Synthesis of Conandroside: A Dihydroxyphenylethyl Glycoside from *Conandron ramaidioides*

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The key intermediate 2-(3,4-di-*O*-benzylphenyl)ethyl 2,6-di-*O*-acetyl-4-*O*-[(*E*,*Z*)-3,4-di-*O*-benzylcaffeoyl)-β-D-glucopyranoside **(3)** was xylosylated with peracetylated xylosyl trichloroacetimidate donor **4** to afford conandroside derivative **5**. Deacetylation of compound **5** with a methanol solution of methylamine resulted in the formation of compound **6**, the monoacetyl derivative **6a** and the caffeoyl-migrated derivative **6b** in yields of 54%, 19% and 15%, respectively. Compound **6** was then debenzylated with 1,4-cyclohexadiene/palladium–carbon to afford conandroside (**1**), which was treated with dimethyl sulfate in the presence of potassium carbonate to produce the methylated conandroside **2**. This compound was found to be identical to the reported "conandroside tetra-*O*-methyl ether" obtained by methylation of the extract from *Conandron ramoidioides*.

Introduction

Dihydroxyphenylethyl glycosides are a unique family of plant components which exist widely in several plant species.[1] Currently more than eighty types of dihydroxyphenylethyl glycosides have been isolated, all of which have a common structure consisting of a phenylethyl glycoside, a phenolic acid ester and a sugar residue. Their reported characteristics include antimicrobial activity,[2] a sedative effect,[3] hepatoprotective activity[4] and others.[5]

Conandroside, 2-(3,4-dihydroxyphenyl) ethyl 4-*O*-[(*E*,*Z*)-caffeoyl]-3-*O*-(β-D-xylopyranosyl)-β-D-glucopuranoside (**1**, see Figure 1), is one example of a dihydroxyphenylethyl glycoside. It was first isolated from *Conandron ramoidioides* as a "bitter glycoside" in 1977 by Nonaka and Nishioka.[6] They described this compound only as its methyl derivative **2** (Figure 1) after methylation of crude extracts, rather than as conandroside itself. Here, we report the first synthesis of conandroside, its spectroscopic characterization and verify its structure by comparison of its methylated derivative with a sample of the methylated natural product.

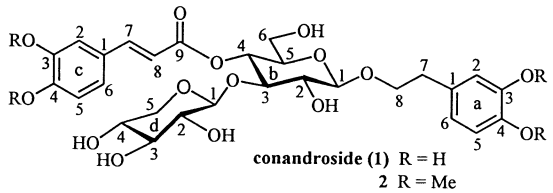

Figure 1. Structures of conandroside (**1**) and compound **2**

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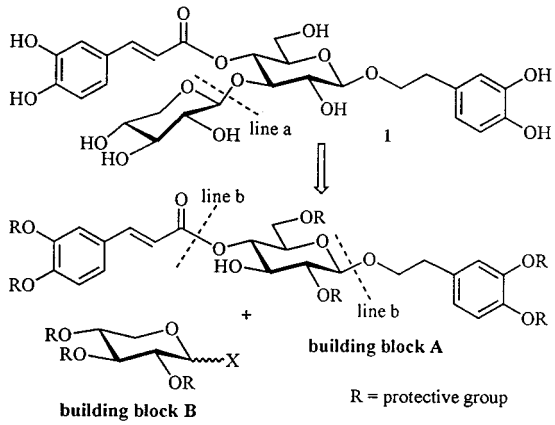
Results and Discussion

The retrosynthesis of conandroside (**1**) is shown in Scheme 1. First, the xylosylic bond (line a) is cut into two building blocks, a dihydroxyphenylethyl 4-*O*-caffeoyl-glycoside derivative (key intermediate A) and a xylosyl moiety (B). Intermediate A is then cut at two line b′s into three building blocks, a caffeoyl group, a phenylethyl group and a glucose residue. Our strategy has the advantage of wide applicability in synthesizing members of the dihydroxyphenylethyl glycoside family, although other synthetic strategies are known;[7] for example, if a rhamnosyl or a glucosyl moiety were introduced into intermediate A, acteoside (verbascoside)[8] or plantamajoside[9] could be synthesized, respectively.



