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Graphical Abstract

Total synthesis of viscumneoside Ⅲ of Viscum coloratum

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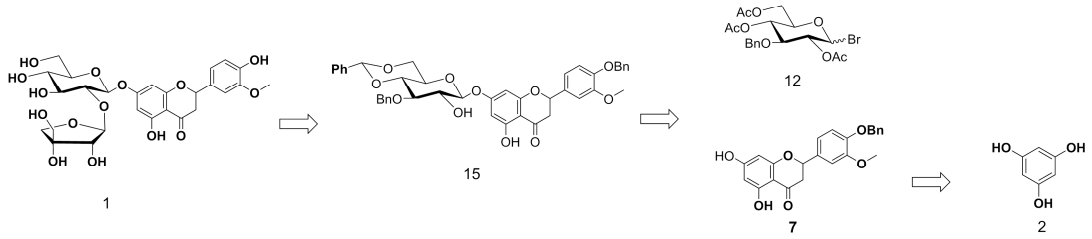

Total synthesis of viscumneoside III of *Viscum coloratum*

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Abstract: The first total synthesis of viscumneoside III, a promising anti-angina pectoris dihydroflavone *O*-glycoside isolated from *Viscum coloratum* was described here. Trichloroacetimidate was employed as the apiofuranosyl donor to construct the key building block of homoeriodictyol-7-*O*-β-D-apiosyl-(1→2)-β-D-glycoside (**1**). The longest linear sequence (from **2** to **1**) in the synthetic route required thirteen steps and afforded the final product **1** with an overall yield of 6.3%.

Keywords: dihydroflavone *O*-glycoside; anti-angina pectoris; apiofuranosyl donor

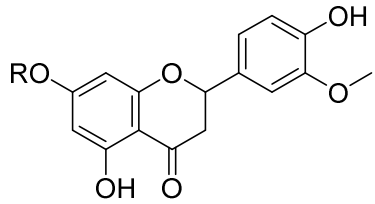
1. Introduction

Viscum coloratum (Kom.) Nakai *(V. coloratum)* is a semi-parasitic plant which grows on branches or stems of deciduous trees. It is known as Hujisheng in Chinese [1-2]. *V. coloratum* is an important medicinal herb that has been used widely in traditional Chinese medicine for treatment of various diseases [3-4], including coronary heart disease with angina pectoris, cancer, hepatitis and hemorrhage [5-6]. Studies have shown that the dihydroflavones from *V. coloratum* are responsible for the anti-angina pectoris activity [7-8].

Viscumneosides I-IV (Fig.1) are the major components of *V. coloratum* that are responsible for its anti-coagulant, anti-inflammatory, antioxidant, anti-tumor and anti-fungal activities [7-9]. Our team has reported the total synthesis of viscumneoside II previously [10], but the total synthesis of viscumneoside III has not been reported so far. Viscumneoside III (**Scheme 1**, **1**) possesses a β-D-apiofuranosyl-(1→2) - β-D-glucopyranose sugar chain, apiofuranose-containing glycosides, such as saponins, cucurbitosides or phenolic glycosides, play a crucial role in the biochemistry of plants. However, the synthesis of apiofuranose-containing glycosides carrying flavanone *O*-glycosides is still a challenge, the synthetic route requires delicate protective manipulation of the hydroxyl groups on the aglycone and sugars because of regioselective construction of two

glycosidic linkages. The promising anti-angina pectoris activity and limited availability from natural sources makes viscumneoside III a suitable target for which to develop synthetic strategies [11-12]. This is of great importance for establishing the structure-activity relationships (SARs) of viscumneosides, which will in turn promote further understanding of the molecular mechanism of its bioactivities and clinical effects.

Herein, we report our work on the first total synthesis of viscumneoside III. Compound **15**, as shown in the retrosynthetic analysis, is the key intermediate for the synthesis of the target compound **1**, which can be built by glycosylation of glycosyl bromides **12** with the partially protected homoeriodictyol **7**. The protecting groups on **12** will ensure the formation of a β-glucosyl linkage in **15** through the neighboring group participation effect of the acetyl at C-2 position. We assume the glycosylation of **7** and **12** will occur only at C-7 of **7**, since the free 5-OH is less reactive due to the chelating effect with the carbonyl at C-4. Also, this study has addressed issues associated with the inherent chemical reactivity of apiose.



