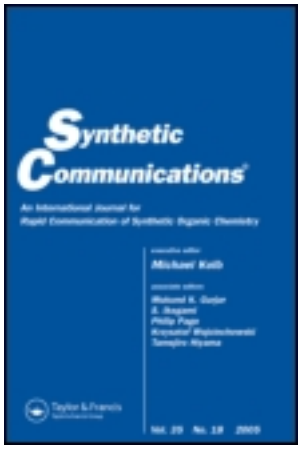

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CONCISE SYNTHESIS OF RING-FISSION METABOLITES OF EPICATECHIN: 5-(3,4-DIHYDROXYBENZYL)DIHYDROFURAN-2(3*H*)-ONE M6

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The ring-fission metabolites of epicatechin, 5-(3,4-dihydroxybenzyl)dihydrofuran-2(3H)-one M6 and 3-methylated M6, were prepared from 3,4-dihydroxybenzaldehyde and furan-2(5H)-one using two new concise methods in excellent yields (three or two steps in 40–60% overall yield).

Keywords: 5-(3,4-Dihydroxybenzyl)dihydrofuran-2(3*H*)-one; epicatechin; metabolite; methylated **M6**

INTRODUCTION

The biologically active compounds in drugs and foods are not always effective by themselves but can act as precursors. By metabolic processes (digestion, fermentation in the colon, detoxification by the hepatic system, etc.), these compounds are converted, and the resulting metabolites might contribute, or even be responsible, for the biological activities observed.[1–3] For the study of their corresponding involvement and roles in the relevant metabolic processes, pure reference standards for these compounds are required. Moreover, these active metabolites become a vast reservoir of potential therapeutic agents, and there is increasing interest and investigation in using them as the original drugs. 5-(3,4-Dihydroxybenzyl)dihydrofuran-2(3*H*)-one (**M6**) and 5-(3,4,5-trihydroxybenzyl)dihydrofuran-2(3*H*)-one (**M4**), as the ring-fission metabolites of epicatechin and epigallocatechin, respectively (Fig. 1), together with the partially methylated derivatives of **M4** and **M6**, were found in urine and plasma after the consumption of green tea.[4–7] A pathway of the microbial degradation of epicatechin to **M6** by the colonic flora has been proposed on the basis of an in vitro study (Scheme 1).[8,9] Recently, **M6** and 3-methylated **M6** were also detected as the metabolites after consumption of fruit and vegetable dietary flavanoids.[10]

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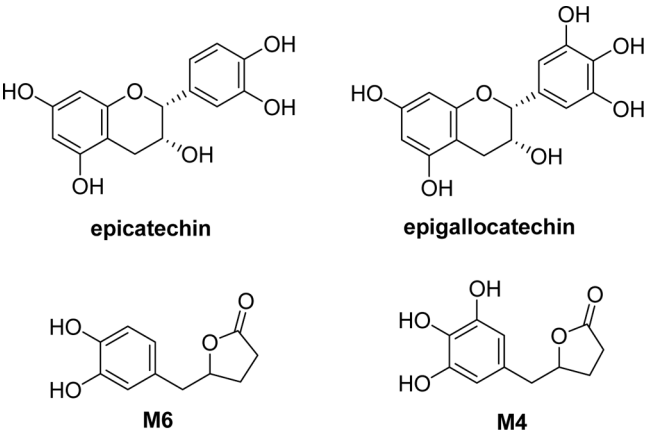
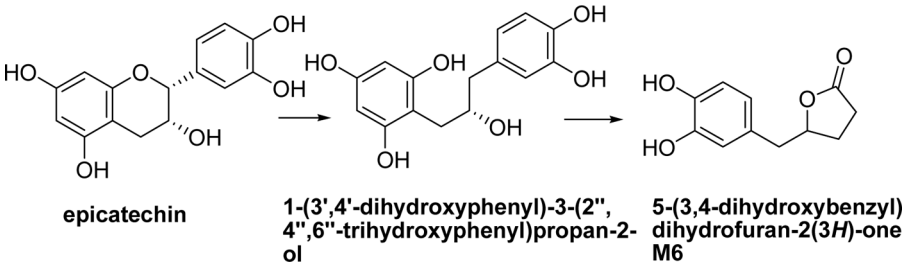


Figure 1. Structures of 5-(3,4-dihydroxybenzyl)dihydrofuran-2(3*H*)-one **M6** and 5-(3,4,5-trihydroxybenzyl)-dihydrofuran-2(3*H*)-one **M4**.