Scheme 1. Retrosynthesis of conandroside (**1**)

Following this synthetic strategy, we began the synthesis of conandroside (**1**) with a xylosylation reaction of key intermediate **3**.[10] For this reaction, two glycosylation methods, the imidate method and the Königs-Knorr method, were considered. The latter method is reported to give lower stereoselectivity and yield than the former.[11] Furthermore, xylosyl donors such as 2,3,4-tri-*O*-acetyl-β-

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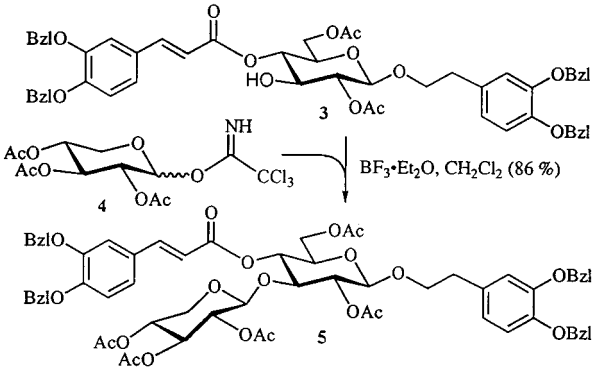
D-xylosyl bromide have been reported to show too high a reactivity[12] to handle under anhydrous conditions. Therefore, the imidate method was selected for the xylosylation reaction in this case.

The key intermediate **3** was thus xylosylated with the xylosyl donor **4**[13] using boron trifluoride diethyl ether complex ($BF_3{\cdot}Et_2O$) as a catalyst in dichloromethane at −20 °C (Scheme 2). The glycosyl donor **4** was completely consumed within one hour. The reaction mixture was then purified by gel-permeation chromatography to give compound **5** in a yield of 86% based on the key intermediate **3**. This xylosylation reaction seems to proceed stereospecifically affording only the β-anomer in high yield.

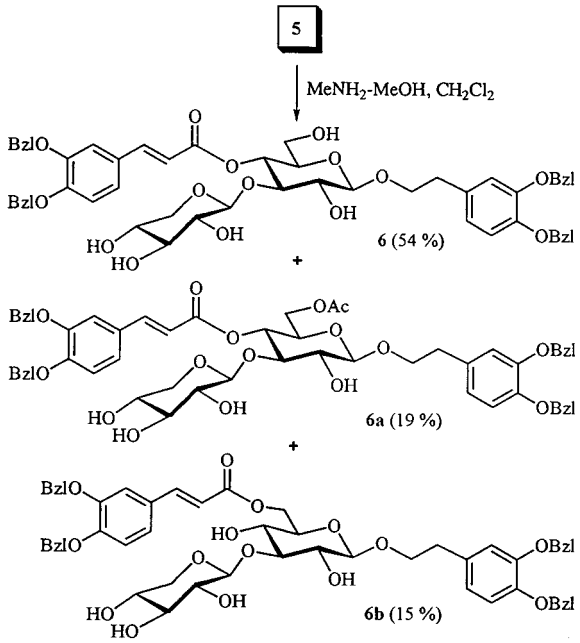


Scheme 2. Xylosylation of compound **3**

The next step was the deprotection of acetyl groups of compound **5** as shown in Scheme 3. The difficulty of this step is the selective deacetylation in the presence of another kind of ester, the caffeoyl ester. As the caffeoyl ester, an α, β-unsaturated ester, is known to be less stable than the acetyl ester, the usual methods, such as using a methanol solution of sodium methoxide, should be avoided in this case. Hence, a methanol solution of methylamine ($MeNH_2$/MeOH)[10] was tried as a reagent for deacetylation of compound **5**.

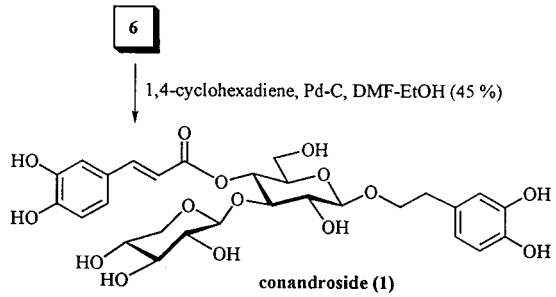
Treatment of compound **5** with $MeNH_2$/MeOH for eight hours at −20 °C affords compounds **6**, **6a** and **6b** in yields of 54%, 19% and 15%, respectively. In the ^1H NMR spectrum of compound **6a**, a signal for one acetyl is seen. It was subsequently found that the acetyl group remains at O-6b, as the signals of H-6b, which appear at δ = 4.14 and 4.22, show low-field shifts of about 0.5 ppm.[14] It is difficult to ascertain why the 6b-*O*-acetyl group exhibits such high stability. The ^1H NMR spectrum of the compound **6b** shows no signal for an acetyl group. However, low-field shifts of H-6b (δ = 4.40 and 4.55) of about 0.8 ppm, bigger than those caused by acetylation, suggest that O-6b is caffeoylated. The signals of H-4b appear at δ = 3.48−3.50 and are shifted to high field by about 0.5 ppm, thus indicating that 4b-OH is free. Consequently, the compound **6b** was thought to be a caffeoyl-migrated derivative.

