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Graphical Abstract

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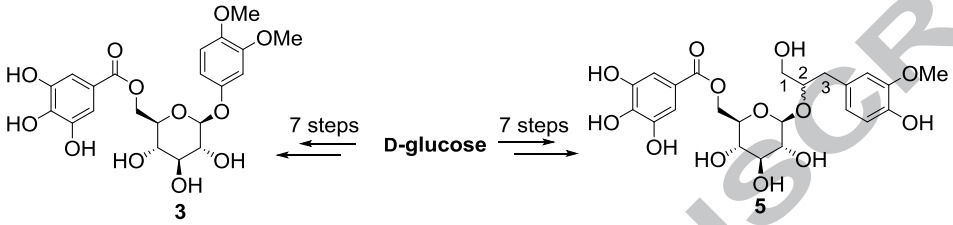

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Synthesis of Tyrosyl-DNA Phosphodiesterase I Inhibitors

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ABSTRACT

The first report for the synthesis of tyrosyl-DNA phosphodiesterase I inhibitors 3,4-dimethoxyphenol-1-*β*-D-(6′-*O*-galloyl)glucopyranoside **3** and 3-(4-hydroxy-3-methoxyphenyl) propane-1,2-diol 2-*β*-D-(6′-*O*-galloyl) glucopyranoside **5** has been accomplished starting from readily available D-glucose as a starting material. An efficient and general approach has been reported for the synthesis of compounds **3** and **5** with an overall yield of 26% and 27% respectively.

Topoisomerase I (Top1) tyrosine residue is covalently bound to the 3′-phosphate moiety of DNA. Tyrosyl-DNA phosphodiesterase I (Tdp1) is an enzyme that repairs DNA lesions.[1-5] Neurological disorders such as spinocerebellar ataxia are caused due to mutation of Tdp1 gene. Hence there is a need to study and synthesize Tdp1 inhibitors that could act synergistically. Recently Tian et. al in 2015[6] isolated compounds macropteranthol **1**, alongwith with four analogues, namely, mallophenol A **2**, 3,4-dimethoxyphenol-1-*β*-D-(6′-*O*-galloyl)glucopyranoside **3**, 3,4,5-trimethoxyphenol-1-*β*-D-(6′-*O*-galloyl) glucopyranoside **4**, and (*S*)-3-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol-2-*β*-D-(6′-*O*-galloyl) glucopyranoside **5a** (Figure 1) from a bark of Australian plant Macropteranthes leichhardtii and reported its inhibitory activity against tyrosyl-DNA phosphodiesterase I. Among all the natural products isolated by Tian et. al, compounds 3, 4-dimethoxyphenol-1-*β*-D-(6′-*O*-galloyl)glucopyranoside **3** and (*S*)-3-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol-2-*β*-D-(6′-*O*-galloyl) glucopyranoside **5a** showed good inhibitory activity against tyrosyl-DNA phosphodiesterase I with IC_{50} value of 1 M. Due to the interesting biological property of compounds **3** and **5a** we report a first synthetic route to compounds **3** and **5** starting from D-glucose.

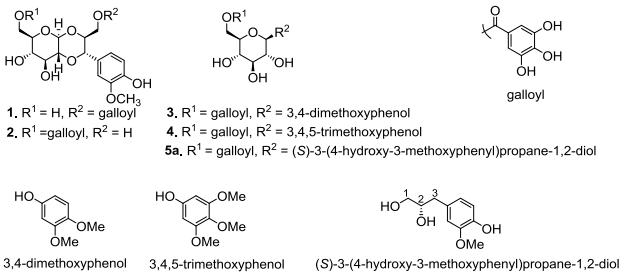
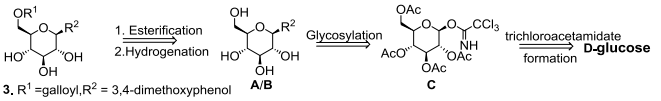


Fig. 1 Structures of tyrosyl-DNA phosphodiesterase I inhibitors

We visualized the retro synthesis of compounds **3** and **5** starting from D-glucose (Scheme 1). Compounds **3** and **5** can be obtained by esterification of compounds **A** and **B** with tri-benzyl protected acid followed by debenzylation whereas compounds **A** and **B** can in turn be obtained by glycosylation with **C**, which can inturn be obtained from D-glucose over a series of transformations.

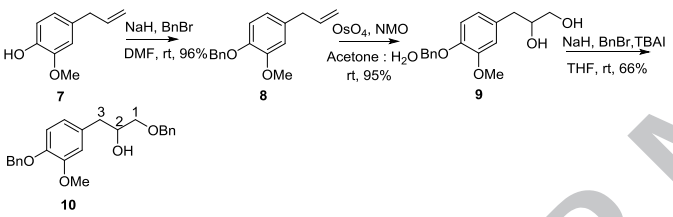


3. R^1 =galloyl,R^2 = 3,4-dimethoxyphenol

5. R^1 =galloyl, R^2 = 3-(4-hydroxy-3-methoxyphenyl)-propane-1,2-diol

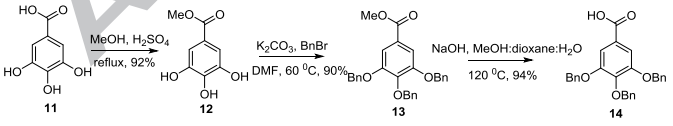
Scheme 1. Retrosynthetic analysis

2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl trichloroacetimidate **6** was prepared from D-glucose using the reported procedure.[7] Synthesis of 1-(benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)propan-2-ol **10** was started from eugenol **7** (Scheme 2). Protection of free hydroxyl in eugenol using benzylbromide afforded benzyl protected eugenol **8** in 96% yield.[8] Dihydroxylation using osmium tetraoxide gave diol **9** which on monoprotection of primary hydroxyl using benzylbromide afforded compound **10** in good yield.



