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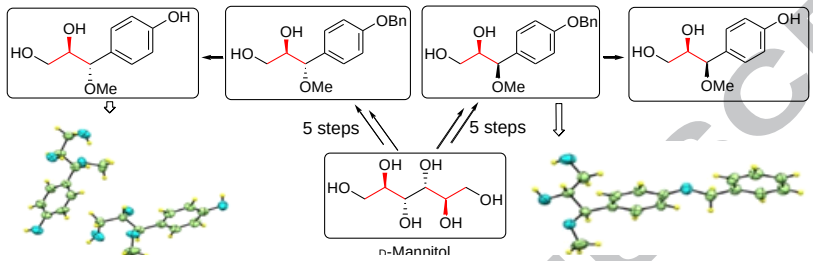

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# Confirmation of the stereochemistry of two naturally occurring epimeric phenylpropanoids *via* synthesis: elucidation of hitherto unknown full stereostructures

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ABSTRACT

Herein we report our efforts toward unequivocal assignment of the hitherto unknown absolute configurations of two naturally occurring phenylpropanoids from *Abies delavayi* and *Abies fabri via* a combination of chiral pool synthesis and single crystal X-ray analysis which also confirmed their previously reported gross structures with relative stereochemistry. Toward this end we have achieved the first stereodivergent syntheses of *threo*-(1*R*,2*R*)-(−)- and *erythro*-(1*S*,2*R*)-(+)-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol. The synthetic *threo*-isomer was found to be identical to the naturally occurring *threo*-isomer, while the natural *erythro*-isomer was postulated to be the enantiomer of the synthetic *erythro*-isomer.



Both *Abies delavayi* and *Abies fabri* are trees found exclusively in China. Systematic phytochemical investigations of *Abies delavayi* by Yang and co-workers in 2014[1] and those of *Abies fabri* by Li and co-workers in 2015[2] resulted in the isolation of two new isomeric phenylpropanoids, 1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol (Fig. 1). The relative configuration of the two chiral centers were assigned by comparing the coupling constants with those of the analogous phenylpropanoids, syringoylglycerols and guaiacylglycerol (Fig. 2) derivatives (*ca.* 5 Hz for the *erythro*-isomer and 7 Hz for the *threo*-isomer).[3] The coupling constant between the two vicinal protons at C-1 and C-2 for the stereoisomer isolated from *Abies delavayi* was determined as 6.6 Hz by Yang and co-workers and they proposed it to be the *threo*-isomer (Fig. 1). The $^{1}$H and $^{13}$C NMR spectroscopic data of the stereoisomer isolated from *Abies fabri* were similar to those of the *threo*-isomer except for one proton signal which was shifted upfield by 0.9 ppm. Hence, Li and co-workers suggested it to be the *erythro*-isomer (Fig. 1) despite a 6.3 Hz coupling constant between the two vicinal protons at C-1 and C-2.

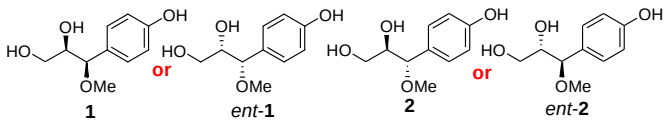



**Figure 1.** Stereoisomers of 1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol.

A mixture of phenylpropanetriols, *threo*- and *erythro*-1-*C*-syringyl-glycerol, which are structurally related to the two above mentioned natural products, was reported to inhibit the production of pro-inflammatory cytokines interleukin (IL)-12 p40, IL-6, and tumor necrosis factor-α in lipopolysaccharide stimulated bone marrow-derived dendritic cells.[4] The interesting biological profile of similar phenylpropanoids make phenylpropanoids **1** and **2** important substrates for biological evaluation.