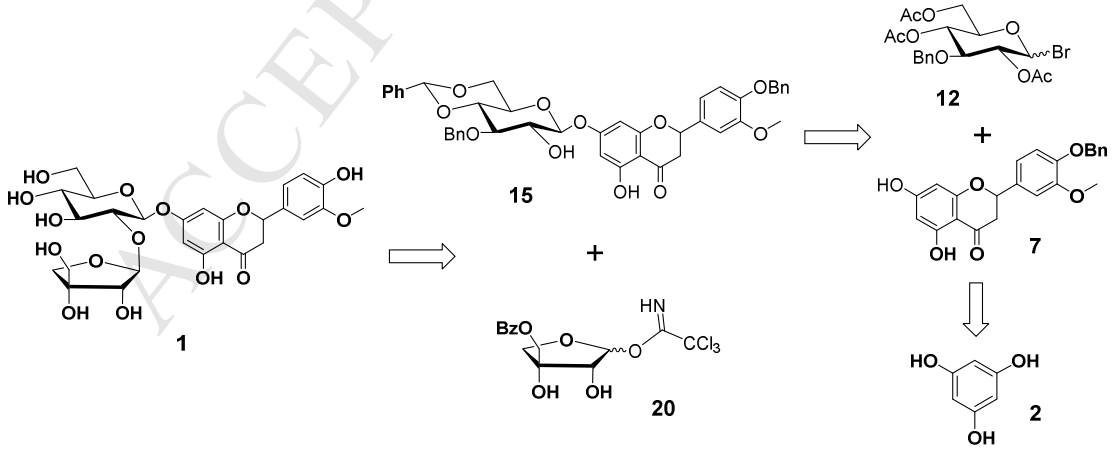
viscumneoside I：R = H

II：R = β-D-Glc

III：R = β-D-Api-(1→2)-β-D-Glc

IV：R = β-D-Api-(1→5)-β-D-Api-(1→2)- β-D-Glc

Figure 1. The structures of viscumneosides I- IV



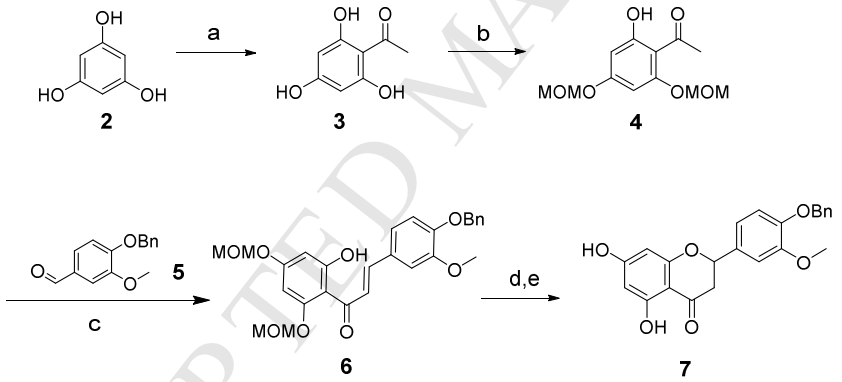
Scheme 1. Retrosynthetic analysis of viscumneoside III (1)

2. Results and discussion

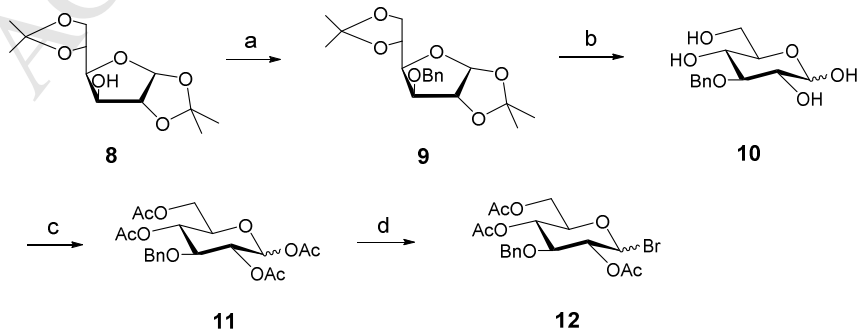
2.1. Synthesis of homoeriodictyol-7-*O*-β-D-glucopyranoside acceptor **15**

The synthesis started from commercially available material 1,3,5-trihydroxybenzene (**2**). 2-Hydroxy-4,6-bis(methoxymethoxy)-acetophenone (**4**) was prepared from **2** by a Friedel-Crafts acylation followed by a MOM (methoxymethyl) protection. Then a base catalyzed aldol condensation of **4** with 4-benzyloxy-3-methoxybenzaldehyde **5** gave chalcone **6** in 85% yield. After cyclization in the presence of sodium acetate and followed by acidification, chalcone **6** was converted to benzyl-protected dihydroflavone **7** in high yield [10, 13] (Scheme 2).

To prepare 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide **12**, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **8** was employed as the starting material. The 3-OH benzylation of **8** was accomplished by using benzyl bromide in the presence of sodium hydride in THF to afford **9**. Removal of the isopropylidene groups on **9** with 50% trifluoroacetic acid provided **10**. Subsequently acetylation of **10** in acetic anhydride and pyridine afforded 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-α/β-D-glucopyranose **11** with an overall yield of 40% from **8**. Bromination of **11** with 33% hydrogen bromide in acetic acid gave **12**[14] (Scheme 3).

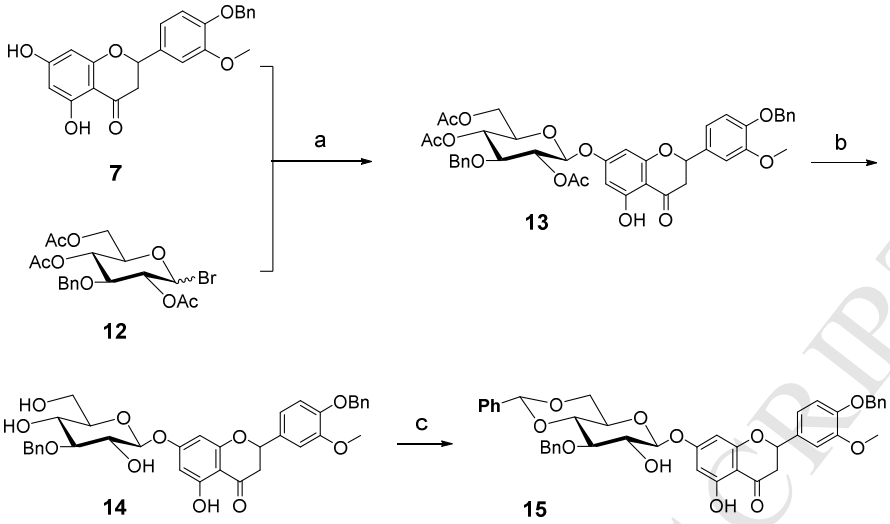


Scheme 2. (a) $AlCl_3$, DCM, CH_3NO_2, AcCl, rt, 19 h, 60%; (b) DIPEA, DCM, MOMCl, rt, 10 h, 64%; (c) EtOH, 20% NaOH, rt, 7 h, 85%; (d) NaOAc, EtOH, reflux, 7h (e) MeOH, 10% HCl, reflux, 1 h, 58% for two steps



Scheme 3. (a) NaH, THF, BnBr, 50 °C , 6 h; (b) 50% CF_3COOH, r.t., overnight, 44% for two

steps; (c) Ac_2O, pyridine, r.t., 8 h, 90%; (d) 33% HBr/CH_3COOH, DCM, 30 min.85%.



