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Stereoselective synthesis of bioactive isosteviol derivatives as α-glucosidase inhibitors

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ABSTRACT

Considerable interest has been attracted in isosteviol and its derivatives because of their large variety of pharmacological activities. In this project, a series of novel compounds containing hydroxyl, hydroxymethyl group and heteroatom-containing frameworks fused with isosteviol structure were synthesized and evaluated as α-glucosidase inhibitors, aimed at clarifying the structure–activity correlation. The results indicated that these isosteviol derivatives were capable of inhibiting in vitro α-glucosidase with moderate to good activities. Among them, indole derivative **15b** exhibited the highest activities and thus may be exploitable as a lead compound for the development of potent α-glucosidase inhibitors.

1. Introduction

During the last few decades, there has been widespread interest in α-glucosidase (EC 3.2.1.20) because of its important role not only in carbohydrate digestion, but also in the processing of glucoproteins and glycolipids. In addition, the α-glycosidase inhibitors have wide application for treatment of carbohydrate mediated diseases such as diabetes,[1–3] cancer,[4,5] HIV[6] and certain forms of hyperlipoproteinemia and obesity.[7] Therefore, considerable endeavors have been made to develop inhibitors that can probe the structure and function of α-glycosidase.[8,9] To date, various types of inhibitors have also been designed based on the structures that resemble the glycosyl cations in a transition state of hydrolysis by glucosidase.[10]

Isosteviol (ent-16-ketobeyeran-19-oic acid **1**) is a tetracyclic diterpenoid with a beyerane skeleton, obtained by acid hydrolysis of stevioside.[11,12] In recent years, isosteviol derivatives have attracted scientific attention because of their remarkably broad spectrum of biological activities including antihypertension,[13] anti-inflammatory,[14] glucocorticoid agonist,[15] antiproliferation,[16] antitumor[17] and inhibition of *ent*-kaurene synthase.[18] Especially, Wang and co-workers reported that isosteviol can decrease the blood glucose concentration in Zucker diabetic fatty rats,[19] which prompted us to study isosteviol derivatives to develop new α-glucosidase inhibitors for the treatment of diabetes.

In this study, a series of novel isosteviol derivatives were synthesized by a facile route, and the α-glucosidase inhibition activities of the derivatives were appraised, which would be aiding in designing and synthesizing novel stronger α-glucosidase inhibitors and clarifying the structure–activity correlation involved in the inhibition process of α-glucosidase.

2. Results and discussion

In order to find a lead compound, **2**–**9** were designed and synthesized with isosteviol as starting material (Scheme 1). Initial synthetic efforts were focused on structural modifications at C-15 and C-16 positions of isosteviol **1**. Treatment of isosteviol obtained by acid hydrolysis of stevioside with CH_3CH_2Br and KOH in DMSO afforded the corresponding ethyl ester of isosteviol **2** in 96% yield.[20] Compounds **3** and **4** were obtained, respectively, in good yields by reduction of **1** and **2** with $NaBH_4$ in C_2H_5OH at 0 °C.[21] The stereostructure of compound **4** was confirmed through X-ray crystallographic analysis (Fig. 1). Treatment of **4** with acrylic acid in CH_2Cl_2 in the presence of DCC and DMAP furnished **5** in 85% yield.

Compounds **6** and **7** were stereoselectively synthesized via an one pot Tollens' reaction in good yield (95%, 90%, respectively).[22] The products were characterized by HRMS, IR and NMR, and the stereostructure of compound **6** was confirmed by X-ray crystallographic analysis (Fig. 2). The mechanism of the one pot Tollens' reaction was proposed as shown in Scheme 2. In addition, compound **9** could be obtained by selective oxidation of **7** with PCC

