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Study on the chemical reactivity difference of primary hydroxyl groups in iridoid glycosides†

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Iridoid glycoside, which belongs to the polyhydroxy compound, is a kind of active ingredient of traditional Chinese medicine with a wide range of sources, and has many pharmacological effects such as anti-cancer, anti-inflammatory, anti-virus, hypoglycemic and so on. Its structure contains many hydroxyl groups, including two primary hydroxyl groups. The chemical reactivity of primary hydroxyl groups has very little difference, so it is very important to control the selectivity of hydroxyl groups under certain conditions. In this paper, the difference between the two primary hydroxyl groups in iridoid glycoside was calculated based on computer simulation and verified this result through designed experiments. This study will provide an important way for site-directed modification of hydroxyl in iridoid glycoside in the future.

1 Introduction

The selective protection of hydroxyl groups on polyols, polyphenols and sugars has always been an important research topic in organic chemistry, especially sugar chemistry.[1] When the specific sugar building blocks were synthesized, kinds of oligosaccharides with various functions and biological activities can also be synthesized.[2] Through selective protection reactions on hydroxyl groups, complex organic chemical synthesis steps can be avoided. The ideal protecting groups are usually cheap, easily available, non-toxic, and easy to separate from the product after the protecting groups are removed.[3] The hydroxyl protecting groups include ester protecting groups, ether protecting groups, acetal or ketal protecting groups and so on.[4–7] Therefore, the chemical reactivity of different hydroxyl groups in polyhydroxy compounds deserves further study.

Iridoid glycosides are a typical class of compounds with multiple hydroxyl groups. Most iridoid glycosides contain two primary hydroxyl groups, which were located on the aglycone and the glucose ring (C10-position and C6′-position), respectively, such as catalpol,[8] geniposide[9] and aucubin,[10] as shown in Fig. 1. For the iridoid glycosides containing two primary hydroxyl groups, the position and number of modifications are worthy of attention when structural modification is carried out, and it is also difficult to modify the structure. Therefore, it is very important to control the selectivity of hydroxyl modification under certain reaction conditions.

Many researchers mainly focused on the exploration of partial silicoetherification of catalpol hydroxyl groups, for example, first silicoetherification then esterification for catalpol structure, or full esterification for catalpol structure only. 2004, Pungitore *et al.*[11] and García *et al.*[12,13] conducted partial silicoetherification of catalpol then Tonn *et al.*[14,15] explored silicoetherification followed by esterification and full esterification of catalpol, in addition, these silyl ether protective compounds have a DNA polymerase inhibitory effect. In 2019, Zhang *et al.*[16] modified the C6-position esterified catalpol derivatives and synthesized a series of 8-hydroxyguanine DNA glycosylase 1 (OGG1) with significant effects on inhibits activity. These hydroxyl protection of catalpol were shown in Fig. 2.

In iridoid glycosides, in addition to the protection of the hydroxyl groups of catalpol, the hydroxyl groups of geniposide and aucubin have also been reported. Lei *et al.*[17] protected all the hydroxyl groups of geniposide with benzyl, and then further structurally modified to obtain a series of geniposide derivatives. Wang *et al.*[18] reported geniposide was first converted to

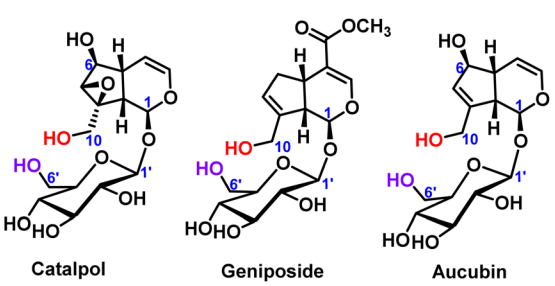

Fig. 1 Chemical structures of catalpol, geniposide and aucubin.