Scheme 4. (a) K_2CO_3, $CHCl_3$, $Bu_4N^+Br^-$, 45 □ , 14 h; (b) MeONa, MeOH, reflux, 8 h, 73% for two steps; (c) benzaldehyde dimethylacetal, p-TsOH.H_2O, CH_2Cl_2, 60 □ , 83%.

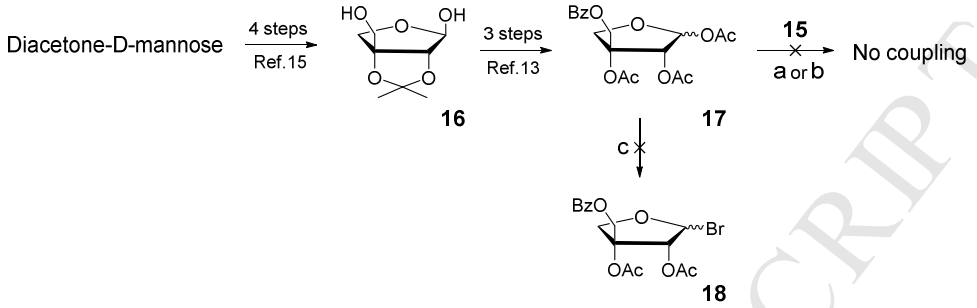
With the glycosyl donor **12** and acceptor **7** in hand, the next step is to construct the key building block glycoside **13**. The glycosylation of α-bromide **12** and homoeriodictyol derivative **7** was performed in 0.25 M potassium carbonate aqueous solution in the presence of TBAB (tetrabutylammonium bromide) at 45 □ , which gave the desired 7-*O*-β-D-glycoside **13** smoothly (**Scheme 4**). Deacetylation of **13** with sodium methoxide in methanol afforded the homoeriodictyol glycoside **14**. Compound **14** was reacted with benzaldehyde dimethylacetal in the presence of *p*-toluenesulfonic acid in dicloromethane at 60 □ to get homoeriodictyol glucopyranoside **15**, which has a free 2-OH for the subsequent reaction.

2.2. Synthesis of apiofuranosyl donor **22**

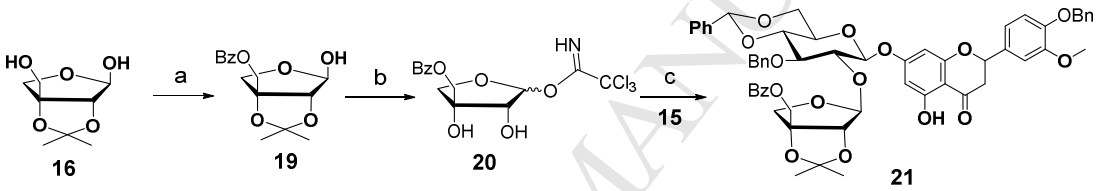
β-D-Apiofuranose derivatives are not readily available, because of the rare natural occurrence of this branched-chain sugar and its ability to exist in four different cyclic tautomers, which complicates apiofuranose derivatization[15]. In our work, the desired form of apiofuranose has a (3*R*)-stereochemistry, as present in natural apiofuranosides. Such apiofuranose derivatives can be synthesized in forms of compounds with fixed 2,3-*cis*-configuration, for instance, *O*-isopropylidene derivative **16**. Compound **16** can be prepared from diacetone-D-mannose in 60% overall yield according to published procedures [16]. After a 3-steps protecting group manipulation [14], acetate **17** was prepared.

As known, although anomeric acetates are often less reactive than many other donors, in fact they can sometimes be used as effective glycosyl donors, offering certain strategic advantages. Thus initially we tried the glycosylation of accepter **15** with the anomeric acetate donor **17**. However, TLC (thin layer chromatography) analysis showed decomposition of the accepter, which

resulted in low yield of the expected glycoside. Therefore glycosyl bromide **18** was considered as an alternative glycosyl donor. But unfortunately, this kind of apiofuranosyl bromide **18** seemed to be very unstable, since significant decomposition was detected by TLC analysis of the reaction mixture when treating of the **17** with HBr in AcOH (**Scheme 5)** .



Scheme 5. (a) TMSOTf, DCM, 4 Å MS, (b) $BF_3.OEt_2$, DCM, 4 Å MS (c) 33% HBr-CH_3COOH, DCM



Scheme 6. (a) BzCl (1.1 equiv), DCM, Py (3 equiv), 0 □ , 5 min, 45%; (b) CCl_3CN (5 equiv), DBU (0.3 equiv), DCM, -20 □ , 10 min, 75%; (c) **15** (0.7 equiv), TMSOTf (0.2 equiv), MS-4 Å, -20 □ , 2 h, 86%;