The last step was a deprotection of the benzyl groups. This requires that the benzyl groups have to be hydrogenated in the presence of a reactive olefinic double bond in the caffeoyl moiety of compound **6**. Compound **6** was thus treated with 1,4-cyclohexadiene as a proton source[10] in the



Scheme 3. Deacetylation of compound **5**

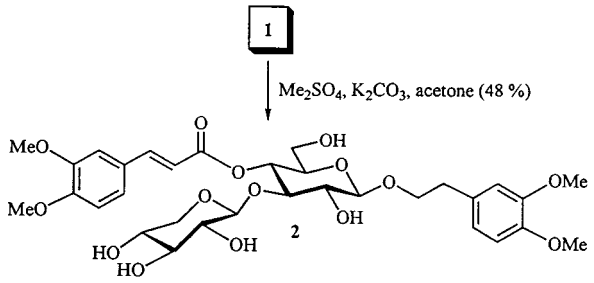
presence of 5% palladium carbon (Pd−C) as a catalyst to afford the target compound **1** (conandroside) in 45% yield (Scheme 4). In addition, a small amount of an unexpected compound, in which the olefinic double bond was saturated, was also obtained.



Scheme 4. Synthesis of conandroside (**1**)

At this stage the first synthesis of conandroside was complete. However, does it have the same structure as that of the natural product isolated from *Conandron ramoidioide*? One previous report describes conandroside,[6] although only the physicochemical data of the "conandroside tetra-*O*-methyl ether" (compound **2**) and not of the conandroside (**1**) itself, are reported. Hence, the synthesized conandroside (**1**) was methylated using the same method as that described (Scheme 5).[6]

The structure of the synthesized compound **2** was confirmed by ^1H NMR spectroscopy and by employing the C−H COSY technique with CD_3OD as solvent (Table 1, first column). In this case each signal appears sharply and separately thus allowing complete assignment. However, Nonaka and Nishioka[6] measured the NMR spectrum in $CDCl_3$. Therefore, the ^1H NMR spectrum of the synthesized compound **2** was again measured in $CDCl_3$ in order to make a better comparison. As shown in Table 1, the ^1H



Scheme 5. Methylation of conandroside (**1**)

NMR spectroscopic data of the synthesized compound **2** are identical to those of the natural compound, although there are small differences owing to the frequency of the NMR spectrometer used. Consequently, the synthesized compound **2** is identical to the "conandroside tetra-*O*-methyl ether" prepared from the natural product, thus confirming that the synthesized conandroside (**1**) has the same structure as that of the natural product isolated from *Conandron ramoidioide*.

Conclusion

The first synthesis of conandroside (**1**) was accomplished from the key intermediate **3** and the physicochemical data for conandroside (**1**) are presented. The synthesized conandroside (**1**) was then methylated to obtain compound **2**, which was found to be identical to the "conandroside tetra-*O*-methyl ether" prepared from natural sources. This synthesis provides a good example of the advantages in using the key intermediate **3** for the synthesis of other members of the dihydroxyphenylethyl glycoside family.