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† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra of all new compounds are given in the Supporting Information. See DOI: https://doi.org/10.1039/d3ra05674k

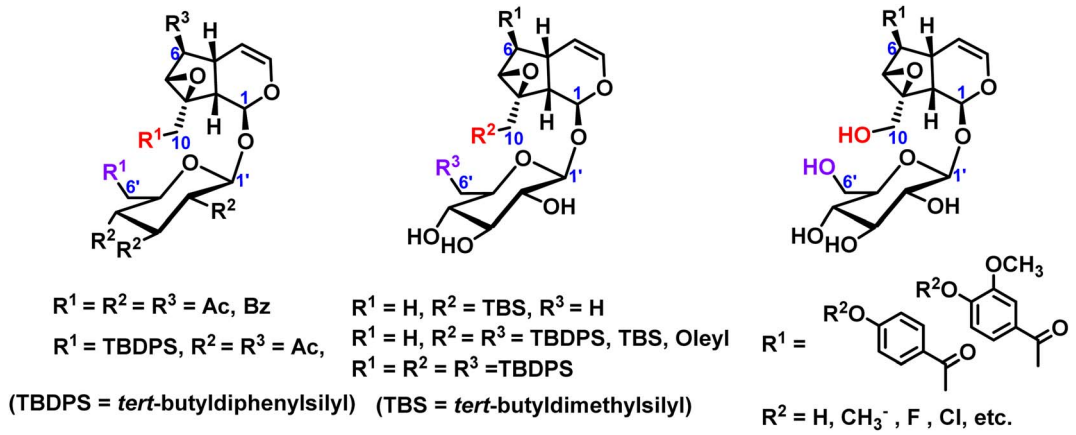


Fig. 2 Modification of hydroxyl groups of catalpol.

intermediate pentaacetyl-geniposide acid by hydrolyzing the ester bond with sodium hydroxide and acetylating the hydroxy compound with acetic anhydride, then reaction with different substituted amines and a series of geniposide derivatives were obtained. The use of *tert*-butyldimethylsilyl chloride permits the selective protection of aucubin at C6′-position of the sugar moiety and C10-position, or C6-position and C10-position, of the aglycone.[19] These hydroxyl protection of geniposide and aucubin were shown in Fig. 3.

However, there is no report on the chemical reactivity of two primary hydroxyl groups in iridoid glycosides. In order to modify the hydroxyl groups in iridoid glycosides, it is necessary for researchers to study this. According to the researches on iridoid glycosides previously reported by our research group[20–22], computer simulation was used to explore the difference between the C10-position and C6′-position primary hydroxyl groups, and experiments were used to verify the difference and control the reaction conditions to generate a single product in order to obtain the higher yield in this paper.

2 Results and discussion

2.1 Computer simulation

2.1.1 Study on the chemical reactivity of primary hydroxyl of catalpol. The emergence of computer-aided drug design has enabled drug design to move from blindly to rational design, and from two-dimensional space to three-dimensional intuitive design, which greatly accelerates the pace of new drug development and saves manpower and labor for new drug development. Rational drug design is based on the understanding of the molecular pathology of the disease process. According to the three-dimensional configuration of the target, and referring to the chemical structure of the effector, the drug for the disease is designed to guide the design to rationalization, and the designed drug has strong activity, specific effect, low side effects. In this paper, Gaussian software,[23] which is widely used in drug design, is used to calculate the energy and optimize the structures of iridoid glycosides, explore the influence of molecular conformation on reactivity, and determine the strength of intermolecular interaction.

Catalpol is a polyhydroxy compound containing six hydroxyl groups, including two primary hydroxyl groups and four secondary hydroxyl groups. Hydroxyl groups in catalpol structure were calculated by Gaussian software, and the structure of catalpol was optimized at the theoretical level of B3LYP/6-311++G(d,p) (Fig. 4).