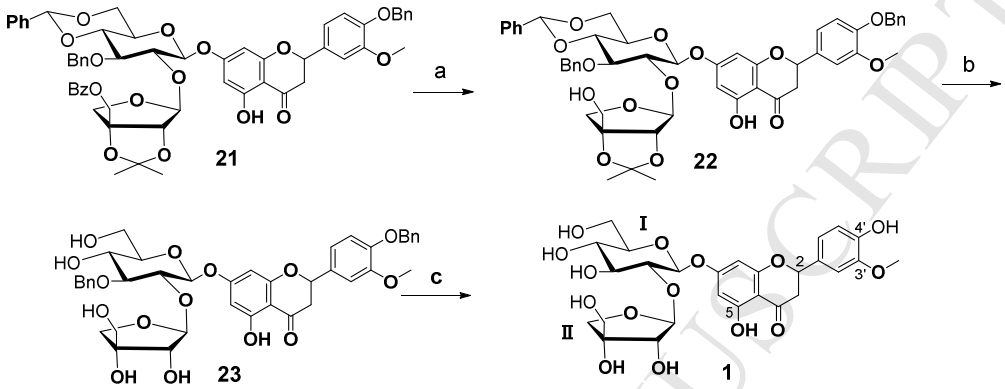
Therefore, other types of apiofuranosyl donors needed to be reasonable designed. Trichloroacetimidate was selected due to its high reactivity and reliability. The primary hydroxyl of compound **16** was selectively benzoylated with benzoyl chloride in the presence of pyridine to afford **19**. By reacting **19** with excess of trichloroacetonitrile catalyzed by DBU, trichloroacetimidate **20** was prepared.

As expected, reaction of **15** with trichloroacetimidate donor **20** in the presence of TMSOTf (trimethylsilyl trifluoromethanesulfonate) in anhydrous dichloromethane at -20 □ (**Scheme 5**) provided the homoeriodictyol disaccharide derivative **21** in 86% isolated yield[19] (**Scheme 6**).

2.3. Total synthesis of viscumneoside III (**1)**

Finally, the final target **1** was obtained by removing all the protecting groups III. Removal of the benzoyls from **21** using sodium methoxide, followed by hydrolysis of the isopropylidene and benzylidene groups using acidic resin beads, and finally hydrogenolysis of the benzyls by 10% Pd/C afforded the deprotected product **1** in high yield (**Scheme 7**). NOE difference spectroscopy experiments were carried out to fully assign the structure of **1**. Selective irradiation of H-1□ (δ

5.08 ppm) showed NOE enhancement of H-6 and H-8 (δ 6.20 ppm), while selective irradiation of H-1^{II} (δ 4.89 ppm) showed NOE enhancements of H-2^{I} (δ 3.55 ppm). This NOE result confirms the structure of **1**. Diastereomers of compound **1** were separated on AD-H chiral column to get two peaks with area ratio of 1:1.All the spectroscopic data recorded for **1** are in accordance with those of its naturally-derived equivalent [7,9].



Scheme 7. (a) MeONa (1.5 eq), DCM/MeOH, reflux, 2 h, 85%; (b) Amberlyst 15 (H^+), MeOH-EtOAc, 70 □ , 4 h ; (c) 10% Pd/C, MeOH-EtOAc, r.t., 1 h, 60% for two steps.

3. Conclusion

The total synthesis of a promising anti-angina pectoris component of the viscumneosides was reported here for the first time. The longest linear sequence (from **2** to **1**) in the synthetic route required thirteen steps and afforded an overall yield of 6.3%. The study addressed issues associated with the inherent chemical reactivity of apiose. Trichloroacetimidate was employed as the apiofuranosyl donor to construct the key building block of Homoeriodictyol-7-*O*-β-D-apiosyl-(1→2)-β-D-glycoside (**1**). It is anticipated that the developed strategy will pave the way for the synthesis of other natural and novel viscumneosides to allow biological investigation as additional promising anti-angina pectoris agents.

4. Experimental section

4.1. General

All solvents were distilled before used by standard methods. ^{1}H NMR and ^{13}C NMR were recorded on Bruker 400 with TMS as internal standard at room temperature and chemical shifts were quoted in parts per million (ppm) downfield from tetramethylsilane. HRMS was obtained on Agilent 1946BESI-MS spectrometer. Flash column chromatography was carried out on silica gel (200-300 mesh). Commercial reagents from TCI (Shanghai) Development Co., Ltd., Alfa Aesar and Sigma Aldrich were without further purification.

4.2. Synthesis of 4'-Benzyloxy-homoeriodictyol-7-*O*-3-benzyloxy-4,5-benzylidene-β-D- glycoside **15**

4.2.1 2-Hydroxy-4,6-bis(methoxymethoxy)-Acetophenone (**3**). 1,3,5-Trihydroxy (200.0 g, 1.59 mol) and $AlCl_3$ (845.1 g, 6.34 mol) was dissolved in dichloromethane (1000.0 ml), followed by drop addition of nitromethane (1000.0 ml) in 30 min. After the reaction mixture was stirred at room temperature for 6 h, acetyl chloride (149.2 g, 1.90 mol) was added dropwise and then poured into water (4000.0 ml). The mixture was extracted with ethyl acetate (2000.0 ml *3).The organic layer was concentrated to dryness and recrystallized with water to get faint yellow solid **3** (161.3 g, 60%). ^{1}H NMR (600 MHz, DMSO) δ: 12.20 (s, 2H, OH), 10.34 (s, 1H, OH), 5.79 (s, 2H, ArH), 2.53 (s, 3H, COCH3); ^{13}C NMR (150 MHz, DMSO) δ: 202.92, 165.22, 164.76, 104.50, 94.99, 32.79. HRMS calcd for $C_8H_8O_4$ m/z [M+H]+ 169.0495, found 169.0490.

