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Structural establishment of polygalatenosides A and B by total synthesis

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Abstract

The first total synthesis of polygalatenosides A (**1**) and B (**2**), originally isolated from the traditional Chinese medicine and reported as antidepressant agents, is described here. Glycosylation between thiogalactosyl donors **6** and **7** and 1-deoxyglucosyl acceptor **5** yielded the corresponding key intermediates **10** and **16**, respectively, with an α(1→2)-glycosidic linkage in moderate yields. In addition, D-configuration of the galactoside residue in **1** and **2** was confirmed in our studies.

Keywords: Polygalatenoside; 1-Deoxyglucose; Antidepressant agents; Traditional chinese medicine

Current antidepressants possess certain therapeutic actions for psychotic diseases, but most of them interacting with multiple targets cause serious side effects such as diarrhea, anxiety, nausea, and even increase of suicidal thoughts and behaviour.[1] Therefore, the process of deveoping safe and potent small molecules for new antidepressant agents has received a lot of attention in medicinal and pharmaceutical chemistry.[2] Not surprisingly, due to the less risk of side effects, the improvement of analytical techniques, new bioassay developments, recent years isolation and structure elucidation of bioactive components from traditional Chinese medicine (TCM) for therapeutical purpose have been demonstrated as attractive approaches for new drug discovery.[3] In TCM, *Polygala tenuifolia* Willdenow is an important herb prescribed to mediate sedative, antipsychotic, cognitive improving, neuron protective, and anti-inflammatory therapeutic effects on the central nervous system.[4] Several biological interesting molecules, such as xanthones, phenolic glycosides, and oligosaccharide esters, from this plant have been reported.[5] Significantly, based on bioassay-guided isolation, Wu and his co-workers have identified five new oligosaccharide derivatives from the roots of *Polygala tenuifolia* Willdenow.[6]

Among these oligosaccharides, polygalatenosides A (**1**) and B (**2**) show potent and selective norepinephrine transporter inhibitory activities, with IC_{50} values of 30.0 and 6.04 μM, respectively. In contrast, polygalatenosides C has no inhibitory activity.[6]

From the structural point of view, compounds **1** and **2** feature the same disaccharide core structure, which consists of a galactose and a 1-deoxyglucose, also named polygalitol or 1,5-anhydro-D-glucitol, with an α(1→2) linkage. The subtle difference between **1** and **2** is a benzoate ester at the C-3 or C-6 position of galactose, respectively (see Fig. 1).

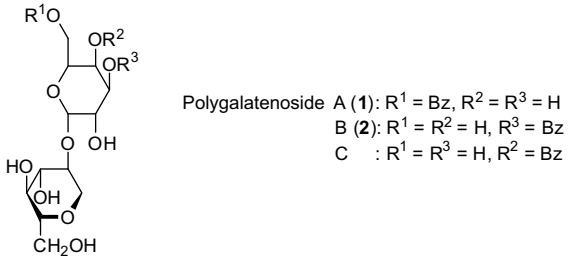

Fig. 1. Structures of polygalatenosides A, B, and C.

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Interestingly, the monosaccharide-1-deoxyglucose has been extensively investigated in carbohydrate metabolism. For example, it can be a diagnostic biomarker for diabetes mellitus.[7] However, only few natural oligosaccharides containing a 1-deoxyglucose moiety have been reported.[8] Moreover, the configuration (L or D) of the galactoside moiety in polygalatenosides A (**1**) and B (**2**) has not been elucidated yet.[6]

One of our research interests is to synthesize or modify bioactive small molecules and further study their structure–activity relationships with disease-associated enzymes.[9] Herein, we report the total synthesis of polygalatenosides A (**1**) and B (**2**), as well as their linkage isomers. In addition, the configurations (L or D) of the galactose residue in **1** and **2** are also assigned.

