1.5 h before concentrated to dryness, and then re-dissolved in H₂O (5 mL). The aqueous solution was extracted with EtOAc (10 mL x 5) and the organic phase was dried over Na₂SO₄, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography to give 0.47 g of **7** in 97% yield as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.65 (d, *J* = 16.1 Hz, 1H), 7.49 (s, 2H), 7.35 (s, 3H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.37–4.24 (m, 2H), 3.90 (dd, *J* = 16.7, 8.3 Hz, 1H), 3.67 (dd, *J* = 16.6, 8.5 Hz, 1H), 3.50 (t, *J* = 6.9 Hz, 1H), 3.38–3.30 (m, 2H), 3.17 (t, *J* = 7.8 Hz, 1H), 2.79 (t, *J* = 7.4 Hz, 2H); ¹³C NMR (150 MHz, CD₃OD) δ 168.46, 156.83, 146.57, 135.69, 131.59, 130.94, 130.57, 130.07, 129.30, 118.71, 116.18, 104.60, 77.98, 75.40, 75.09, 72.49, 71.87, 64.91, 49.46, 49.31, 49.17, 49.03, 48.89, 48.75, 48.60, 36.55; HRESIMS calcd for $C_{23}H_{26}O_8Na$ $[M+Na]^+$ 453.1520, found 453.1523.

((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-(2-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethoxy)tetrahydro-2*H*-pyran-2-yl)methyl cinnamate (eutigoside C). To a solution of **7** (0.24 g, 0.56 mmol) in MeCN (10 mL) and water (2 mL), (diacetoxyiodo)benzene (0.20 g, 0.62 mmol) was added in one portion. After 1 h, the reaction was quenched with 5 mL of saturated aqueous Na₂S₂O₃ solution followed by 10 mL of saturated aqueous NaHCO₃ solution. The resulting mixture was further diluted with saturated aqueous NaCl solution and EtOAc, and the organic layers were separated. The aqueous phase was extracted with EtOAc before the combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography to give eutigoside C as a white solid (205 mg, 82%). ¹H NMR (400 MHz, CD₃OD) δ 7.72 (d, *J* = 16.1 Hz, 1H), 7.63 (s, 2H), 7.42 (s, 3H), 6.99 (s, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.08 (d, *J* = 9.6 Hz, 2H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.26 (d, *J* = 7.1 Hz, 1H), 3.92 (s, 1H), 3.66 (s, 1H), 3.52 (s, 1H), 3.34 (d, *J* = 18.6 Hz, 2H), 3.18 (s, 1H), 2.05 (s, 2H), 1.29 (s, 1H); ¹³C NMR (150 MHz, CD₃OD) δ 185.81, 166.44, 152.40, 152.29, 144.52, 129.56, 128.04, 127.29, 125.98, 125.87, 116.68, 102.38, 75.88, 73.35, 72.98, 69.69, 67.17, 63.87, 62.80, 38.98; HRESIMS calcd for $C_{23}H_{26}O_9Na$ $[M+Na]^+$ 469.1469, found 469.1458.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the National Key Research and Development Program of China (Grant No. 2018YFC0310900) and Natural Science Foundation of Shandong Province (Grant No. ZR2020KH002).

REFERENCES

1. X. Y. Tian, M. X. Li, T. Lin, Y. Qiu, Y. T. Zhu, X. L. Li, W. D. Tao, P. Wang, X. X. Ren, and L. P. Chen, *Eur. J. Med. Chem.*, 2021, **209**, 112563.
2. Z. Xue and B. Yang, *Molecules*, 2016, **21**, 991.
3. B. B. Gao, G. M. She, and D. M. She, *Chem. Biodivers.*, 2013, **10**, 96.
4. F. Guangmiao, P. Haihong, and H. W. Yung, *Curr. Med. Chem.*, 2008, **15**, 2592.
5. L. Wu, M. I. Georgiev, H. Cao, L. Nahar, H. R. El-Seedi, S. D. Sarker, J. Xiao, and B. Lu, *Med. Res. Rev.*, 2020, **40**, 2605.
6. S. V. Luca, A. Miron, S. Ignatova, and K. Skalicka-Woźniak, *Phytochem. Rev.*, 2019, **18**, 377.
7. P. Shu, L. Zhang, A. Liu, J. Li, Q. Liu, N. Sun, Y. Zhang, X. Wei, M. Cui, Z. Ju, and Z. Xu, *ChemistrySelect*, 2020, **5**, 10817.
8. S. K. Mulani, J. H. Guh, and K. K. Mong, *Org. Biomol. Chem.*, 2014, **12**, 2926.
9. S. Y. Park, H. J. Lee, W. J. Yoon, G. J. Kang, J. Y. Moon, N. H. Lee, S. J. Kim, H. K. Kang, and E. S. Yoo, *Arch. Pharm. Res.*, 2005, **28**, 1244.
10. C. Moon, K. Ahn, J. Kim, J. Kim, S.-H. Kim, T. H. Oh, N. H. Lee, Y. Jee, J. W. Hyun, J. W. Park, and T. Shin, *Phytother. Res.*, 2010, **24**, 840.
11. I. A. Khan, C. A. J. Erdelmeier, O. Sticher, and T. Rali, *J. Nat. Prod.*, 1992, **55**, 1270.
12. S. Y. Park, H. C. Yang, J. Y. Moon, N. H. Lee, S. J. Kim, J. H. Kang, Y. K. Lee, D. B. Park, E. S. Yoo, and H. K. Kang, *Arch. Pharm. Res.*, 2005, **28**, 1047.
13. H. J. Lee, T. H. Oh, W. J. Yoon, G. J. Kang, E. J. Yang, S. S. Park, N. H. Lee, H. K. Kang, and E. S. Yoo, *J. Pharm. Pharmacol.*, 2008, **60**, 917.
14. S. Q. Yan, M. X. Xie, Y. J. Wang, Q. Xiao, N. Ding, and Y. X. Li, *Tetrahedron*, 2020, **76**, 130950.
15. S. Q. Yan and Y. X. Li, *Chin. J. Org. Chem.*, 2019, **39**, 561.
16. S. Q. Yan, M. X. Xie, Y. J. Wang, and Y. X. Li, *Chin. J. Org. Chem.*, 2019, **39**, 412.
17. S. Q. Yan, S. M. Ren, N. Ding, and Y. X. Li, *Carbohydr. Res.*, 2018, **460**, 41.
18. S. Q. Yan, Y. Y. Zhu, Y. J. Wang, Q. Xiao, N. Ding, and Y. X. Li, *Tetrahedron Lett.*, 2020, **61**, 151886.
19. S. Q. Yan, N. Ding, W. Zhang, P. Wang, Y. X. Li, and M. Li, *Carbohydr. Res.*, 2012, **354**, 6.
20. J. Mease and K. P. Reber, *J. Org. Chem.*, 2016, **81**, 12006.