4.2.2 2,4,6-Trihydroxyacetophenone (**4**). Compound **2** (110.1 g, 0.76 mol) was dissolved in dichloromethane. The mixture was cooled to 0□ and N-Ethyldiisopropylamine (293 g, 2.27 mol) was added slowly followed by the addition of chloromethyl methyl ether (137.1 g, 1.96 mol) dropwise. After being stirred at room temperature overnight, the reaction was quenched with ammonium chloride saturated aqueous solution (1300.0 ml) and washed with brine (1300.0 ml). The organic layer was concentrated and purified by column chromatography to give white solid **3** (111.6 g, 64%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 13.69 (s, 1H, OH), 6.22 (d, *J* = 2.3 Hz, 2H, ArH), 5.23 (s, 2H, O-CH_2-O), 5.14 (s, 2H, O-CH_2-O), 3.50 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 2.62 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.18 , 166.81 , 163.46 , 160.37 , 106.91 , 97.12 , 94.50 , 94.00 , 56.68 , 56.39 , 32.94. HRMS calcd for $C_{12}H_{16}O_6$ m/z $[M+Na]^+$: 279.0839; found: 279.0843.

4.2.3 2-Hydroxy-4,6-bis(methoxymethoxy)-Acetophenone (**6**). A mixture of compound **4** (90.1 g, 0.35 mol) and 4-benzyloxy-3-methoxybenzaldehyde **5** (85.1 g, 0.35 mol) was dissolved in ethanol (900.0 ml). To this solution was added 20% NaOH aqueous solution (540.0 ml). After being stirred under room temperature overnight, the solution was adjusted to pH 6 with 20% HCl aqueous solution and filtrated to get the crude product **6**. The crude product was dried in vacuum at 50□ for 2 hours and recrystallized by ethanol (1200.0 ml) to afford yellow solid **6** (143.4 g, 85%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 13.89 (s, 1H, OH), 7.83 (d, *J* = 15.5 Hz, 1H, β-CH=), 7.75 (d, *J* = 15.5 Hz, 1H, α-CH=), 7.44 (d, *J* = 7.4 Hz, 2H, ArH), 7.38 (t, *J* = 7.5 Hz, 2H, ArH), 7.32 (t, *J* = 7.3 Hz, 1H, ArH), 7.16 (d, *J* = 1.8 Hz,1H, ArH), 7.14 (dd, *J* = 8.3, 1.9 Hz, 1H, ArH), 6.90 (d, *J* = 8.3 Hz, 1H, ArH), 6.32 (d, *J* = 2.3 Hz, 1H, ArH), 6.22 (d, *J* =2.3 Hz, 1H, ArH), 5.28 (s, 2H, O-CH_2-O), 5.21 (s, 2H, O-CH_2-O), 5.19 (s, 2H, O-CH_2-Ar), 3.93 (s, 3H, OCH_3), 3.53 (s,3H, OCH_3), 3.48 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 192.74 , 167.34 , 163.34 , 159.79 , 150.37 , 149.80 ,142.81 , 136.62 , 128.89 , 128.66 , 128.05 , 127.22 , 125.40 , 122.60 , 97.60 , 95.33 , 94.75 , 94.10 , 70.93 , 56.97 , 56.47 ,55.96. HRMS calcd for $C_{27}H_{28}O_8$ m/z $[M+H]^+$:

480.1857, found 480.1856.

4.2.4 2-(4-(Benzyloxy)-3-methoxyphenyl)-5,7-dihydroxychroman-4-one (**7**). Compound **6** (62.1 g, 0.13 mol) and sodium acetate (42.4 g.0.52 mol) was added to the mixtures of ethanol (2480.0 ml) and water (248.0 ml), and then the reaction was stirred for 8 hours under reflux condition. The suspension was cooled to room temperature and filtrated. The filtrate was concentrated to dryness. The residue was dissolved in methanol and added 20% HCl aqueous solution (90.0ml) dropwise under reflux condition. The reaction was stirred for 2 hours under reflux condition. The reaction then cooled to room temperature and filtrated to afford yellow solid **7** (29.4 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.05 (s, 1H, OH), 7.44 (d, *J* = 7.3 Hz, 2H, ArH), 7.37 (t, *J* = 7.3 Hz, 2H, ArH), 7.31 (t, *J* = 7.2 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 6.90 (d, *J* = 0.9 Hz, 2H, ArH), 6.00 (d, *J* = 2.3 Hz, 1H, ArH), 5.98 (d, *J* = 2.3 Hz, 1H, ArH), 5.54 (s, 1H, OH), 5.34 (dd, *J* = 13.0, 2.9 Hz, 1H, 2-H), 5.18 (s, 2H, O-CH2-Ar), 3.93 (s, 3H, OCH3), 3.10 (dd, *J* = 17.2, 13.1 Hz, 1H, 3-H), 2.79 (dd, *J* = 17.2, 3.0 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.91 , 164.47 , 164.39, 163.18 , 149.96 , 148.72 , 136.87 , 131.23 , 128.61 , 127.96 , 127.24 , 118.82 , 113.92 , 110.03 , 103.23 , 96.74 , 95.45 , 79.22 , 71.08 , 56.15 , 43.28 . HRMS calcd for $C_{23}H_{20}O_6$ m/z $[M+H]^+$: 392.1333, found 392.1328