According to our retrosynthetic analysis illustrated in Figure 2, a convergent approach was chosen that involved the synthesis of the protected disaccharide cores **3** and **4**, which were prepared from thiogalactoside donors **6** and **7**, respectively, with 1-deoxyglucosyl acceptor **5** via glycosylation. A benzoyl group was conjugated at the C-6 hydroxyl group of galactose moiety in disaccharide **3** and at the C-3 hydroxyl group of that in **4** before the removal of all benzyl protecting groups. Due to no detailed information about the configuration (D or L) of the galactose moiety in **1** and **2**, we decided to choose widespread natural occurrence of D-galactose as our starting materials for initial synthetic studies. For the preparation of 1-deoxyglycosyl acceptor **5**, our synthetic effort started with the commercially available D-glucal (**8**) followed by benzylation, regioselective hydroboration, and the addition of aqueous hydrogen peroxide to give 1,5-anhydro-3,4,6-tri-*O*-benzyl-D-glucal (**5**) in high yield (74% yield overall from **8**, Scheme 1).[10]

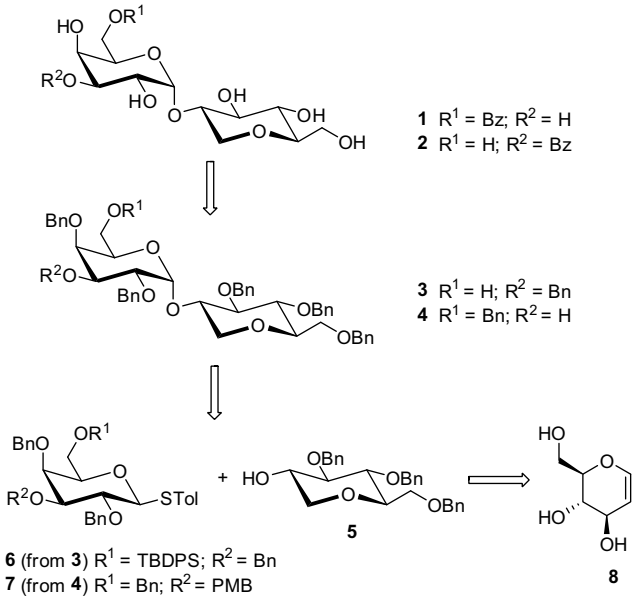
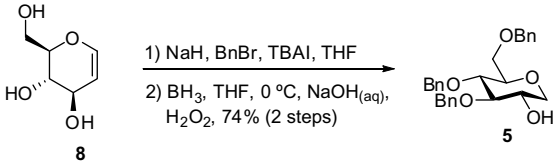
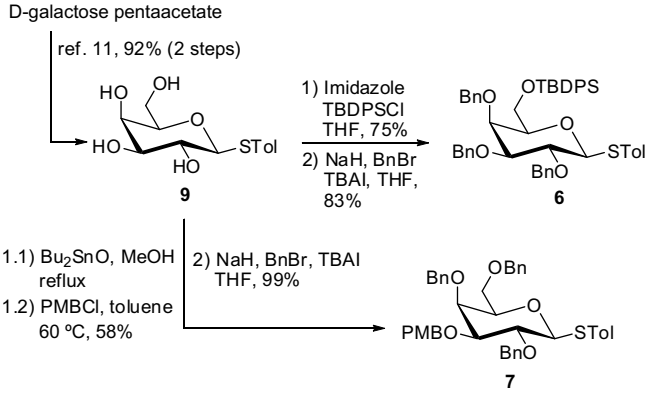


Fig. 2. Retrosynthetic analysis of **1** and **2**.



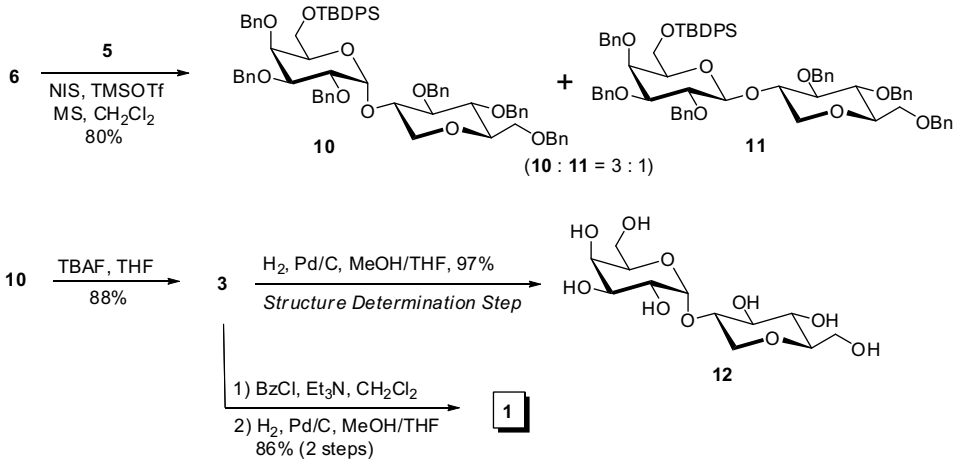
Scheme 1. Preparation of 1-deoxyglucosyl acceptor **5**.