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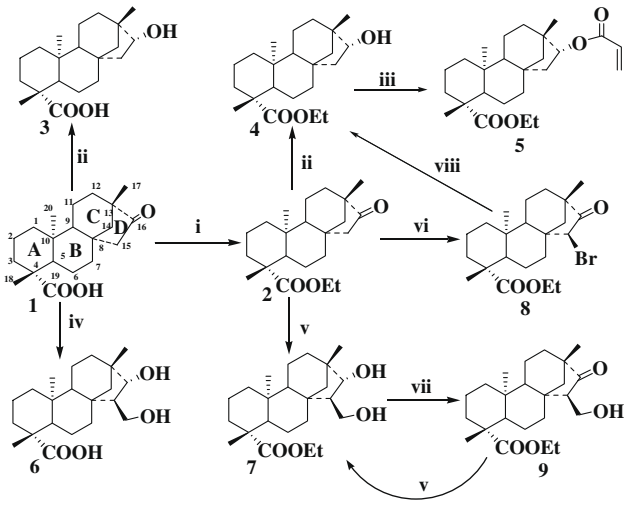


Scheme 1. Reagents and conditions: (i) EtBr, DMSO, KOH, rt, 3 h, 96%; (ii) $NaBH_4$, C_2H_5OH, 0 °C, 1 h, 92–96%; (iii) DCC/DMAP, acrylic acid, CH_2Cl_2, rt, 12 h, 85%; (iv) HCHO, NaOH, C_2H_5OH, 60 °C, 1 h, 95%; (v) HCHO, C_2H_5ONa, C_2H_5OH, 60 °C, 3 h, 90%; (vi) EtBr, DMSO, KOH, 80 °C, 3 h, 96%; (vii) PCC, CH_2Cl_2, rt, 1 h, 82%; (viii) $NaBH_4$, C_2H_5OH, rt, 1 h, 96%.

in CH_2Cl_2, and treatment of **9** with HCHO in presence of C_2H_5ONa in C_2H_5OH also gave the corresponding **7**, which elucidated the rationality of the proposed mechanism.

Meanwhile, treatment of **2** with an excess bromoethane in DMSO in the presence of KOH under reflux gave 15-bromoisosteviol ethyl ester **8**, and the stereostructure of 15-bromoisosteviol ethyl ester was confirmed according to X-ray crystallographic analysis of 15-bromoisosteviol methyl ester.[23] Unexpectedly, treatment of **8** with excess sodium borohydride in C_2H_5OH gave the debrominated compound instead of the expected α-bromohydrin.[24]

The results obtained above showed that the newly introduced hydroxymethyl or bromine group at C-15 was always stereoselectively posited on exo position. From the crystal structure of compounds **4** and **6**, we found that the steric hindrance of C10-CH_3 and ring C may be the reason for that substituent at C-15 could not be posited on the endo position. Meanwhile, the newly introduced hydroxy group at C-16 was stereoselectively posited on the endo position because of the steric hindrance effects of C13-CH_3 and ring C.

In vitro activity screening of the above isosteviol derivatives showed that **3**–**9** demonstrated α-glycosidase inhibition activity (Table 2), especially, compound **7** had higher inhibition activity against α-glycosidase (**7** vs **6**). Therefore, the introduction of hydroxyl, hydroxymethyl and ester group may enhance the inhibition activity against α-glycosidase.

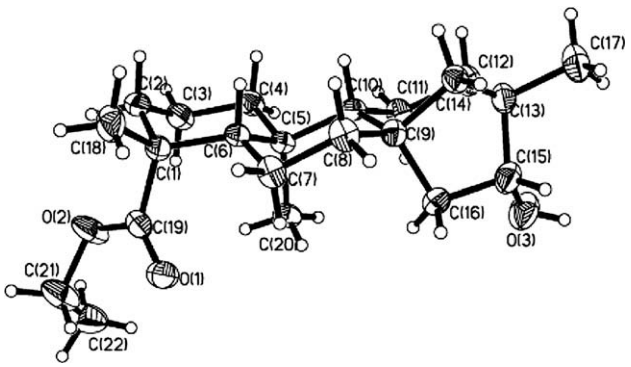


Figure 1. X-ray structure of compound **4**.