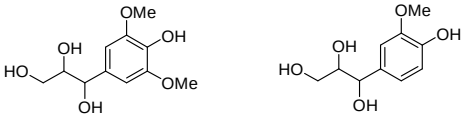


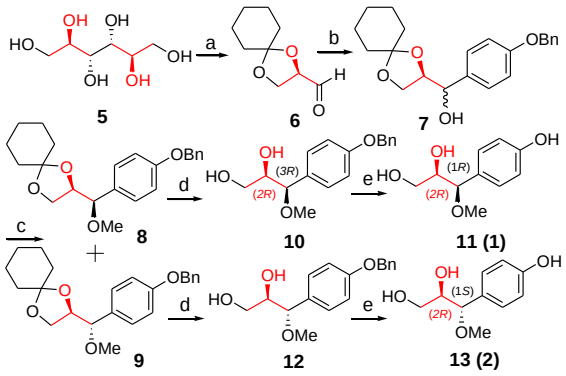

**Figure 2.** Analogous phenylpropanoids.

To the best of our knowledge, no research group has reported the determination of the full stereostructures of these two natural products. Our plan was to sequentially arrange classical reactions to achieve the stereodivergent syntheses of one *threo*- and one *erythro*-stereoisomer with known absolute stereochemistry at one of the two stereogenic centers (Fig. 1). Unambiguous stereochemistry at the two chiral centers would then be assigned by X-ray crystallographic analysis of any two of the synthesized compounds, one from each series (i.e. *threo*- and *erythro*-series).

Our continued interest in the chiral pool synthesis of potentially bioactive chiral natural products and their synthetic analogues,[5] made us interested in the asymmetric synthesis of these molecules.

We initiated the project by transforming D-(+)-mannitol **5** into *R*-(+)-glyceraldehyde derivative **6** (Scheme 1) following a two-step literature procedure.[6] The reaction of aldehyde **6** and the Grignard reagent prepared from 4-benzyloxybromobenzene,[7] for 6 h at reflux gave a mixture of epimeric alcohols **7** in *ca.* 1:1 ratio (determined by $^{1}$H NMR spectroscopy) in moderate yield (58%). Chelation controlled or oxidation-reduction reactions to modulate the diastereoselectivity were not attempted as our aim was the stereodivergent syntheses of both the *threo*- and *erythro*-compounds. Since, at this stage the isomeric alcohols could not be separated by column chromatography, the mixture was treated

with methyl iodide and sodium hydride to give the corresponding methyl ethers **8** and **9** in 96% combined yield. To our delight, the two epimeric methyl ethers could be easily separated by column chromatography which led to the isolation of diastereoisomer **8** in 39% yield ($R_f$ = 0.48, 15% ethyl acetate-hexane) and diastereoisomer **9** in 48% yield ($R_f$ = 0.55, 15% ethyl acetate-hexane). The more polar methyl ether **8** underwent acid-induced deketalization to give diol **10** (90%), which upon hydrogenolysis using 10% Pd-C afforded phenol **11** in almost quantitative yield. Similarly, the less polar methyl ether **9** was transformed into diol **12** (96%) and finally phenol **13** (93%).




**Scheme 1.** Reagents and conditions: (a) (i) cyclohexanone, $BF_3$•$OEt_2$, $HC(OEt)_3$, dry DMSO, rt, 24 h, 65%; (ii) $NaIO_4$, $CH_3CN$-$H_2O$ (3:2), rt, 6 h, 95%; (b) 4-benzyloxyphenylmagnesium bromide, dry THF, reflux, 6 h, 58%; (c) NaH, MeI, dry THF, 0 °C-rt, 24 h, 39% **8**, 48% **9**; (d) 80% aq. TFA, MeOH, 50 °C, 4 h, 90% **10**, 96% **12**; (e) $H_2$/Pd-C, MeOH, 36 h, 99% **11**, 93% **13**.

Single crystals of compounds **10** and **13**, suitable for X-ray diffraction, were grown from methanol-hexane and ethyl acetate-hexane, respectively. X-ray crystallography not only confirmed their structures but also established the *threo*- and *erythro*-relative configurations of the two chiral centers in **10** and **13**, respectively.[8] Compound **10** (Fig. 3) crystallized with a monoclinic space group $P2_1$ while compound **13** (Fig. 4) crystallized with a monoclinic space group C2. Since, chirality at the C-2 stereogenic centers of compounds **10** and **13** was translated from the C-2 stereogenic center of $C_2$-symmetric D-(+)-mannitol **5**, the absolute configuration of the two stereocenters of *threo*-3-(4-(benzyloxy)phenyl)-3-methoxypropane-1,2-diol **10** and *erythro*-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol **13** must undoubtedly be (2*R*,3*R*) and (1*S*,2*R*), respectively. This also indirectly established the absolute configuration of *threo*-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol **11**, prepared by the benzyl deprotection of benzyl ether **10**, as (1*R*,2*R*).