Scheme 2. Preparation of galactosyl donors **6** and **7**.

Synthesis of D-galactosyl donor **6** is shown in Scheme 2. Selective silylation of the primary hydroxy group in thiogalactoside **9**, derived from D-galactose pentaacetate via a well-known two-step process,[11] followed by per-O-benzylation gave the desired donor **6** in 62% yield.[12] Next, regioselective monoalkylation of **9** at the C-3 hydroxyl group with *p*-methoxybenzyl chloride(PMBCl) by the Bu_2SnO method,[13] followed by per-O-benzylation, provided galactosyl donor **7** in 57% yield (Scheme 2).

With acceptor **5** as well as donors **6** and **7** in hand, glycosylation between these acceptors and donors could be explored. As shown in Scheme 3, the treatment of thioglycoside **6** with acceptor **5** in the presence of *N*-iodosuccinimide and 0.1 equiv of TMSOTf (trimethylsilyl trifluoromethanesulfonate) as an activator[14] yielded two corresponding disaccharides **10** (60%) and **11** (20%), which were readily separated by silica gel column chromatography (elution solvent: 10% EtOAc in hexanes). The stereochemistry of glycosidic linkages between two disaccharides **10** and **11** was difficult to be directly distinguished by ^{1}H NMR spectrum due to the signals overlapping. Thus, to clarify and prove the structures of **10** and **11**, further selective deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group in **10** by treatment with tetra-*n*-butylammonium fluoride (TBAF)[15] in THF gave disaccharide **3** (88%). Subsequent catalytic hydrogenolysis of **3** with Pd/C in a THF/methanol solution (1:3) to remove all benzyl groups furnished disaccharide **12** in 97% yield. Likewise, disaccharide **13** was generated from **11** in 90% yield for two steps. In the ^{1}H NMR spectrum of **12**, the smaller coupling constant (3.4 Hz) of the anomeric proton at δ 5.08 was characteristic for an α-glycosidic linkage. On the other hand, the ^{1}H NMR spectrum of isomer **13** showed



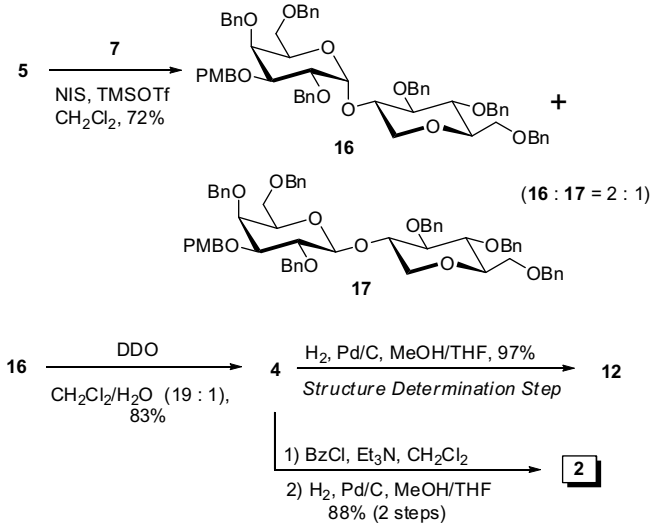
Scheme 3. Synthesis of polygalatenoside A (**1**).

the larger coupling constant (7.9 Hz) for the anomeric proton at δ 4.5 ppm, indicating a β linkage of the glycosidic bond in **13**. These results encouraged us to directly synthesize our target molecule **1**. After benzoylation at the C-6 hydroxyl group of the galactoside moiety in **3** and global debenzylation under standard conditions, polygalatenoside A (**1**)[16] was successfully synthesized in 86% yield. Likewise, the linkage isomer **14**[16] was prepared in 82% yield from **11** for three steps.