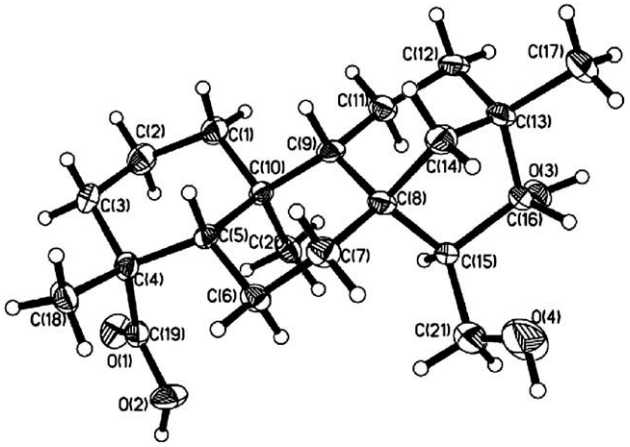


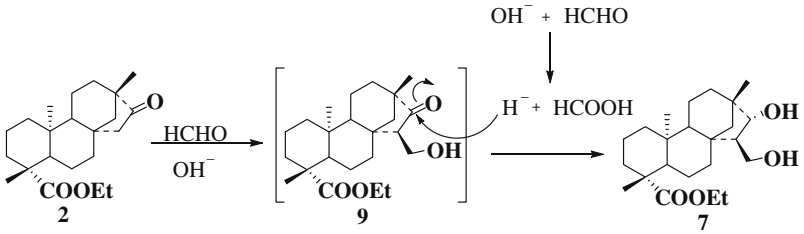
Figure 2. X-ray structure of compound **6**.

With compound **6** in hand, some efforts were carried out for functional group conversion at the carboxyl group in order to probe the effect of different ester group on inhibition activity against α-glycosidase. Therefore a series of ester derivatives were synthesized from 1,3-diol **6** and *p*-toluenesulfonates in presence of K_2CO_3 in CH_3CN (Scheme 3). Without functional protection, the reaction could be carried out smoothly. It should be noted that the use of *p*-toluenesulfonates instead of alcohols could not only improve the reaction rates, but also avoid the intermolecular condensation of compound **6**. The structures of **10a**–**10j** were characterized by NMR, IR and HRMS spectra, respectively, and the stereostructure of **10f** was confirmed by X-ray crystallographic analysis (Fig. 3).

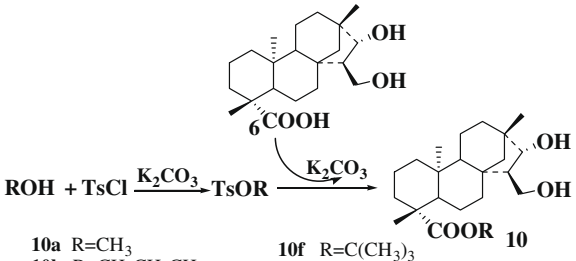
Over the years, the literature has provided many examples of α,β-unsaturated ketones which possess interesting biological properties.[25,26] It suggested that there would be potential interest in simpler lipophilic structures containing an α-methylene cyclopentanone subunit. In this regard, an isosteviol derivative containing α-methylene cyclopentanone fragment (**13**) was synthesized from **7** as shown in Scheme 4. Selective esterification of 1,3-diol **7** with benzoyl chloride in presence of Et_3N in toluene gave the corresponding 1,3-diol monoester **11b** (85%). Then, 1,3-diol monoesters **11b** was oxidized by PDC to give the corresponding production **12b**, which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine at 80 °C for 12 h to give the α-methylene ketone **13** in moderate yield (61%). The regioselectivity of 1,3-diol monoester **11b** was confirmed by X-ray crystallographic analysis of **12b** (Fig. 4). In order to improve the yield of α-methylene ketone **13**, the reaction condition was optimized. Selective esterification of 1,3-diol **7** with acetyl chloride instead of benzoyl chloride in presence of Et_3N gave the corresponding 1,3-diol monoester **11a** in good yield (96%), then α-methylene ketone **13** was easily obtained by oxidation and β-elimination in good yield.

Treatment of isosteviol **1** and its ethyl ester **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 gave the corresponding lactones **14a** and **14b** by Baeyer–Villiger oxidation.[27,28] The structure of the product **14b** was confirmed unambiguously by the disappearance of the signals due to the carbonyl groups in the IR and ^{13}C NMR spectra and the presence of lactone signal at δ_C 172. The regioselectivity of **14b** was confirmed by X-ray crystallographic analysis (Fig. 5).