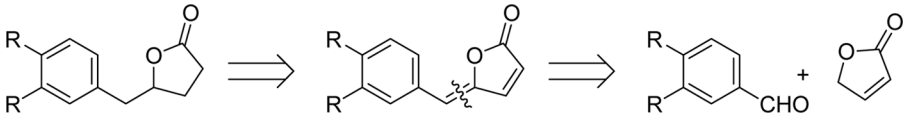


Scheme 1. Pathway of the microbial degradation of epicatechin within the digestive system.

To evaluate the importance of these compounds, pure standards are required for analytical purposes. It has been found that **M6** exhibited excellent antioxidant properties and that **M4** was capable of inhibiting the growth of immortalized and malignant human cell lines.[11] This might suggest that these two metabolites contribute to the anti-inflammatory and cancer-preventive activities of green tea,[12] which requires further research on the biological activity of **M6**, **M4**, and their methylated derivatives.

RESULTS AND DISCUSSION

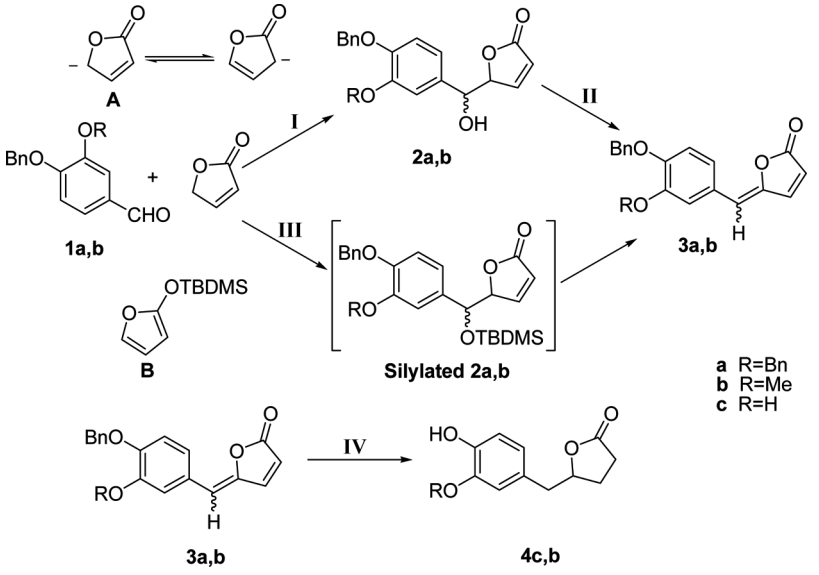
Over the past years, several groups have tried different synthetic approaches to prepare these compounds as reference standards or to investigate their possible therapeutic use. Lambert et al. employed δ-phenyl-γ, δ-unsaturated methyl ester as a key intermediate.[11] Following six or seven steps of transformation, including epoxidation, reduction, and lactonization, the target compound was finally afforded in about 10% overall yield. Watanabe reported that a 1,2-epoxy-3-phenylpropan derivative could serve as a key intermediate to react with ethyl sodium malonate