The optimized six C–O bond lengths connected to –OH were shown in Table 1. The numbers of hydroxyl groups (Fig. 4) were automatically numbered according to Gauss software, while the numbers in chemical structure were numbered according to the rules of IUPAC (International Union of Pure and Applied Chemistry), but in fact, they were the same hydroxyl groups. It can be seen from Table 1, the bond lengths of C43–O46 are the longest, 1.437. Scanning iridoid glycosides showed that the bond length of its hydroxyl group was 1.428. To scan the dihedral angle O17–H18···O46 of the hydroxyl group can be obtained an angle of 172.43°. It can be seen that it is affected by the hydrogen bond. When the angle of forming the hydrogen bond is larger, and the hydrogen bond is stronger, and the electron cloud density is more inclined to O atoms, so that the longer the bond length of C43–O46, the more unstable. The reaction is more likely to occur at the bond length of C43–O46, that is, the C10-position hydroxyl group is more likely to react than the C6′-position hydroxyl group.

2.1.2 Study on the chemical reactivity of primary hydroxyl of geniposide. Geniposide is a polyhydroxy compound containing five hydroxyl groups, including two primary hydroxyl groups and three secondary hydroxyl groups. The chemical

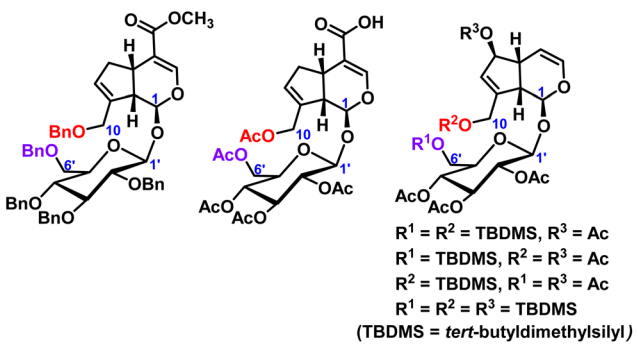


Fig. 3 Modification of hydroxyl groups of geniposide and aucubin.

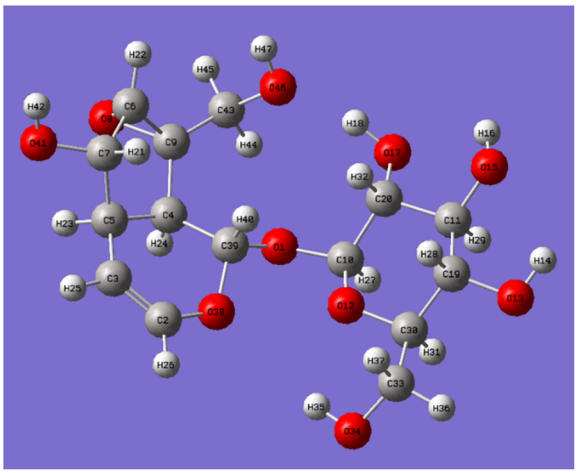


Fig. 4 Optimized geometry of catalpol molecule.

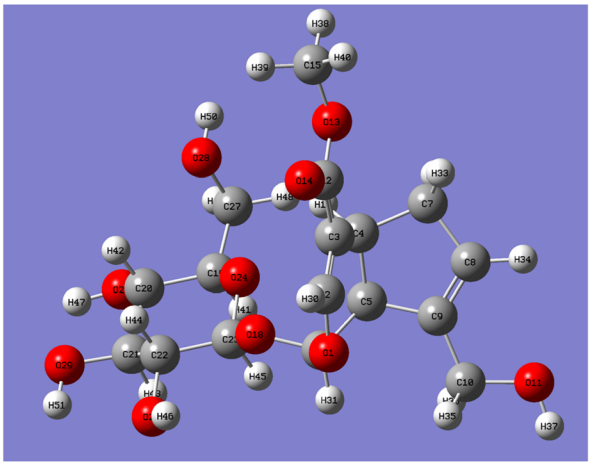


Fig. 5 Optimized geometry of geniposide molecular.