The Fischer indole reaction has remained an extremely important and useful method for the synthesis of a variety of indole intermediates and biologically active compounds.[29–31] So, indole isosteviol derivatives **15a** and **15b** were obtained using acetic acid saturated with gaseous HCl as catalyst via Fischer reaction in good



Scheme 2. Proposed mechanism for synthesis of compound **7**.



Scheme 3. Syntheses of **10**.

yields (80%, 91%)[32] In the ^{1}H and ^{13}C NMR spectra of **15b**, additional resonances were observed at δ_H 7.05, 7.07, 7.32, 7.67, 7.81 and δ_C 111.6, 119.5, 119.6, 119.7, 121.8, 124.9, 138.8, 148.6, respectively, suggesting the introduction of indole fragment.

Oximation of isosteviol **1** and its ethyl ester **2** with hydroxylamine hydrochloride in presence of sodium bicarbonate in ethanol gave the corresponding 16-*E*-oxime isosteviol **16a** and 16-*E*-oxime isosteviol ethyl ester **16b**,[27] which were further converted to the 16-amino isosteviol **17a** and 16-amino isosteviol ethyl ester **17b**, respectively, by reduction of the oxime with Ni/H_2 in THF in good yields (82%, 88%). Unexpectedly, when ethanol was used instead of THF in the reduction reaction of 16-*E*-oxime isosteviol ethyl ester **16b**, 16-aminoethyl isosteviol ethyl ester **18** was obtained.

It is well known that certain oxime when subjected to Beckmann rearrangement condition[33,34] do not rearrange into lactam but undergo Beckmann fragmentation into olefinic nitrile product.[35] In order to investigate the behavior of the 16-*E*-oxime isosteviol, a further study was performed under different acid conditions in Table 1. The results obtained showed that lactam products accompanied with olefinic nitrile products occurred simultaneously under different acid conditions. When H_2SO_4 (acetone, 40 °C) was used, beckmann fragmentation occurred readily, giving rise to a 3:1 mixture of olefinic nitriles **20a** and **20b**, which could not be separated by chromatography method, due to the olefinie isomers had very similar physical properties and polarities.

The inhibitory activities of these compounds were then evaluated against α-glucosidase as described in Table 2. Several interesting structure–activity relationships have been obtained from the analyses of the IC_{50} values of compounds **1–9**. The first observation is that all the hydroxyl and hydroxymethyl substituted isosteviols exhibit much higher inhibitory activities than the precursor isosteviol. This result is in agreement with the fact that hydroxyl isosteviols always possess a variety of biological activities,[36] and suggest that modification of isosteviol with hydroxyl groups onto the beyerane skeleton is an efficient approach to increase their inhibitory activities. It was also found that inhibitory activities show significant dependence on the number of hydroxyl groups. For example, compound **7** bearing two hydroxyl groups has stronger activity than compound **4** bearing one hydroxyl group. In addition, isosteviol derivatives containing carboxy group show much lower bioactivity than their ester derivatives (**3** vs **4** and **6** vs **7**).

The ester derivatives **10a–10j** obtained from 1,3-diol **6** have better inhibitory activities than their precursor isosteviol. But the increase in bioactivity is not linear. The above results suggested that the ester derivatives containing hydrophobic ester group exhibit much higher inhibitory activities than that containing hydrophilic ester group (**10a, 10b**, **10d** vs **10i**).

It was reported that compounds containing α,β-unsaturated ketone show much high cytotoxic activities.[25] However, isosteviol derivative containing α-methylene cyclopentanone fragment **13** show much lower inhibitory activity against α-glucosidase. In addition, introduction of lactone, amine and oxime group into the isosteviol structure result in higher inhibition activities (**14, 16, 17, 18** vs **1**), especially, the lactam derivative **19b** (IC_{50} = 72.4 μM), and indole derivative **15b** (IC_{50} = 68.2 μM) exhibit more inhibitory potency against α-glucosidase, indicating that D-ring fused heterocyclic analogues might deserve some attention for further α-glucosidase inhibition activities design.