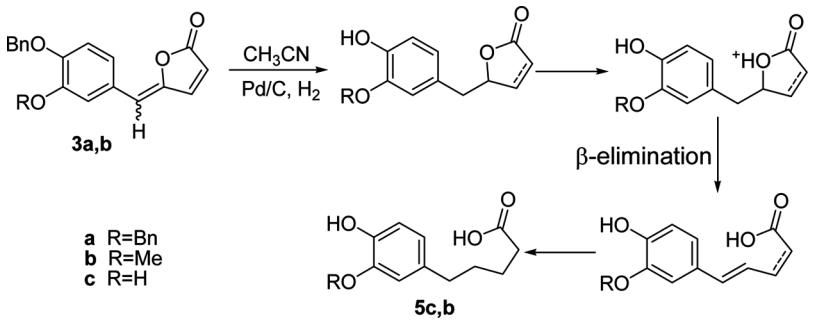
Scheme 2. Retrosynthetic analysis of 5-phenyl-γ-valerolactone.

and then lactonization and decarboxylation generated the target compound with about 9% overall yield in four steps.[13] Both methods were somewhat tedious, but on the other hand the two intermediates had to be prepared in advance by several steps. An internal urgent need for gram amounts of the pure metabolites necessitated development of an efficient and simple synthetic method to prepare **M6** and methylated **M6**. We envisaged a concise and efficient route with potential to be applied to the synthesis of other polyphenol metabolites like **M4** because of the similarity of the structure (Scheme 2). A selective catalytic reduction of the two double bonds of the aldol condensation product that is prepared from readily accessible benzaldehyde derivatives and furan-2(5*H*)-one was expected to give the γ-valerolactones in an easy and scalable way.

Indeed, 5-(3,4-dihydroxybenzyl)dihydrofuran-2(3*H*)-one **M6** and 3-methylated **M6** could be successfully synthesized according to the proposed route. The synthesis started with the addition reaction of furan-2(5*H*)-one to protected 3,4-dihydroxylphenyl aldehyde (Scheme 3). In the first approach, lithiated furan-2(5*H*)-one **A** was in situ generated as nucleophile by treatment of furan-2(5*H*)-one with



Scheme 3. Synthesis of 5-(3–4-dihydroxybenzyl)dihydrofuran-2(3*H*)-one **M6** and 3-methylated **M6**. Reagents and conditions: (I) LDA, THF, −78 °C (**2a**: 59%, **2b**: 52%); (II) MsCl, pyridne, rt (**3a**: ~100%, **3b**: 81%); (III) TBDMSOTf, DIEA, THF, DBU, rt (**3a**: 47%, **3b**: 54%); (IV) CH_3CN, Pd/C, H_2, rt (**4c**: 91%, **4b**: 80%).



Scheme 4. Formation mechanism of by-products **5c** and **5b**.

LDA.[14,15] The reaction went exclusively at the γ-position of furan-2(5*H*)-one, and the regiospecific products, 5-[[3,4-bis(benzyloxy)phenyl](hydroxy)methyl]furan-2(5*H*)-one **2a** and 5-[[4-(benzyloxy)-3-methoxyphenyl](hydroxy)methyl]furan-2(5*H*)-one **2b**, were obtained in moderate yield. Afterward, the hydroxyl group of **2a** and **2b** was mesylated in pyridine at room temperature, and consecutive β-elimination afforded the conjugated dienes 5-[3,4-bis(benzyloxy)benzylidene]furan-2(5*H*)-one **3a** and 5-[4-(benzyloxy)-3-methoxybenzylidene]furan-2(5*H*)-one **3b** as a mixture of *Z*- and *E*-isomer in excellent yield.

In the second, more efficient approach, *tert*-butyldimethylsily triflate (TBDMSOTf) was employed to facilitate the condensation of benzaldehyde **1** with furan-2(5*H*)-one. The intermediate (furan-2-yloxy) *tert*-butyldimethylsilane **B** was probably produced in the reaction from furan-2(5*H*)-one and TBDMSOTf in the presence of a base.[16–18] It subsequently reacted with **1a** and **1b** to form the silyl substituted intermediates **2a** and **2b** respectively, which were once isolated as by-products. Most of the final products were the expected condensation products **3a** and **3b**. It was obvious that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) had further eliminated TBDMSOH to give **3a** and **3b**. Consequently, **3a** and **3b** could be obtained directly from aldehyde and furan-2(5*H*)-one in a one-pot reaction.