Experimental Section

General Remarks: All melting points (mp) are uncorrected. – NMR spectra were taken with a JEOL JNM-ECP500 FT NMR (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts and coupling constants are given in ppm and Hz, respectively. The assignments of the signals were determined using a decoupling and/or a 2D-COSY technique. – Anhydrous CH_2Cl_2 was obtained by distilling from P_2O_5. – Op-

Table 1. ^{1}H NMR peaks (d ppm) of compound **2**[a]

	Synthetic (500 MHz) CD_3OD	$CDCl_3$	Natural[b] (400 MHz) $CDCl_3$
Phenethyl alcohol			
2a	6.92 (d, 2.0)		
5a	6.85 (d, 8.5)		
6a	6.80 (dd, 2.0, 8.5)		
7a	2.87−2.90 (m)	2.84−2.89 (m)	2.88 (t, 7.5)
8a	3.75−3.87 (m)		
8′a	4.10 (m)		
D-Glucose			
1b	4.44 (d, 8.0)	4.39 (d, 7.5)	4.37 (d, 7.5)
2b	3.50 (dd, 8.0, 9.5)		
3b	3.75−3.87 (m)		
4b	4.93 (t, 9.0)	5.08 (t, 9.5)	5.05 (t, 8.5)
5b	3.52−3.58 (m)		
6b	3.52−3.58 (m)		
6′b	3.63−3.65 (m)		
Caffeic acid			
2c	7.23 (d, 1.5)		
5c	6.97 (d, 8.0)		
6c	7.18 (dd, 1.5, 8.0)		
7c	7.66 (d, 16.0)	7.61 (d, 16.0)	7.61 (d, 16.0)
8c	6.43 (d, 16.0)	6.27 (d, 16.0)	6.26 (d, 16.0)
D-Xylose			
1d	4.45 (d, 7.5)	4.52 (d, 7.0)	4.52 (d, 7.0)
2d	3.16 (dd, 7.5, 9.0)		
3d	3.28 (t, 9.0)		
4d	3.32−3.38 (m)		
5d	3.09 (dd, 10.0, 11.5)		
5′d	3.63 (dd, 5.0, 11.5)		
Hydroxyl group		2.76 (bs), 3.04 (bs), 4.18 (bs), 5.00 (bs), 5.12 (bs)	
Methoxy group	3.79 (s), 3.82 (s) 3.86 (s), 3.87 (s)	3.80 (s) 3.82 (s) 3.85 (s) 3.86 (s)	3.80 (s), 3.82 (s) 3.86 (s)

[a] Splitting patterns and *J* values (Hz) are given in parentheses. – [b] These data were measured by G. Nonaka and I. Nishioka (ref.[6]).

tical rotations were measured at 20 °C using a HORIBA SEPA-200 polarimeter. − Column chromatography was performed on silica gel (Wakogel C-200). − Preparative TLC was done on silica gel plates (Kieselgel 60 F_{254}, Merck). − Unless otherwise indicated, the usual workup for each reaction mixture consists of extraction with EtOAc, washing with brine, drying over Na_2SO_4, and evaporation of the solvents in vacuo.