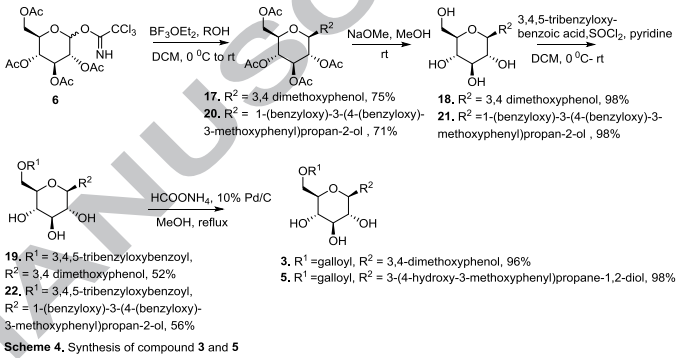
Scheme 2. Synthesis of compound **10**

Synthesis of 3,4,5-tribenzyloxybenzoic acid **14** was achieved from gallic acid over series of transformations (Scheme 3). Esterification of gallic acid **11** using methanol in acidic conditions afforded ester **12** in 92% yield, which on tri-benzylation gave compound **13** in 90% yield. Hydrolysis of ester in compound **13** under basic conditions afforded 3,4,5-tribenzyloxybenzoic acid **14** in good yield.



Scheme 3. Synthesis of 3,4,5-tribenzyloxygallic acid **14**

Synthesis of compound **3** was accomplished from 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl trichloroacetimidate **6** over a series of transformations (Scheme 4). Glycosylation of 3,4-dimethoxyphenol with trichloroacetimidate **6** using BF_3OEt_2 afforded selectively the -glycosylated compound **17** due to the neighbouring group effect of the acetate in 75% yield. Deacetylation of acetates in compound **17** using sodium methoxide afforded compound **18** in 98% yield. Selective esterification of primary hydroxyl in compound **18** using 3,4,5-tribenzyloxybenzoic acid by insitu formation of 3,4,5-tribenzyloxybenzoyl chloride afforded compound **19** in 52% yield. Benzyl deprotection using ammonium formate in presence of 10% Pd/C in methanol under reflux conditions afforded the target compound **3** in good yield.



Scheme 4. Synthesis of compound **3** and **5**

Similarly synthesis of compound **5** was also accomplished from 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl trichloroacetimidate **6** (Scheme 4). Glycosylation of eugenol derived compound **10** with trichloroacetimidate **6** in presence of BF_3OEt_2 gave -glycosylated product **20** in 1:3 diastereomeric ratio at C-2 centre as seen from ^{1}H NMR spectrum. It was not possible to separate the diastereomers of compound **20** on column chromatography. Deacetylation using sodium methoxide in methanol afforded compound **21** (1:3 diastereomeric ratio) in 98% yield. Selective esterification of primary alcohol in compound **21** with 3,4,5-tribenzyloxybenzoic acid by insitu formation of 3,4,5-tribenzyloxybenzoyl chloride afforded compound **22** (1:3 diastereomeric ratio) in 56% yield. Deprotection of the benzyl groups in compound **22** using ammonium formate in presence of 10% Pd/C in methanol at reflux conditions completed the synthesis of target compound **5** in good yields. The ^{1}H NMR spectrum showed 1:3 ratio of

stereoisomer at C-2 position. Both isomers in compound **5** showed same R_f on TLC and hence continuous efforts to separate the isomers using various solvent system failed. HPLC was recorded for compounds **5** and **20**. It showed presence of two isomers but no proper separation of isomers was seen even after continuous efforts. It was thus difficult for us to separate the isomers at every step in synthesis of compound **5**. Thus we report the synthesis of compound **5** as a 1:3 diasteromeric mixture at C-2 position. The spectral data ie. IR, ^{1}H, ^{13}C NMR and HRMS of synthesized tyrosyl-DNA phosphodiesterase I inhibitors **3** was found to be in good agreement with those reported in the isolation paper[9] and peaks in the ^{1}H and ^{13}C NMR that of **5** was found to be in agreement with one of the isomer i.e **5a**.[10, 11]

In conclusion, we have completed the total synthesis of tyrosyl-DNA phosphodiesterase I inhibitors **3** and **5** in 7 steps with an overall yield of 26% and 27% respectively in a simple and efficient manner. The present approach towards the synthesis of compounds **3** and **5** in general would be useful for the synthesis of similar types of analogs and congeners of these bioactive natural products.

Acknowledgments

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Supplementary Material

Supplementary data (detailed experimental procedure, characterization of the products and copies of spectra are provided) associated with this article can be found, in the online version.

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Highlights

Efficient glycosylation.

Synthesis of tyrosyl inhibitors using cheap and readily available starting materials.

Simple and efficient synthesis of compounds **3** and **5** with good overall yield.