Finally, **3a** and **3b** could be hydrogenated to reduce the two double bonds and remove the benzyl groups as well in the presence of Pd/C powder, consequently furnishing the target compounds 5-(3,4-dihydroxybenzyl)dihydrofuran-2(3*H*)-one **4c** and 5-(4-hydroxy-3-methoxybenzyl)dihydrofuran-2(3*H*)-one **4b** in 91% and 80% yields,[19] respectively (Scheme 3). However, an interesting by-product, 5-(3,4-dihydroxyphenyl)pentanoic acid **5c** or 5-(4-hydroxy-3-methoxyphenyl)pentanoic acid **5b**, which was produced by scission of lactone ring, was isolated. The formation could be minimized by using acetonitrile as solvent. The mechanism for formation could be rationalized as in Scheme 4.

CONCLUSION

In summary, we have described two alternative concise methods to synthesize the ring-fission metabolites of epicatechin, 5-(3,4-dihydroxybenzyl)dihydrofuran-2(3*H*)-one **M6** and 3-methylated **M6**, with satisfactory yield from the readily

available starting material. It is expected that 5-(3,4,5-trihydroxybenzyl)-dihydrofuran-2(3*H*)-one **M4** and its derivatives can be prepared by these methods too in gram quantities.

EXPERIMENTAL

5-[[3,4-Bis(benzyloxy)phenyl](hydroxyl)methyl]furan-2(5*H*)-one (**2a**) and 5-[[4-(benzyloxy)-3-methoxyphenyl](hydroxy)methyl]furan-2(5*H*)-one (**2b**) were prepared following the procedure reported in the literature.[14]

Compound **2a** was obtained as a yellow solid in the yield of 59%, as a mixture of *syn–anti* isomers (80:20). ^{1}H NMR (400 MHz, $CDCl_3$): 7.46–7.31 (m, 10H), 7.08–6.67 (m, 4H), 6.10 (*syn*) and 6.02 (*anti*) (d, $J = 5.7$ Hz, 1H), 5.20 (AB, $J = 12.3$ Hz, 2H), 5.18 (s, 2H), 5.04–5.02 (m, 1H), 4.96 (*syn*) and 4.53 (*anti*) (d, $J = 4.2$ Hz and 7.5 Hz respectively, 1H), 2.35 (s, br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.8, 152.7, 149.1, 148.9, 137.0, 131.3, 128.5, 127.9, 127.4, 127.3, 123.0, 119.2, 114.9, 113.1, 86.4, 72.7, 71.3, 71.2.

Compound **2b** was obtained as a yellow solid in the yield of 52%, as a mixture of *syn–anti* isomers (86:14). ^{1}H NMR (400 MHz, $CDCl_3$): 7.44–7.26 (m, 6H), 6.95–6.71 (m, 3H), 6.15 10 (*syn*) and 6.03 (*anti*) (d, $J = 5.8$ Hz, 1H), 5.15–5.11 (m, 3H), 4.97 and 4.60 (*anti*) (d, $J = 4.5$ Hz and 6.5 Hz respectively, 1H), 3.89 (s, 3H), 2.62 (s, br, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3): 172.8, 152.9, 150.0, 148.3, 136.9, 131.4, 128.5, 127.9, 127.2, 123.1, 118.4, 114.0, 108.7, 86.4, 73.0, 71.1, 56.1.

5-[3,4-Bis(benzyloxy)benzylidene]furan-2(5*H*)-one (**3a**) and 5-[4-(benzyloxy)-3-methoxybenzylidene]furan-2(5*H*)-one (**3b**) were prepared following the procedure reported in the literature[14] from **2a** and **2b,** respectively. Alternatively, they could be synthesized following the procedure described later directly from the corresponding benzaldehyde **1** and furan-2(5*H*)-one.