2-(3,4-Di-*O*-benzylphenyl)ethyl 2,6-Di-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-*O*-[(*E*,*Z*)-3,4-di-*O*-benzylcaffeoyl]-β-D-glucopyranoside (5): To a stirred solution of **3**[10] (2.0 g, 2.2 mmol) and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl trichloroacetimidate (**4**)[13] (2.8 g, 6.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was added $BF_3{\cdot}Et_2O$ (80 μL, 0.65 mmol) at −20 °C. The reaction mixture was stirred for 1 h at this temperature, then neutralized with Et_3N (92 μL), and concentrated in vacuo to give an oily residue. The residue was purified using gel-permeation chromatography [Sephadex LH-20, $CHCl_3$/MeOH (1:1, v/v)] to give **5** (2.2 g, 86%) as a colorless solid: R_f = 0.45 (EtOAc/*n*-hexane, 1:1, v/v). − $[\alpha]_D^{20}$ = −69.20 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92, 1.97, 2.01, 2.02, 2.04 (5 s, 15 H, 5 × Ac), 2.74−2.78 (m, 2 H, H-7a, H-7′a), 3.30 (dd, $J_{4d,5d}$ = 6.5 Hz, $J_{5d,5'd}$ = 12.0 Hz, 1 H, H-5d), 3.56 (m, 1 H, H-8a), 3.68 (m, 1 H, H-5b), 3.89 (t, $J_{2b,3b}$ = $J_{3b,4b}$ = 9.5 Hz, 1 H, H-3b), 3.99 (dd, $J_{4d,5'd}$ = 4.0 Hz, $J_{5d,5'd}$ = 12.0 Hz, 1 H, H-5′d), 4.06 (m, 1 H, H-8′a), 4.14−4.22 (m, 2 H, H-6b, H-6′b), 4.33 (d, $J_{1b,2b}$ = 8.0 Hz, 1 H, H-1b), 4.62 (d, $J_{1d,2d}$ = 6.0 Hz, 1 H, H-1d), 4.74−4.82 (m, 1 H, H-4d), 4.77 (dd, $J_{1d,2d}$ = 6.0, $J_{2d,3d}$ = 7.0 Hz, 1 H, H-2d), 4.97−5.04 (m, 2 H, H-2b, H-3d), 5.09−5.21 (m, 9 H, H-4b, 4 × CH_2Ph), 6.21 (d, $J_{7c,8c}$ = 16.0 Hz, 1 H, H-8c), 6.69 (d, $J_{5a,6a}$ = 8.5 Hz, 1 H, H-6a), 6.82 (s, 1 H, H-2a), 6.85 (d, $J_{5a,6a}$ = 8.5 Hz, 1 H, H-5a), 6.91 (d, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-5c), 7.06 (d, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-6c), 7.12 (s, 1 H, H-2c), 7.25−7.48 (m, 20 H, 4 × Ph), 7.59 (d, $J_{7c,8c}$ = 16.0 Hz, 1 H, H-7c). − ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.5, 20.6, 20.7, 20.8 (*C*H_3CO), 35.5 (C-7a), 61.3 (C-5d), 62.5 (C-6b), 68.4 (C-4d), 69.0 (C-4b), 69.7 (C-2d), 70.3 (C-3d), 70.5 (C-8a), 70.8, 71.2, 71.3, 71.4 (4 × $C_6H_5CH_2O$), 71.9 (C-5b), 72.4 (C-2b), 79.9 (C-3b), 100.6 (C-1d), 100.8 (C-1b), 113.8 (C-2c), 114.2 (C-5c), 114.9 (C-8c), 115.3 (C-5a), 116.1 (C-2a), 121.7 (C-6a), 123.2 (C-6c), 127.1−128.6 (C-1c, $C_6H_5CH_2O$), 132.1 (C-1a), 136.7, 136.9, 137.4, 137.5 ($C_6H_5CH_2O$), 145.7 (C-7c), 147.4, 148.8, 149.0, 151.3 (C-3a, C-3c, C-4a, C-4c), 165.5 (C-9c), 169.0, 169.3, 169.6, 170.0, 170.6 (5 × CH_3CO). − $C_{66}H_{68}O_{20}$ (1181.2): calcd. C 67.11, H 5.80; found C 66.96, H 5.72.