4.2.5 3-*O*-(Phenylmethyl)-α/β-D-glucopyranose (**10)**. A mixture of 60% sodium-hydrogen (20.8 g, 0.52 mol) and TBAI (7.4 g, 0.02 mol) in tetrahydrofuran (300.0 ml) was stirred in ice bath for 30 minutes. A solution of Diacetone-D-Glucose **8** (104.1 g, 0.40 mol) in tetrahydrofuran (300.0 ml) and Benzyl Bromide (82.1 g, 0.48 mol) was added dropwise to the reaction successively. The reaction was stirred for 8 h at 50 □ and quenched with methanol (20.0 ml) and filtrated through Celite, The filtrate was concentrated to get rude product **9**. Compound **9** in the mixture of trifluoroacetic acid (150.0 ml) and water (150.0 ml) was stirred overnight. The reaction was diluted with brine (300.0 ml), washed with mixture of ether (80.0 ml) and ethyl acetate (400.0 ml). The water layer was concentrated and purified by crystallization from ethyl acetate to give derivative **10** (51.6 g, 44%). ^{1}H NMR (400 MHz, DMSO) δ 7.42-7.24 (m, 5H, -ArH), 6.67 (d, *J* = 6.4 Hz, 1H, 1-CH), 5.05 (dd, *J* = 5.4, 3.7 Hz, 2H, 2-OH and 4-OH), 4.85 – 4.73 (m, 2H, OCH_2Ar), 4.51 (t, *J* = 5.8 Hz, 1H, 1-OH), 4.39 – 4.25 (m, 1H, 6-OH), 3.69 (m, 1H, 2-CH), 3.46 (m, 1H, 4-CH), 3.26 – 3.03 (m, 4H, 3-CH ,5-CH and 6-CH_2). ^{13}C NMR (150MHz, DMSO) δ 139.68, 127.88, 127.40, 126.96, 96.90, 85.30, 76.70, 74.75, 73.61, 69.86, 61.05. HRMS calcd for $C_{13}H_{18}O_6$ m/z $[M+Na]^+$: 293.0996, found 293.1001

4.2.6 1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (**11**). A mixture of **10** (50.0 g, 0.17 mol) in acetic anhydride (200.0 ml) and pyridine (200.0 ml) was stirred overnight at room temperature, then it was diluted with ethyl acetate and washed with 2M HCl and saturated

$NaHCO_3$ aqueous solution. Purification of the residue by crystallization from ethanol to give **11** (71.3 g, 90%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.14 (m, 5H, Ar), 5.63 (t, *J* = 9.2 Hz, 1H, CH-1), 5.22 - 5.03 (m, 2H, CH-2 and CH-4), 4.61 (m, 2H, ArCH2), 4.21(m, 1H, α-CH2), 4.11 (m, 1H, β-CH), 3.84 - 3.62 (m, 2H, CH-3 and CH-3), 2.09 - 1.97 (m, 12H, 4CH3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.84, 169.39, 169.35, 169.18, 137.69, 128.62, 128.08, 127.92, 92.12, 80.10, 74.32, 73.14, 71.68, 69.19, 61.93, 20.98, 20.85, 20.84, 20.81. HRMS calcd for $C_{21}H_{26}O_{10}$ m/z $[M+Na]^+$: 461.1418, found 461.1420.

4.2.7 4'-Benzyloxy-homoeriodictyol-7-*O*-3-benzyloxy-β-D-glycoside (**14**). A mixture of **11** (45.0 g, 0.10 mol) and 45% HBr/AcOH (180.0 ml) in dichlormethane (450.0 ml) was stirred for 20 minutes at 0□ The reaction was diluted with dichlormethane and washed with brine and saturated $NaHCO_3$ aqueous solution, the organic phase was separated and concentrated. The residue was purified by column chromatography to afford glycosyl donor **12,** used directly to the next step for its instability at room temperature. A mixture of **12** (29 g, 0.05mol), **7** (14.9 g, 0.04 mol) and TBAB(3.7 g, 0.01 mol) in 0.25M K_2CO_3 (500.0 ml) aqueous solution and chloroform (500.0 ml) was stirred overnight at 45□ . The organic layer was concentrated and purified by column chromatography to give rude product **13** (26.0 g). A solution of rude product **13** (26.0 g) in 30% sodium methylate (3.0 ml) in methanol (520.0 ml) was stirred for 3 h under reflux condition. The reaction was quenched with water (250.0 ml) and filtered to afford **14** (17.8 g, 73% for two steps). $[\alpha]_D^{20}$ -9.0°(c 0.1, C_3H_6O); ^{1}H NMR (400 MHz, DMSO) δ 12.09 (s, 1H, OH-5), 7.52 – 6.99 (m, 13H, Ar), 6.18 (m, 2H, H-6 and H-8), 5.67 (s, 1H, OH-4□), 5.55 (dd, 1H, *J* = 12.8, 2.5 Hz, H-2), 5.32 (d, 1H, *J* = 25.1 Hz, OH-2□), 5.13 (d, 2H, *J* = 11.2 Hz, $ArCH_2O$-4'), 5.07 (dd, 1H, *J* = 9.5, 7.5 Hz, H-1□), 4.90 – 4.82 (m, 2H, $ArCH_2O$-3□), 4.68 – 4.56 (m, 1H, H-2□), 3.82 (d, 3H, *J* = 8.2 Hz, CH_3O-5'), 3.71 (d, 1H, *J* = 10.2 Hz, OH-6□), 3.48 (m, 6H, H-3□, H-4□, H-5□,H-6□ and H-3a), 2.79 (dd, *J* = 17.0, 2.5 Hz, 1H, H-3b). ^{13}C NMR (150 MHz, DMSO) δ 197.16, 165.22, 163.02, 162.73, 149.15, 148.10, 139.50, 137.08, 131.13, 128.48, 127.99, 127.91, 127.80, 127.54, 127.14, 119.41, 113.30, 111.15, 103.27, 99.53, 96.68, 95.77, 84.89, 78.78, 77.10, 73.79, 72.90, 69.99, 69.03, 60.33, 55.81, 42.18. HRMS calcd for $C_{36}H_{36}O_{11}$ $[M+H]^+$ 667.2150, found 667.2149.