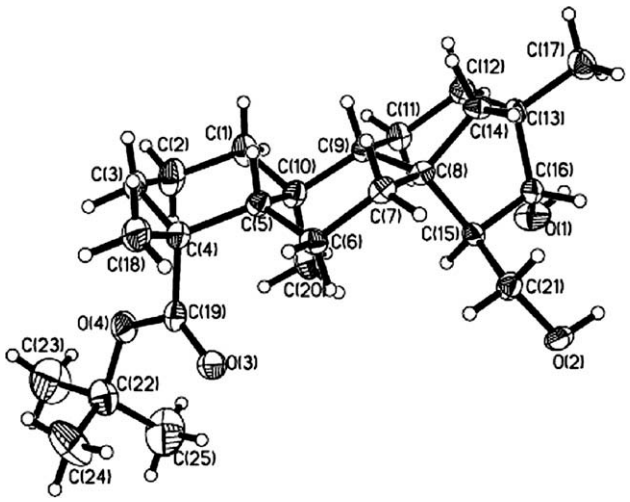
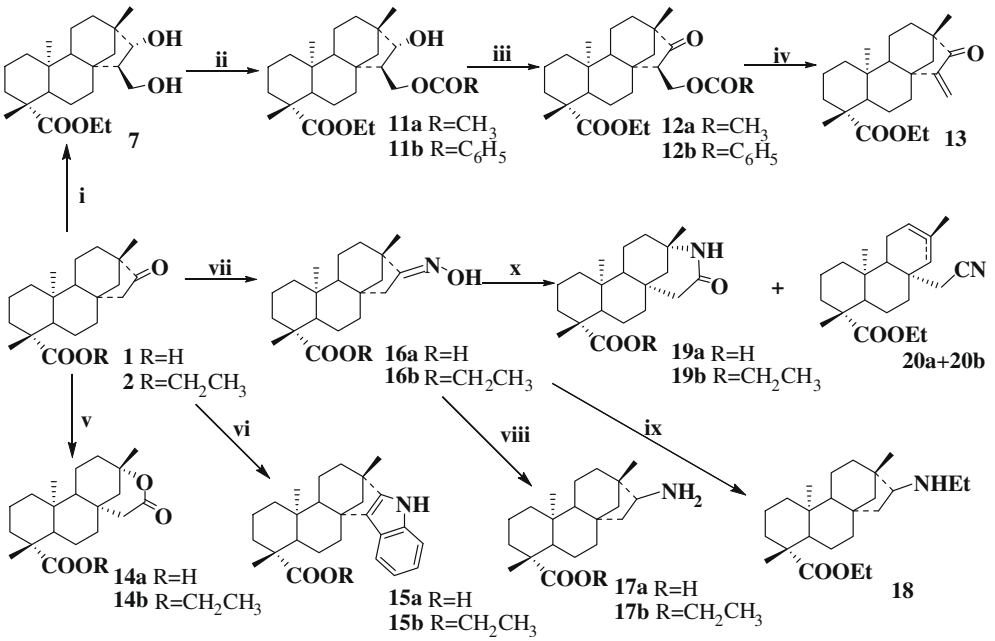


Figure 3. X-ray structure of compound **10f**.

3. Conclusion

In summary, a series of novel compounds containing hydroxyl, hydroxymethyl group and heteroatom-containing frameworks fused with isosteviol structure have been successfully synthesized in high yields, and their inhibitory activities against α-glucosidase were evaluated. The results obtained revealed that these isosteviol derivatives were capable of inhibiting α-glucosidase with moder-



Scheme 4. Reagents and conditions: (i) HCHO, C_2H_5ONa, C_2H_5OH, 60 °C, 3 h, 90%; (ii) RCOCl/Et_3N, toluene, rt, 2 h, (85–96%); (iii) PDC, CH_2Cl_2, rt, 3 h, (71–79%); (iv) DBU, pyr, 80 °C, 6–12 h, (61–85%); (v) *m*-CPBA, CH_2Cl_2, 0 °C, 5 h, (60–71%); (vi) HCl/AcOH, $C_6H_5NHNH_2$, reflux, 3 h, (80–91%); (vii) $HONH_3Cl$, $NaHCO_3$, C_2H_5OH, 60 °C, 2 h, (90–95%); (viii) Ni, H_2, THF, 40 °C, 2 h, (82–88%); (ix) Ni, H_2, C_2H_5OH, 40 °C, 2 h, 86%; (x) TsCl/DMF, 80 °C, or H_2SO_4/acetone, 40 °C, or $BF_3{\cdot}OEt_2$/toluene, 100 °C.

ate to good activities, indicating that structural modification of isosteviol is a practical approach to increase their inhibitory activities. Among all the derivatives, indole derivative **15b** showed the highest activities, and thus may be exploitable as potentially potent α-glucosidase inhibitors. Further efforts aiming at developing potent α-glucosidase inhibitors based on appropriately modified D-ring fused heterocyclic analogues are continuing in our laboratory, which will be reported in due course.