2-(3,4-Di-*O*-benzylphenyl)ethyl 4-*O*-[(*E*,*Z*)-3,4-Di-*O*-benzylcaffeoyl]-3-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside (6): To a solution of **5** (1.8 g, 1.5 mmol) in CH_2Cl_2 (21.4 mL) was added 40% $MeNH_2$ in MeOH (32 mL) at −20 °C. The reaction mixture was stirred at this temperature for 8 h and then concentrated in vacuo. The residue was purified by TLC using a solvent mixture of MeOH/CH_2Cl_2 (1:19, v/v) to give **6** (799 mg, 54%) as a colorless solid: R_f = 0.60 (MeOH/CH_2Cl_2, 1:9, v/v). − $[\alpha]_D^{20}$ = −12.07 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD, 3:1, v/v): δ = 2.85−2.90 (m, 2 H, H-7a, H-7′a), 3.09 (dd, $J_{4d,5d}$ = 10.0 Hz, $J_{5d,5'd}$ = 11.5 Hz, 1 H, H-5d), 3.27 (dd, $J_{1d,2d}$ = 7.5 Hz, $J_{2d,3d}$ = 9.0 Hz, 1 H, H-2d), 3.34 (t, $J_{2d,3d}$ = $J_{3d,4d}$ = 9.0 Hz, 1 H, H-3d), 3.43−3.50 (m, 2 H, H-5b, H-4d), 3.54 (dd, $J_{1b,2b}$ = 8.0 Hz, $J_{2b,3b}$ = 9.5 Hz, 1 H, H-2b), 3.59 (dd, $J_{5b,6b}$ = 5.5 Hz, $J_{6b,6'b}$ = 12.5 Hz, 1 H, H-6b), 3.67−3.76 (m, 3 H, H-8a, H-6′b, H-5′d), 3.78 (t, $J_{2b,3b}$ = $J_{3b,4b}$ = 9.5 Hz, 1 H, H-3b), 4.07 (m, 1 H, H-8′a), 4.39 (d, $J_{1b,2b}$ = 8.0 Hz, 1 H, H-1b), 4.41 (d, $J_{1d,2d}$ = 7.5 Hz, 1 H, H-1d), 4.99 (t, $J_{3b,4b}$ = $J_{4b,5b}$ = 9.5 Hz, 1 H, H-4b), 5.12, 5.14, 5.18, 5.20 (4 s, 8 H, 4 × CH_2Ph), 6.24 (d, $J_{7c,8c}$ = 15.5 Hz, 1 H, H-8c), 6.76 (dd, $J_{2a,6a}$ = 2.0 Hz, $J_{5a,6a}$ = 8.0 Hz, 1 H, H-6a), 6.88 (d, $J_{5a,6a}$ = 8.0 Hz, 1 H, H-5a), 6.89 (d, $J_{2a,6a}$ = 2.0 Hz, 1 H, H-2a), 6.95 (d, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-5c), 7.10 (dd, $J_{2c,6c}$ = 1.5 Hz, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-6c), 7.15 (d, $J_{2a,6a}$ = 1.5 Hz, 1 H, H-2c), 7.31−7.48 (m, 20 H, 4 × Ph), 7.60 (d, $J_{7c,8c}$ = 15.5 Hz, 1 H, H-7c). − ^{13}C NMR (500 MHz, $CDCl_3$/CD_3OD, 3:1, v/v): δ = 35.7 (C-7a), 61.4 (C-6b), 66.0 (C-5d), 69.5 (C-4d), 69.6 (C-4b), 71.0 (C-8a), 71.2, 71.7, 71.8 ($C_6H_5CH_2O$), 73.6 (C-2b), 74.1 (C-2d), 74.7 (C-5b), 76.5 (C-3d), 84.8 (C-3b), 102.7 (C-1b), 105.8 (C-1d), 114.2 (C-2c), 114.6 (C-5c), 115.2 (C-8c), 115.7 (C-2a), 116.5 (C-5a), 122.1 (C-6a), 123.4 (C-6c), 127.4−128.7 (C-1c, $C_6H_5CH_2O$), 132.1 (C-1a), 136.8, 137.0, 137.4, 137.5 ($C_6H_5CH_2O$), 145.9 (C-7c), 147.7, 149.1, 149.2, 151.6 (C-3a, C-3c, C-4a, C-4c), 167.2 (C-9c). − $C_{56}H_{58}O_{15}{\cdot}0.8H_2O$ (985.5): calcd. C 68.25, H 6.10; found C 68.29, H 5.95.