tert-Butyldimethylsily triflate was added to the solution of furan-2(5*H*)-one (0.097 g, 0.082 mL) in dichloromethane (10 mL). Then 3,4-dibenzoxyl benzaldehyde (0.368 g, 1.157 mmol) and diisobutyl ethyl amine (0.448 g, 0.604 mL) were added to the mixture. After the reaction was stirred at rt for 1 h, 1,8-diazabicyclo[5,4,0]undec-7-ene (0.352 g, 0.347 mL) was added dropwise. The reaction mixture was stirred for another 1 h. Then the solvent in the reaction was removed under reduced pressure. The residue was purified by flash chromatography (60% ethyl acetate in hexane) to give a yellow solid of **3a** as a 75:25 mixture of (*Z*)- and (*E*)-isomers (0.167 g, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.16 (m, 13H), 6.86 (d, $J = 8.4$, 1H), 6.13 (*E*) and 6.03 (*Z*) (d, $J = 5.5$ and 5.2 Hz respectively, 1H), 6.57 (*E*) and 5.81 (*Z*) (s, 1H), 5.17 (s, 2H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 150.0, 148.6, 147.1, 145.0, 136.8, 136.6, 128.4 (2), 127.8 (2), 127.5, 127.1, 126.3, 125.2, 116.7, 116.3, 114.1, 114.0, 71.1, 70.7.

Compound **3b** was prepared as yellow oil as a 70:30 mixture of (*Z*)–(*E*)-isomers according to the procedure for **3a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (*E*) (d, J = 5.5, 1H), 7.40–7.13 (m, 7H), 6.81 (d, $J = 8.0$, 1H), 6.23 (*E*) and 6.08 (*Z*) (d, $J = 5.5$ and 5.2 Hz respectively, 1H), 6.65 (*E*) and 5.89 (*Z*) (s, 1H), 5.13 (s, 2H), 3.88 (*Z*) and 3.85 (*E*) (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 149.7, 149.5, 147.2, 145.1, 136.6, 128.6, 128.0, 127.2, 126.4, 124.7, 116.9, 114.4, 113.6, 70.8, 56.1.

5-(3,4-Dihydroxybenzyl)dihydrofuran-2(3*H*)-one (**4c**) and 5-(4-hydroxy-3-methoxybenzyl)dihydrofuran-2(3*H*)-one (**4b**) were prepared as follows: Compound **3a** (2.882 g, 7.51 mmol) and 10% Pd/C powder (0.432 g) were suspended in CH_3CN (80 mL) under a hydrogen atmosphere. The reaction mixture was stirred at rt for 15 h. Upon thin-later chromatography (TLC) revealing completion of the reaction, the catalyst was filtered and washed with CH_3CN (50 mL). Removal of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (60% ethyl acetate in hexane) to give a white solid of **4c** (1.431 g, 91% yield). Mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 2H), 6.83–6.77 (m, 3H), 4.76–4.69 (m, 1H), 2.89 (ABd, $J = 14.4$, 5.6 Hz, 2H), 2.51–2.41 (m, 1H), 2.36–2.22 (m, 2H), 2.01–1.93 (m, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3): 177.3, 145.9, 144.8, 129.4, 121.7, 117.4, 116.1, 81.7, 41.3, 29.0, 27.8. Compound **4b** was prepared according to the procedure of **4c**. White solid. Mp 111–112 °C. Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87–6.70 (m, 3H), 5.56 (s, 1H), 4.76–4.70 (m, 1H), 3.89 (s, 3H), 2.93 (ABd, $J = 14.0$, 5.6 Hz, 2H), 2.50–2.40 (m, 1H), 2.35–2.21 (m, 2H), 2.00–1.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.1, 146.6, 144.7, 127.6, 122.2, 114.5, 112.1, 80.9, 56.0, 40.9, 28.7, 26.9.

The by-product **5b** was isolated from the reaction for the preparation of **4b** as a yellow oil and characterized accordingly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84–6.66 (m, 3H), 3.89 (s, 3H), 2.58 (t, $J = 7.2$ Hz, 2H), 2.39 (t, $J = 7.1$ Hz, 2H), 1.69–1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 179.8, 146.4, 143.7, 133.9, 120.9, 114.2, 110.9, 55.9, 35.2, 33.8, 31.0, 24.2.

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