Our next attention was focused on the preparation of **2** and its linkage isomer **15**, and the synthetic route is illustrated in Scheme 4. Glycosylation between acceptor **7** and donor **5** gave two corresponding disaccharides **16** (48%) and **17** (24%). Selective removal of PMB group in **16** was performed under DDQ oxidative conditions[17] to provide **4** (83%). Subsequent global debenzylation of **4** was carried out to give disaccharide **12**, which was obviously confirmed as an α-glycosidic linkage by ^{1}H NMR spectroscopy. To prepare our target molecule **2**, benzoylation of the C-3 hydroxy group of the galactoside moiety in **4** and then global debenzylation smoothly furnished polygalatenoside B (**2**)[18] in 87% yield. Likewise, the β-linkage isomer **15**[18] was prepared in high yield (88% yield overall from **17** for three steps, Fig. 3). It was noted that benzoylated sugars **2** and**15** were labile in aqueous medium. Presumably, the benzoyl group in **2** and **15** was prone to undergo acyl migrations.[19] In contrast, compound **1** and its linkage isomer **14** were stable under aqueous conditions. To circumvent this problem, normal phase silica gel column chromatography was employed with a MeOH/CH_2Cl_2 mixture as elution solvent for purification. In addition, CD_3OD was chosen as the solvent instead of D_2O in NMR experiments. These modifications gave us satisfactory results.

To our delight, the NMR data and optical rotation values of **1** and **2** were all in good agreement with those reported.[6,16,18] Accordingly, D-configuration of the galactose residue in **1** and **2** was confirmed.

In summary, we have successfully accomplished the first total synthesis of polygalatenosides A (**1**) and B (**2**) via a convergent and straightforward approach. Donor sugars **6** and **7** were prepared from D-galactose pentaacetate for four steps in 57% and 53% yields, respectively; acceptor sugar **5** was prepared from D-glucal in 74% yield for two steps. This general synthetic strategy is able to introduce various substituent esters at the C-3 or C-6 positions of the galactose residue in this unique disaccharide core to



Scheme 4. Synthesis of polygalatenoside B (**2**).

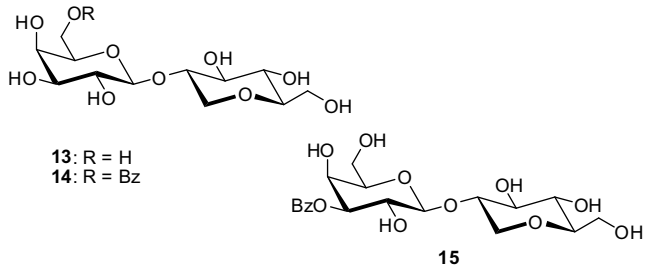


Fig. 3. Structures of linkage isomer **13** and their derivatives **14** and **15**.

evaluate their biological activities. The further chemical modifications and biological screening data will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.032.