2-(3,4-Dihydroxyphenyl)ethyl 4-*O*-(*E*,*Z*)-caffeoyl-3-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside (1, Conandroside): A mixture of **6** (346 mg, 0.36 mmol), 5% Pd−C (346 mg) and 1,4-cyclohexadiene (668 μL, 7.1 mmol) in DMF/EtOH (1:1, v/v, 2.4 mL) was stirred at 40 °C for 5 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give a yellow oily residue. The residue was purified by preparative TLC using a solvent mixture of $CHCl_3$/MeOH/H_2O (30:10:1, v/v/v) to give conandroside (**1**) (98 mg, 45%) as a pale-yellow solid: R_f = 0.21 ($CHCl_3$/MeOH/H_2O, 30:10:1, v/v/v). − $[\alpha]_D^{20}$ = −28.27 (*c* = 0.5, MeOH). − ^{1}H NMR (500 MHz, CD_3OD): δ = 2.71−2.77 (m, 2 H, H-7a, H-7′a), 3.04 (t, $J_{4d,5d}$ = $J_{5d,5'd}$ = 10.5 Hz, 1 H, H-5d), 3.11 (dd, $J_{1d,2d}$ = 7.5 Hz, $J_{2d,3d}$ = 8.5 Hz, 1 H, H-2d), 3.24 (t, $J_{2d,3d}$ = $J_{3d,4d}$ = 8.5 Hz, 1 H, H-3d), 3.29−3.34 (m, 1 H, H-4d), 3.44 (dd, $J_{1b,2b}$ = 8.0 Hz, $J_{2b,3b}$ = 9.0 Hz, 1 H, H-2b), 3.48−3.53 (m, 2 H, H-5b, H-6b), 3.57−3.63 (m, 2 H, H-6′b, H-5′d), 3.69 (m, 1 H, H-8a), 3.80 (t, $J_{2b,3b}$ = $J_{3b,4b}$ = 9.0 Hz, 1 H, H-3b), 4.01 (m, 1 H, H-8′a), 4.38 (d, $J_{1b,2b}$ = 8.0 Hz, 1 H, H-1b), 4.40 (d, $J_{1d,2d}$ = 7.5 Hz, 1 H, H-1d), 4.88 (t, $J_{3b,4b}$ = $J_{4b,5b}$ = 9.0 Hz, 1 H, H-4b), 6.23 (d, $J_{7c,8c}$ = 16.0 Hz, 1 H, H-8c), 6.53 (dd, $J_{2a,6a}$ = 2.0 Hz, $J_{5a,6a}$ = 8.0 Hz, 1 H, H-6a), 6.64 (d, $J_{5a,6a}$ = 8.0 Hz, 1 H, H-5a), 6.66 (d, $J_{2a,6a}$ = 2.0 Hz, 1 H, H-2a), 6.75 (d, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-5c), 6.92 (dd, $J_{2c,6c}$ = 2.0 Hz, $J_{5c,6c}$ = 8.0 Hz, 1 H, H-6c), 7.02 (d, $J_{2c,6c}$ = 2.0 Hz, 1 H, H-2c), 7.53 (d, $J_{7c,8c}$ = 16.0 Hz, 1 H, H-7c). − ^{13}C NMR (500 MHz, CD_3OD): δ = 36.5 (C-7a), 62.3 (C-6b), 67.3 (C-5d), 70.9 (C-4b), 71.0 (C-4d), 72.2 (C-8a), 74.9 (C-2b), 75.7 (C-2d), 75.9 (C-5b), 77.6 (C-3d), 85.2 (C-3b), 103.9 (C-1b), 106.8 (C-1d), 115.1 (C-2c), 115.2 (C-8c), 116.3 (C-2a), 116.6 (C-5c), 117.1 (C-5a), 121.3 (C-6a), 123.0 (C-6c), 127.8 (C-1c), 131.4 (C-1a), 144.6, 146.1, 146.8, 149.6 (C-3a, C-3c, C-4a, C-4c), 147.2 (C-7c), 167.2 (C-9c). − $C_{28}H_{34}O_{15}{\cdot}2.3H_2O$ (652.0): calcd. C 51.58, H 5.97; found C 51.34, H 6.11.

2-(3,4-Di-*O*-methylphenyl)ethyl 4-*O*-[(*E*,*Z*)-3,4-di-*O*-methylcaffeoyl)-3-*O*-(β-D-xylopyranosyl)-β-D-glucopyranoside (2): A stirred mixture of **1** (28 mg, 0.05 mmol), Me_2SO_4 (44 μL, 0.5 mmol) and K_2CO_3 (64 mg, 0.5 mmol) in acetone (2.0 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature and filtered and the solvent was evaporated in vacuo. The residue was purified by TLC using a solvent mixture of MeOH/CH_2Cl_2 (1:19, v/v) to give **2** (14.7 mg, 48%) as a colorless oil: R_f = 0.39 (MeOH/CH_2Cl_2, 1:9, v/v). − $[\alpha]_D^{20}$ = −48.00 (*c* = 1.0, MeOH). − ^{1}H NMR (500 MHz, CD_3OD): δ = 2.87−2.90 (m, 2 H, H-7a, H-7′a), 3.09 (dd, $J_{4d,5d}$ = 10.0 Hz, $J_{5d,5'd}$ = 11.5 Hz, 1 H, H-5d), 3.16 (dd, $J_{1d,2d}$ = 7.5 Hz, $J_{2d,3d}$ = 9.0 Hz, 1 H, H-2d), 3.28 (t, $J_{2d,3d}$ = $J_{3d,4d}$ = 9.0 Hz, 1 H, H-3d), 3.32−3.38 (m, 1 H, H-4d), 3.50 (dd, $J_{1b,2b}$ = 8.0 Hz, $J_{2b,3b}$ = 9.3 Hz, 1 H, H-2b), 3.52−3.58 (m, 2 H, H-5b, H-6b), 3.63 (dd, $J_{4d,5'd}$ = 5.0 Hz, $J_{5d,5'd}$ = 11.5 Hz, 1 H, H-5′d), 3.63−3.65 (m, 1 H, H-6′b), 3.75−3.87 (m, 2 H, H-8a, H-3b), 3.79, 3.82, 3.86, 3.87 (4 s, 12 H, 4 × Me), 4.10 (m, 1 H, H-8′a), 4.44 (d, $J_{1b,2b}$ = 8.0 Hz, 1 H, H-1b), 4.45 (d, $J_{1d,2d}$ = 7.5 Hz, 1 H,