Table 1 Optimized geometric parameters of catalpol molecule[a]

Geometrical parameters		
Gauss software number	Chemical structure number	Bond lengths (Å)
C43–O46	C10–O	1.437
C11–O15	C3′–O	1.425
C7–O41	C6–O	1.422
C19–O13	C4′–O	1.421
C33–O34	C6′–O	1.418
C20–O17	C2′–O	1.416

[a] Note: according to the Gaussian software and the chemical structure of the carbon atom number is different, but the same row of carbon atoms is the same carbon atom in the catalpol structure.

reactivity difference of different hydroxyl groups of geniposide was also calculated by Gaussian software, and the conformation of geniposide was optimized at the theoretical level of B3LYP/6-311++G(d,p). The numbers of hydroxyl groups were automatically numbered according to Gauss software, while the numbers in chemical structure were numbered according to the rules of IUPAC, but in fact, they were the same hydroxyl groups (Fig. 5).

The five C–O bond lengths connected to the hydroxyl group after optimization were shown in Table 2. It can be seen from Table 2 that the bond lengths of C10–O11 and C27–O28 are longer, which are 1.4216 Å and 1.4133 Å, respectively, which are the hydroxyl groups at the C10-position on the five-membered ring and the hydroxyl groups at the C6′-position on the sugar ring. Compared with C27–O28, the bond length of C10–O11 is longer and more unstable, that is, compared with the C6′-position, the reaction is more likely to occur at the C10-position.

2.1.3 Study on the chemical reactivity of primary hydroxyl of aucubin. Aucubin is a polyhydroxy compound containing six hydroxyl groups, including two primary hydroxyl groups and four secondary hydroxyl groups. The difference in the chemical reactivity of aucubin hydroxyl groups at different positions was calculated by Gaussian software. The conformation of aucubin was optimized at the B3LYP/6-311++G(d, p) theoretical level. The numbers of hydroxyl groups were automatically numbered according to Gauss software, while the numbers in chemical structure were numbered according to the rules of IUPAC, but in fact, they were the same hydroxyl groups (Fig. 6).

After optimizing the structure of aucubin, the six C–O bond lengths connected to the hydroxyl group are shown in Table 3. Aucubin is a polyhydroxy compound containing six hydroxyl groups, including two primary hydroxyl groups and four secondary hydroxyl groups. The chemical reactivity differences of different hydroxyl groups were calculated by Gaussian theory, and the aucubin was optimized at the theoretical level of B3LYP/6-311++G(d,p). The six C–O bond lengths connected to the hydroxyl group after optimization were shown in the Table 3, and the C42–O45 bond length at the C10-position is the longest, which is 1.42943 Å. Due to the influence of hydrogen bonds, the electron cloud density is more inclined to oxygen atoms, which makes the bond length of C42–O45 longer and more unstable. That is, compared with the C6′-position, the reaction is more likely to occur at the C10-position, which proves that the primary hydroxyl chemical reactivity on aucubin is better than that on glucose.

Computer simulation was used to theoretically analyze the structure of catalpol, geniposide, and aucubin. By comparing

Table 2 Optimized geometric parameters of geniposide molecule[a]

Geometrical parameters		
Gauss software number	Chemical structure number	Bond lengths (Å)
C10–O11	C10–O	1.422
C27–O28	C6′–O	1.413
C20–O26	C4′–O	1.406
C22–O25	C2′–O	1.405
C21–O29	C3′–O	1.405

[a] Note: according to the Gaussian software and the chemical structure of the carbon atom number is different, but the same row of carbon atoms is the same carbon atom in the geniposide structure.

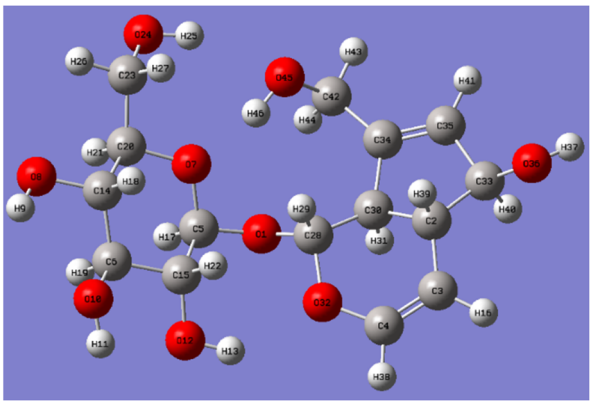


Fig. 6 Optimized geometry of aucubin molecular.