4.3. Preparation of 4'-Benzyloxy-homoeriodictyol-7-*O*-(5-*O*-Benzoyl-2,3-*O*-isopropylidene)-β-D-apiose (1→2)-(3-benzyloxy-4,5-benzylidene)-β-D-glycoside **21**

4.3.1 4'-Benzyloxy- homoeriodictyol-7-O-3-benzyloxy-4,5-benzylidene-β-D-glycoside (**15**). **14** (4.0 g, 6.20 mmol) was dissolved in acetone (48.0 ml), $PhCH(OMe)_2$ (17.0 g,111.69 mmol) and $TsOH.H_2O$ (1.8 g, 9.31 mmol) and the mixture was stirred for 2 h at room temperature. The reaction was quenched with Et_3N and diluted with ethyl acetate and washed with brine. The

residue was purified by chromatography to afford **15** (3.8 g, 83%).^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (d, *J* = 16.1 Hz, 1H, OH-5), 7.75 – 6.84 (m, 18H, Ar), 6.47 – 6.09 (m, 2H, H-6 and H-8), 5.56 (d, *J* = 17.5 Hz, 1H, $ArCHO_2$), 5.34 (t, *J* = 15.2 Hz, 1H, H-1□), 5.20 (s, 2H, $ArCH_2O$-4'), 5.11–4.96 (m, 3H, H-2 and $ArCH_2O$-3□), 4.87 (t, *J* = 14.5 Hz, 1H, H-2□), 4.39 (dd, *J* = 10.4, 4.9 Hz, 1H, H-4□), 3.96 (d, *J* = 17.8 Hz, 3H, OCH_3-3'), 3.88 – 3.69 (m, 4H, H-6□, H-3 ^{I} and OH-2 ^{I}), 3.59 (m, 1H, H-3a), 3.21 – 3.00 (m, 1H, H-5 ^{I}), 2.87 (m, 1H, H-3b). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.54, 164.87, 163.95, 162.93, 149.99, 148.81, 138.30, 137.19, 136.94, 131.14, 129.17, 128.69, 128.56, 128.38, 128.14, 128.05, 127.99, 127.55, 127.36, 126.16, 118.97, 113.94, 110.15, 104.31, 101.39, 97.52, 96.20, 80.91, 80.35, 79.40, 74.84, 73.69, 71.08, 68.52, 66.65, 56.21, 43.24. HRMS calcd for $C_{21}H_{26}O_{10}$ m/z $[M+Na]^+$: 755.2463, found 755.2471.

4.3.2 3'-*O*-Benzoyl-2,3-*O*-isopropylidene-α/β-D-apiofuranoside (**19**). To a stirred solution of **16** (3.6 g, 18.67 mmol) and pyridine (4.4 g, 56.0 mmol) in anhydrous dichloromethane (71.0 ml) was added benzoyl chloride (2.8 g, 19.60 mmol) dropwise at 0°C and the mixture was stirred at 0°C for 2 h and partitioned between CH_2Cl_2/H_2O. The organic layer was washed with 20% HCl aqueous solution and brine, dried over $MgSO_4$, filtrated and evaporated. The residue was purified by column chromatography to give **19** (2.5 g, 45%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.09 (m, 2H, Ar), 7.61 - 7.45 (m, 3H, Ar), 5.52 (s, 1H, H-1), 4.67 - 4.51 (m, 3H, H-5 and H-2), 4.22 – 4.11 (m, 2H, H-4), 1.61 – 1.43 (m, 6H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.45, 133.74, 133.48, 130.00, 129.85, 128.82, 128.67, 114.11, 102.41, 90.45, 87.41, 74.66, 66.04, 27.63. HRMS calcd for $C_{15}H_{18}O_6$ m/z $[M+Na]^+$: 317.0996, found 317.0999.

4.3.3 4'-Benzyloxy-homoeriodictyol-7-*O*-(5-*O*-Benzoyl-2,3-*O*-isopropylidene)-β-D-apiose (1→2)-(3-benzyloxy-4,5-benzylidene)-β-D-glycoside (**21**). To a solution of hemiacetal **19** (2.6 g, 8.84 mmol)in dry dichloromethane (26.0 mL) was added trichloroacetonitrile (7.7 g, 53.04 mmol) and1,8-Diazabicyclo[5.4.0]undec-7-ene (0.4 g, 2.6 mmol) at -20℃ under nitrogen. After stirring for 10 min, the mixture was concentrated and purified by column chromatography to afford glycosyl donor **20,** used directly to the next step for its instability at room temperature. A mixture of **15** (3.1 g, 4.2 mmol), **20** (2.7 g, 6.3 mmol) and molecular sieves 4 Å (6.0 g) in anhydrous dichloromethane (120.0 ml) was stirred for 30 min at 22℃, then the mixture was cooled to -20 ℃ and TMSOTf (0.3 g,1.3 mmol) was added by syringe. The stirring continued for 2 h at -20 ℃. The mixture was quenched with Et_3N (0.2 ml) and concentrated. The residue was purified by column chromatography to afford homoeriodictyol disaccharide derivative **21** (3.1 g, 86%). $[\alpha]_D^{20}$ -37.8°(c 0.1, C_3H_6O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H, OH-5), 8.10-7.28 (m, 25H, Ar), 6.99 (d, 1H, *J* =1.8Hz, H-1 ^{II}), 6.91 (m, 2H, $ArCHO_2$ and H-1 ^{I}), 6.08 (m, 3H, H-2 and $ArCH_2O$-4'), 5.60 (d, 2H, *J* = 3.2 Hz, $ArCH_2O$-3 ^{I}), 5.20 (m, 2H, H-4 I and H-2 ^{II}), 4.98-4.79 (m, 3H, H-2 ^{I}, H-6α ^{I}, and