4. Experimental

4.1. General methods

All reagents and solvents were obtained from commercial suppliers. All the reactions were monitored by TLC. Melting points were determined on a Beijing Keyi XT5 apparatus and the temperature was not corrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR200) Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100 MHz with TMS as internal standard. Mass spectra were taken by Waters Q-Tof micro mass spectrometer. X-ray analysis was taken on a Rigaku RAXIS-IV.

4.2. General procedure for α-glucosidase inhibition assay

Inhibition rate was determined at 37 °C in 0.067 M K_2HPO_4/KH_2PO_4 buffer (pH 6.8). The reaction mixture contained 40 μl of enzyme solution, 40 μl of inhibitor and 20 μl of substrate. The substrate and α-glucosidase (Baker's yeast) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Both inhibitor and substrate were first dissolved in dimethylsulfoxide (DMSO), and then diluted with 0.067 M K_2HPO_4/KH_2PO_4 buffer to make the final concentration of DMSO 10%. The enzymatic reaction was started after incubation of the enzyme (0.04 U/mL) for 30 min in the presence of the inhibitor (0.1 mM) by the addition of substrate (0.5 mM). The mixture was incubated at 37 °C for 5 min, and the reaction was quenched by the addition of 0.1 M Na_2CO_3 (pH 9.8). The absorption at 405 nm was measured immediately and taken as the relative rate for the hydrolysis of substrate. All the experiment was carried out in triplicate.

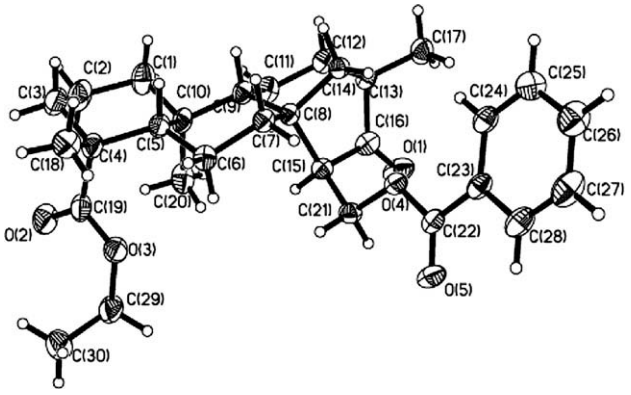


Figure 4. X-ray structure of compound **12b**.

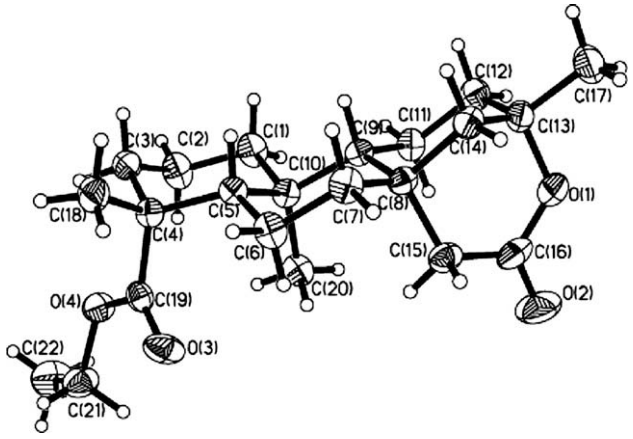
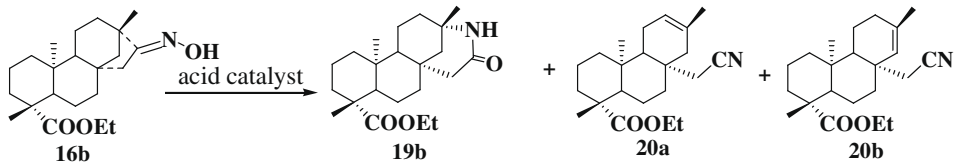


Figure 5. X-ray structure of compound **14b**.