Table 3 Optimized geometric parameters of aucubin molecule[a]

Geometrical parameters		
Gauss software number	Chemical structure number	Bond lengths (Å)
C42–O45	C10–O	1.429
C33–O36	C6–O	1.427
C6–O10	C3′—O	1.422
C14–O8	C4′—O	1.418
C15–O12	C2′—O	1.416
C23–O24	C6′—O	1.415

[a] Note: according to the Gaussian software and the chemical structure of the carbon atom number is different, but the same row of carbon atoms is the same carbon atom in the aucubin structure.

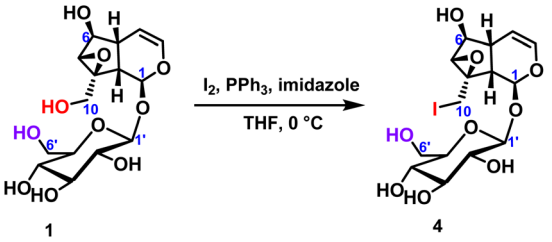
their bond lengths, it was found that the primary hydroxyl chemical reactivity at the C10-position was higher than that at the C6′-position. In order to prove this result, the experimental data were further verified.

2.2 Experiments

2.2.1 Synthesis of C10-position iridoid glycosides derivatives

2.2.1.1 Iodination reaction of iridoid glycosides. The iodination reaction of catalpol was carried out to explore the chemical reactivity of the two primary hydroxyl groups in catalpol.[24] The temperature was 0 °C, the iodine element was 6 equivalents, and the reaction was carried out for 18 hours to obtain the compound **4** with only C10-position substitution, and the yield was up to 70%. It was further verified that the chemical reactivity of the hydroxyl group at the C10-position was higher than that of the hydroxyl group at the C6′-position (Scheme 1). After selective hydroxy iodination of catalpol at the C10-position, subsequent reactions were performed on the C10-position iodocatalpol to further verify the hydroxyl selectivity.

2.2.1.2 Oxidation reaction of iridoid glycosides. The oxidation reaction of geniposide was occurred under the condition of IBX

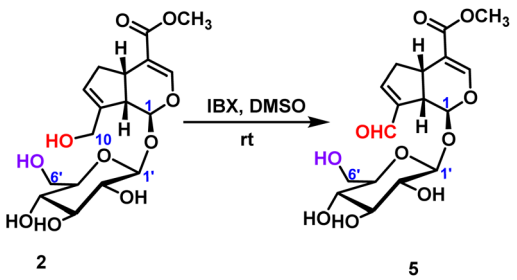


Scheme 1 Iodine reaction of C10-hydroxyl of catalpol.

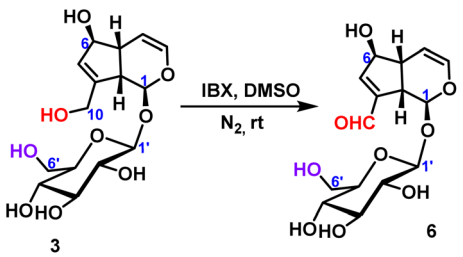
(2-iodoxybenzoic), and only the hydroxyl group at the C10-position was oxidized to form an aldehyde group, and 78% yield was obtained (Scheme 2).

The oxidation of aucubin was carried out under the same conditions as geniposide to obtain the oxidation product with a C10-position aldehyde group in a yield of 67% (Scheme 3).