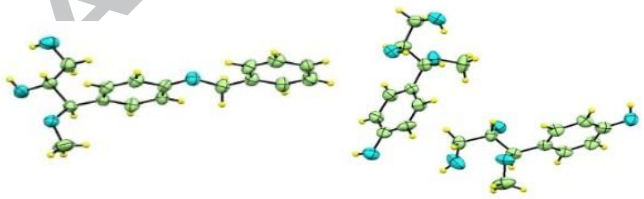


**Figure 3.** Crystal structure of **10**.



**Figure 4.** Crystal structure of **13**.

The NMR spectroscopic data of synthetic *threo*-(1*R*,2*R*)-**11** (stereostructure as **1**, Fig. 1) and *erythro*-(1*S*,2*R*)-**13** (stereostructure as **2**, Fig. 1) were similar to those reported[1,2] for the natural products *threo*- and *erythro*-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol, respectively. This confirmed the correct assignment of the relative configuration of both natural products.

The specific rotation of synthetic *threo*-(−)-(1*R*,2*R*)-**11**, $[\alpha]_D^{25}$ = −7.95 (*c* 0.90, MeOH), was also comparable to that reported in the literature[1] for the natural *threo*-(−)-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol isolated from *Abies delavayi*, $[\alpha]_D^{20}$ = −8.2 (*c* 0.50, MeOH). Hence, the natural isomer isolated by Yang and co-workers was unequivocally assigned the absolute configuration of (1*R*,2*R*).

The specific rotation reported[2] for the natural *erythro*-isomer isolated from *Abies fabri* by Li and co-workers was $[\alpha]_D^{20}$= −1.0 (*c* 0.15, MeOH). Synthetic *erythro*-(1*S*,2*R*)-(+)-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol **13** had a specific rotation of $[\alpha]_D^{20.4}$ = +15.45 (*c* 0.55, MeOH); $[\alpha]_D^{25}$ = +16.3 (*c* 3.21, MeOH). The magnitude of specific rotation observed for the natural *erythro*-isomer is lower compared to that of the synthetic *erythro*-(1*S*,2*R*)-**13** (**2**). However, as the sign of specific rotations were opposite, the *erythro*-isomer isolated from *Abies fabri* was proposed to be *ent*-**2** (Fig. 1), the enantiomer of **13**. Hence, the absolute configuration of the natural *erythro*-isomer isolated by Li and co-workers was postulated to be (1*R*,2*S*). In the absence of reported data regarding the enantiopurity of the isolated natural product, it may be assumed that the smaller magnitude of specific rotation of the natural *erythro*-sample is due to the co-existence of two enantiomers, **2** (1*S*,2*R*) and *ent*-**2** (1*R*,2*S*) (Fig. 1).

In summary, we have reported the short and efficient stereodivergent syntheses of *threo*-(1*R*,2*R*)-(−)- and *erythro*-(1*S*,2*R*)-(+)-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol for the first time in six steps from commercially available, inexpensive D-(+)-mannitol. Our work corroborated the previously proposed relative stereochemistry of these two natural products. Furthermore, the naturally isolated *threo*-isomer was unequivocally assigned to have the (1*R*,2*R*) configuration while the *erythro*-isomer was postulated to have the (1*R*,2*S*) configuration. The application of this strategy for the synthesis of stereoisomers of similar phenylpropanoids, such as the naturally occurring 4-*n*-butoxyl-phenylpropanetriol[9] and *threo*-1-(4-hydroxyphenyl)-1-ethoxy-2,3-propanediol,[10] together with independent determination of their absolute configurations is currently being investigated in our laboratory.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found in the online version.

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Highlights:

- Epimeric (−)- and -(+)-1-(4-hydroxyphenyl)-1-methoxy-2,3-propanediol are prepared.
- Conveyance of stereochemistry from D-mannitol to C-2 of both the target molecules.
- Establishment of stereochemistry at C-1 *via* single crystal X-ray analysis.
- First assignment of absolute configurations to two natural phenylpropanoids.