H-4α□), 4.44 – 4.35 (m, 4H, H-3□, H-6β□, H-4β□ and H-5α□), 4.05 (m, 1H, H-5β□), 3.95 (s, 3H, OCH_3-3'), 3.79-3.77 (m, 1H, H-5□), 3.10-3.02 (m, 1H, H-3a), 2.77-2.72 (m, 1H, H-3b), 1.31-1.28 (m, 6H, $2CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.39, 166.14, 164.61, 163.95, 162.99, 150.11, 148.90, 137.90, 137.22, 136.98, 133.37, 131.29, 131.16, 129.82, 129.31, 128.82, 128.77, 128.65, 128.58, 128.51, 128.21, 127.50, 126.19, 119.03, 114.09, 110.16, 108.08, 104.28, 102.35, 98.52, 96.98, 90.44, 90.09, 87.43, 86.87, 81.46, 76.14, 74.94, 74.37, 71.24, 68.66, 66.53, 56.32, 43.55, 30.04, 27.68.

4.4. Total synthesis of viscumneoside III (**1**)

4.4.1 4'-Benzyloxy-homoeriodictyol-7-*O*-(5-*O*-Benzoyl-2,3-*O*-isopropylidene)-β-D-apiose (1→2)- (4,5-benzylidene)-β-D-glycoside (**22**). A mixture of **21** (2.8 g, 2.80 mmol) and sodium methylate (0.2 g, 4.21 mmol) in dichloromethane (28.0 ml) and methanol (28.0 ml) was stirred for 2 h at 45□ and concentrated. The residue was redissolved in methanol (40.0 ml) and filtered to afford **22** (2.2 g, 85%).^{1}H NMR (400 MHz, DMSO) δ 7.80 – 6.76 (m, 20H, Ar), 5.71 (m, 1H, H-1□), 5.44 (m, 1H, $ArCHO_2$), 5.16-5.10 (m, 4H, H-2, $ArCH_2O$-4' and H-1□), 4.87-4.72 (m, 2H, H-4□ and H-2□), 4.23(m, 2H, $ArCH_2O$-3□), 3.93-3.40 (m, 11H, H-2□, H-3□, H-5□, H-6□, H-5□, OH-5□ and CH_3O-3'), 2.50 (m, 2H, H-3), 1.34 (t, *J* = 9.2 Hz, 6H, $2CH_3$). ^{13}C NMR (150 MHz, DMSO) δ 189.71, 166.17, 163.42, 149.17, 148.42, 138.22, 137.54, 136.94, 133.36, 129.71, 129.15, 128.81, 128.45, 128.30, 128.19, 127.93, 127.76, 125.96, 121.33, 113.54, 112.11, 110.86, 109.78, 107.07, 100.09, 96.93, 92.88, 85.24, 80.91, 79.28, 74.90, 74.25, 73.77, 69.89, 67.82, 65.20, 55.38, 27.98. HRMS calcd for $C_{51}H_{52}O_{15}$ $[M+Na]^+$ 927.3198, found 927.3197.

4.4.2 Homoeriodictyol-7-*O*-β-D-apiose (1→2)-β-D-glycoside (**1**). A mixture of **22** (1.2 g, 1.32 mmol) and Amberlyst 15(H^+) in methanol (23.0 ml) and ethyl acetate (23.0 ml) was stirred for 4 h at 70□ , filtered and the filtrate was diluted with methanol (75.0 ml) and ethyl acetate (75.0 ml). The residue and 10% Pd/C (0.2 g) was stirred for 1 h at 22□ under hydrogen. The mixture was filtered and the filtrate was concentrated to give crude product. Purification of the crude product was performed by pre-HPLC on Luna C18 eluted with acetonitrile furnished the target molecule **1** (0.5 g, 60% for two steps). $[\alpha]_D^{20}$ -108.0°(c 0.1, C_3H_6O); ^{1}H NMR (400 MHz, MeOD) δ7.12 (d, 1H, *J* = 1.5 Hz, H-2'), 6.95 (dd, 1H, *J* = 8.1, 1.7 Hz, H-6'), 6.86 (d, 1H, *J* = 8.1 Hz, H-5'), 6.21-6.19 (dd, 2H, *J* = 11.8, 2.1 Hz, H-6 and H-8), 5.60 (d, *J* = 14.8 Hz ,1H, H-1□), 5.44-5.41 (dd, 1H, *J* = 12.8, 2.5 Hz, H-2), 5.08 (d, 1H, *J* = 7.4 Hz, H-1□), 4.39 (s, 1H, H-2□), 4.10-3.87 (m, 6H, H-2□, H-3□, H-4□ and H-5□), 3.72–3.36 (m, 7H, H-4□, H-5□, H-6□ and CH_3O-3'), 3.23 (m, 1H, H-3b), 2.83 (m, 1H. H-3a). ^{13}C NMR (150 MHz, MeOD) δ 198.69, 166.73, 165.17, 164.82, 149.34, 148.37, 131.53, 120.83, 116.27, 111.60, 108.87, 105.09, 99.61, 97.88, 96.81, 94.12, 87.35, 81.06, 78.89, 78.35, 77.41, 75.88, 71.35, 65.01, 62.44, 56.67, 44.22. LC-MS (m/z): 619.2 $[M+Na]^+$. Anal.

Calcd for $C_{27}H_{32}O_{15}$: C, 54.36; H, 5.41; Found: C, 54.33; H, 5.42.

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