H-1d), 4.93 (t, $J_{2b,3b} = J_{3b,4b} = 9.3$ Hz, 1 H, H-4b), 6.43 (d, $J_{7c,8c} = 16.0$ Hz, 1 H, H-8c), 6.80 (dd, $J_{2a,6a} = 2.0$ Hz, $J_{5a,6a} = 8.5$ Hz, 1 H, H-6a), 6.85 (d, $J_{5a,6a} = 8.5$ Hz, 1 H, H-5a), 6.92 (d, $J_{2a,6a} = 2.0$ Hz, 1 H, H-2a), 6.97 (d, $J_{5a,6a} = 8.0$ Hz, 1 H, H-5c), 7.18 (dd, $J_{2c,6c} = 1.5$ Hz, $J_{5c,6c} = 8.0$ Hz, 1 H, H-6c), 7.23 (d, $J_{2c,6c} = 1.5$ Hz, 1 H, H-2c), 7.66 (d, $J_{7c,8c} = 16.0$ Hz, 1 H, H-7c). – ^{13}C NMR (500 MHz, CD_3OD): δ = 36.7 (C-7a), 56.4, 56.5 (CH_3) 62.4 (C-6b), 67.3 (C-5d), 71.0 (C-4b, C-4d), 71.9 (C-8a), 74.9 (C-2b), 75.7 (C-2d), 76.0 (C-5b), 77.6 (C-3d), 85.4 (C-3b), 103.9 (C-1b), 106.9 (C-1d), 111.5 (C-2c), 112.7 (C-5c), 113.1 (C-5a), 114.2 (C-2a), 116.5 (C-8c), 122.3 (C-6a), 124.0 (C-6c), 128.8 (C-1c), 133.1 (C-1a), 146.6 (C-7c), 148.9, 150.3, 150.8, 152.9 (C-3a, C-3c, C-4a, C-4c), 168.2 (C-9c). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.84–2.89 (m, 2 H, H-7a, H-7′a), 3.80, 3.82, 3.85, 3.86 (4 s, 12 H, 4 × Me), 4.39 (d, $J_{1b,2b} = 7.5$ Hz, 1 H, H-1b), 4.52 (d, $J_{1d,2d} = 7.0$ Hz, 1 H, H-1d), 5.08 (t, $J_{3b,4b} = J_{4b,5b} = 9.5$ Hz, 1 H, H-4b), 6.27 (d, $J_{7c,8c} = 16.0$ Hz, 1 H, H-8c), 6.69–7.05 (m, 6 H, H-2a, H-5a, H-6a, H-2c, H-5c, H-6c), 7.61 (d, $J_{7c,8c} = 16.0$ Hz, 1 H, H-7c). – ^{13}C NMR (500 MHz, $CDCl_3$): δ = 35.6 (C-7a), 55.9 (CH_3) 61.0 (C-6b), 65.7 (C-5d), 69.1 (C-4d), 69.6 (C-4b), 71.2 (C-8a), 73.3 (C-2b), 73.8 (C-2d), 74.2 (C-5b), 76.3 (C-3d), 83.6 (C-3b), 102.6 (C-1b), 105.0 (C-1d), 109.9 (C-2c), 111.1 (C-5c), 111.3 (C-8c), 112.4 (C-2a), 114.6 (C-5a), 120.9 (C-6a), 122.9 (C-6c), 127.0 (C-1c), 130.5 (C-1a), 146.3 (C-7c), 147.6, 148.8, 149.2, 151.5 (C-3a, C-3c, C-4a, C-4c), 167.2 (C-9c). – $C_{32}H_{42}O_{15}·H_2O$ (684.7): calcd. C 56.14, H 6.48; found C 56.03, H 6.41.

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