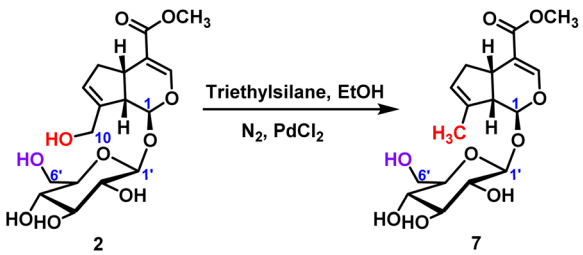
2.2.1.3 Reduction reaction of iridoid glycosides. For the reduction reaction, palladium chloride was used as the catalyst to obtain the target product 7 with the reduction of C10-position hydroxyl group, and the yield was 40% (Scheme 4). It was



Scheme 2 Oxidative reaction of C10-hydroxyl of geniposide.



Scheme 3 Oxidative reaction of C10-hydroxyl of aucubin.



Scheme 4 Reduction reaction of C10-hydroxyl of geniposide.

further verified that the chemical reactivity of C10-position hydroxyl group was higher than that of C6′-position hydroxyl group.

Through the iodination experiments, oxidation experiments and reduction experiments in chemical reactions, it was verified that the hydroxyl chemical reactivity at the C10-position in different iridoid glycosides was higher than that at the C6′-position.

3 Conclusions

The chemical reactivity of the two primary hydroxyl groups in iridoid glycosides can be obtained by computer simulation results that the chemical reactivity of the C10-position hydroxyl group is higher than that of the C6′-position hydroxyl group, and it is further proved by the experiments of iodination, oxidation and reduction of the iridoid glycosides. This important discovery lays the foundation on polyhydroxy iridoid glycosides compounds in the future.

4 Experimental

4.1 Reagents and instruments

All reagents and solvents were obtained from commercial sources and used without further purification unless otherwise indicated. All reactions were performed in oven-dried glass ware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light or developed by treatment with anisaldehyde stain or iodine stain). ^{1}H NMR and ^{13}C-NMR spectra were recorded on a Bruker AV-400 spectrometer at 500 and 125 MHz, in DMSO-d_6, using DMSO-d_6 as the reference standard (2.50 ppm). Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard. Multiplicities were given as *s* (singlet), brs (broad singlet), *d* (doublet), *t* (triplet), *q* (quartet), *p* (pentet) and *m* (multiplet). Coupling constants (*J*) are reported in Hz. All the experiments were recorded and data were processed using standard Bruker software. MS data were obtained on a Mainer System Saimofei LCQ fleet mass spectrometer. Thin-layer chromatography was performed on silica gel 60 F254 (Qingdao Marine Chemical Ltd, P. R. China). Column chromatography purification was conducted on silica gel (200–300 mesh, Qingdao Marine Chemical Ltd, P. R. China).

4.2 Experimental methods

4.2.1 General procedure for the synthesis of oxidation products 5 and 6. The iridoid glycoside (0.2 mmol, 1 eq) was dissolved in DMSO (2 mL) under nitrogen protection and room temperature, and then 2-iodoacylbenzoic acid (0.22 mmol, 1.1 eq) was added and stirred until the end of the reaction. The reaction system was freeze-dried to remove DMSO, and then the reaction system was filtered with methanol, and the oxidation product of iridoid glycosides was obtained by silica gel column chromatography with dichloromethane and methanol.

4.2.2 General procedure for the synthesis of reduction products 7. Iridoid glycosides (0.2 mmol, 1 eq) and triethylsilane (0.4 mmol, 2 eq) were dissolved in ethanol (1 mL) under nitrogen, and then catalytic amount of palladium chloride (II) (10 mol%) was added. To the end of the reaction. The reaction solution was diluted with methanol, then the reaction solution was dried by a rotary evaporator, and the reduction product of iridoid glycosides was obtained by silica gel column chromatography with dichloromethane and methanol.