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16. Data of **1**: $[\alpha]_D^{20}$ +165.4 (*c* 0.017, MeOH) (lit.[6] $[\alpha]_D^{20}$ +171 (*c* 0.01, MeOH)); ^{1}H NMR (600 MHz, D_2O, ambient temperature) δ 7.55–8.08 (m, 5H), 5.11 (d, 1H, $J = 3.7$ Hz), 4.48–4.59 (m, 3H), 4.12–4.15 (m, 2H), 3.95 (dd, 1H, $J = 3.2$, 10.3 Hz), 3.89 (dd, 1H, $J = 3.8$, 10.3 Hz), 3.83 (dd, 1H, $J = 1.6$, 12.1 Hz), 3.53–3.63 (m, 3H), 3.26–3.32 (m, 2H), 3.03 (dd, 1H, $J = 9.4$ Hz); ^{13}C NMR (150 MHz, D_2O, ambient temperature) δ 168.21, 133.93, 129.59, 129.13, 128.74, 95.72, 80.33, 75.22, 73.34, 69.73, 69.21, 69.10, 68.75, 67.93, 65.83, 64.39, 61.05; HRMS calcd for $C_{19}H_{26}O_{11}$ $[M+H]^+$ 453.1367, found 453.1467. Data of linkage isomer **14**: $[\alpha]_D^{20}$ +27.7 (*c* 1.1, MeOH); ^{1}H NMR (600 MHz, D_2O, ambient temperature) δ 4.54 (dd, 1H, $J = 8.7$, 11.5 Hz), 4.50 (d, 1H, $J = 7.8$ Hz), 3.37 (dd, 1H, $J = 4.0$, 11.6 Hz), 4.07 (dd, 1H, $J = 4.4$, 11.1 Hz), 3.97 (d, 1H, $J = 3.3$ Hz), 3.93 (dd, 1H, $J = 4.0$, 8.5 Hz), 3.78 (dd, 1H, $J = 2.0$, 12.3 Hz), 3.66 (dd, 1H, $J = 3.4$, 9.9 Hz), 3.53–3.58 (m, 4H), 3.29 (dd, 1H, $J = 9.5$ Hz), 3.18–3.22 (m, 2H); ^{13}C NMR (150 MHz, D_2O, ambient temperature) δ 168.28, 133.89, 129.46, 129.05, 128.78, 103.61, 79.95, 79.08, 76.03, 72.60, 72.46, 70.80, 69.53, 68.35, 68.19, 63.83, 60.83; HRMS calcd for $C_{19}H_{26}O_{11}$ $[M+H]^+$ 453.1367, found 453.1382.
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18. Data for **2**: $[\alpha]_D^{20}$ +323.7 (*c* 0.005, MeOH) (lit.[6] $[\alpha]_D^{20}$ +343.1 (*c* 0.003, MeOH)); ^{1}H NMR (600 MHz, CD_3OD, ambient temperature) δ 7.39–8.06 (m, 5H), 5.21 (dd, 1H, $J = 3.1$, 10.6 Hz), 4.98 (d, 1H, $J = 3.8$ Hz), 4.25 (dd, 1H, $J = 6.1$ Hz), 4.16 (d, 1H, $J = 2.8$ Hz), 4.13 (dd, 1H, $J = 3.9$, 10.6 Hz), 4.03 (dd, 1H, $J = 5.2$, 11.2 Hz), 3.77 (dd, 1H, $J = 1.9$, 11.8 Hz), 3.63–3.71 (m, 2H), 3.53–3.61 (m, 2H), 3.39–3.46 (m, 2H), 3.18–3.24 (m, 3H), 3.11–3.14 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD, ambient temperature) δ 168.06, 134.39, 131.73, 130.98, 129.58, 99.13, 82.57, 78.17, 76.95, 75.43, 72.11, 72.07, 68.91, 68.20, 67.75, 63.21, 62.61; HRMS calcd for $C_{19}H_{26}O_{11}$ $[M+Na]^+$ 453.1367, found 453.1336. Data for linkage isomer **15**: $[\alpha]_D^{20}$ +51.9 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD, ambient temperature) δ 7.50–8.16 (m, 5H), 5.03 (dd, 1H, $J = 3.2$, 10.1 Hz), 4.65 (d, 1H, $J = 7.7$ Hz), 4.27 (dd, 1H, $J = 5.3$, 11.3 Hz), 4.19 (d, 1H, $J = 3.1$ Hz), 3.98 (dd, 1H, $J = 7.8$, 10.0 Hz), 3.86 (dd, 1H, $J = 1.9$, 11.9 Hz), 3.75–3.81 (m, 2H), 3.35 (dd, 1H, $J = 9.3$ Hz), 3.28 (dd, 1H, $J = 10.9$ Hz), 3.18–3.22 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD, ambient temperature) δ 167.83, 134.42, 131.57, 130.97, 129.58, 106.25, 82.31, 81.30, 78.77, 77.88, 76.60, 71.57, 70.66, 70.26, 67.90, 63.10, 62.25; HRMS calcd for $C_{19}H_{26}O_{11}$ $[M+Na]^+$ 453.1367, found 453.1396.
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