4.2.3 Methyl(1S,4aS,7aS)-7-formyl-1-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,4a,5,7a-tetrahydrocyclopenta[*c*]pyran-4-carboxylate (5). Yield, 78%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78–9.61 (m, 1H), 7.41 (d, J = 16.4 Hz, 1H), 7.18 (d, J = 12.2 Hz, 1H), 5.83 (t, J = 4.7 Hz, 1H), 4.48 (s, 1H), 4.43 (d, J = 7.9 Hz, 1H), 3.71–3.65 (m, 1H), 3.64 (s, 3H), 3.44 (dd, J = 14.5, 8.1 Hz, 2H), 3.23 (dd, J = 11.2, 3.4 Hz, 3H), 3.14 (dd, J = 9.0, 7.2, 4.8 Hz, 3H), 3.09–3.03 (m, 1H), 2.97–2.86 (m, 2H), 2.52 (dd, J = 5.0, 2.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 190.60, 167.06, 156.58, 152.09, 143.87, 110.95, 99.29, 93.18, 77.55, 77.09, 73.43, 70.10, 61.14, 55.41, 51.51, 45.46, 33.06. HRMS (ESI+): Calculated for $C_{17}H_{23}O_{10}$ [M + Na]$^+$: 409.1105, found: 409.1101.

4.2.4 (1S,4aR,5S,7aS)-5-hydroxy-1-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,4a,5,7a-tetrahydrocyclopenta[*c*]pyran-7-carbaldehyde (6). Yield, 67%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.04 (d, J = 1.9 Hz, 1H), 6.18 (dd, J = 6.2, 1.6 Hz, 1H), 5.55 (t, J = 9.5 Hz, 1H), 5.40 (t, J = 10.7 Hz, 1H), 4.96–4.90 (m, 2H), 4.83–4.80 (m, 2H), 4.46 (t, J = 5.5 Hz, 2H), 4.41 (d, J = 7.9 Hz, 1H), 4.10 (d, J = 5.0 Hz, 1H), 3.67 (dd, J = 11.1, 4.6 Hz, 1H), 3.48–3.42 (m, 1H), 3.18 (s, 1H), 3.10 (d, J = 5.6 Hz, 1H), 3.05 (d, J = 9.4 Hz, 1H), 2.97 (td, J = 8.4, 5.0 Hz, 1H), 2.72 (dd, J = 10.0, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 194.10, 154.93, 145.60, 139.41, 104.55, 98.15, 92.17, 79.04, 77.47, 77.12, 72.94, 70.34, 61.32, 44.68, 42.31. HRMS (ESI+): Calculated for $C_{15}H_{21}O_9$ [M + H]$^+$: 345.1180, found: 345.1182.

4.2.5 Methyl(1S,4aS,7aS)-7-methyl-1-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-1,4a,5,7a-tetrahydrocyclopenta[*c*]pyran-4-carboxylate (7). Yield, 40%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (d, J = 1.0 Hz, 1H), 5.17 (d, J = 6.5 Hz, 1H), 5.05 (d, J = 5.3 Hz, 1H), 4.99 (d, J = 5.0 Hz, 1H), 4.95 (d, J = 5.4 Hz, 2H), 4.54 (d, J = 7.9 Hz, 2H), 4.49 (t, J = 5.7 Hz, 1H), 3.68–3.65 (m, 1H), 3.64 (s, 3H), 3.63 (d, J = 1.9 Hz, 1H), 3.42 (d, J = 5.7 Hz, 1H), 3.19–3.13 (m, 2H), 3.04 (dd, J = 15.9, 7.2, 3.7 Hz, 2H), 2.69–2.62 (m, 1H), 2.06–1.99 (m, 1H), 1.76 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.38, 152.00, 139.01, 127.03, 111.49, 98.95, 95.94, 77.80, 77.16, 73.74, 70.52, 61.54, 51.46, 48.97, 38.71, 34.44, 16.35. HRMS (ESI+): Calculated for $C_{17}H_{25}O_9$ [M + Na]$^+$: 395.1312, found: 395.1308.

Author contributions

Y. F. K. supervised chemistry experiments, interpreted the data, participated to the writing of the manuscript. J. D. X. and B. Y. conducted chemical experiments. P. B. Z. and S. P. W. carried out computer simulation. J. Y. Z. and C. H. D. performed the project administration. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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