Table 1
Beckmann rearrangement and fragmentation of 16-*E*-oxime isosteviol ethyl ester **16b**



Entry	Catalyst/solvent	*T* (°C)	Time (h)	Yield of **19b** (%)[a]	Yield of **20a** + **20b** (%)[a]
1	TsCl/DMF	80	10	55	38
2	H_2SO_4/acetone	40	6	6	88 (**20a**/**20b** = 3:1)[b]
3	$BF_3{\cdot}OEt_2$/toluene	100	12	77	22

[a] Yields of isolated products.
[b] Determined by ^{1}H NMR spectra.

4.3. The preparation of isosteviol derivatives

4.3.1. *ent*-16-Oxobeyeran-19-oic acid (1)[12]

Isosteviol **1** was synthesized by hydrolysis of stevioside with dilute sulfuric acid. Mp 228–230 °C; IR (KBr): 3455, 2954, 2927, 2852, 2679, 1738, 1697, 1474, 1453, 1406, 1372, 1320, 1271, 1238, 1179, 950, 797 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (dd, *J* = 18.6, 3.8 Hz, 1H), 2.17 (d, *J* = 13.4 Hz, 1H), 1.90–1.82 (m, 2H), 1.81 (d, *J* = 18.6 Hz 1H), 1.77–1.38 (m, 10H), 1.26 (s, 3H), 1.22–1.14 (m, 3H), 1.07–0.99 (m, 1H), 0.98 (s, 3H), 0.95–0.88 (m, 1H), 0.79 (s, 3H); HRMS (ESI, *m/z*) calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$ 341.2093. Found: 341.2085.

4.3.2. Ethyl *ent*-16-oxobeyeran-19-oate (2)

The isosteviol ethyl ester **2** was obtained by treating isosteviol **1** with CH_3CH_2Br and KOH in DMSO at room temperature in good yield (92%) according to the literature method.[20] Mp 125–127 °C; IR (KBr): 2957, 2926, 2847, 1726, 1451, 1377, 1227, 1146, 1096, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (q, *J* = 7.2 Hz, 2H), 2.96 (dd, *J* = 18.4, 2.8 Hz, 1H), 2.17 (d, *J* = 11.2 Hz, 1H), 1.99 (d, *J* = 18.8 Hz, 1H), 1.88–1.58 (m, 8H), 1.47–1.28 (m, 6H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.24–1.19 (m, 2H), 1.18 (s, 3H), 1.07 (s, 3H), 1.05–0.84 (m, 1H), 0.77 (s, 3H); HRMS (ESI, *m/z*) calcd for $C_{22}H_{34}O_3Na$ $[M+Na]^+$ 369.2406. Found: 369.2400.

4.3.3. *ent*-16β-Hydroxybeyeran-19-oic acid (3)[21]

A solution of isosteviol **1** (0.318 g, 1 mmol) and sodium borohydride (0.057 g, 1.5 mmol) in dry ethanol (10 mL) was stirred at 0 °C for 1 h. After that the reaction mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. At last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **3** (0.294 g, 92%), mp 168–169 °C; IR (KBr): 3475, 2990, 2943, 2896, 2841, 1653, 1453, 1371, 1187, 1056, 998, 621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (m, 1H), 2.01 (d, *J* = 12.8 Hz, 1H), 1.76–1.62 (m, 5H), 1.59–1.52 (m, 3H), 1.45–1.41 (m, 2H), 1.31–1.17 (m, 3H), 1.09 (s, 3H), 1.06–0.86 (m, 6H), 0.82 (s, 3H), 0.75 (s, 3H); HRMS (ESI) calcd for $C_{20}H_{33}O_3$ $[M+H]^+$ 321.2430. Found: 321.2425.

4.3.4. Ethyl *ent*-16β-hydroxybeyeran-19-oate (4)

A solution of isosteviol ethyl ester **2** (0.346 g, 1 mmol) and sodium borohydride (0.057 g, 1.5 mmol) in dry ethanol (10 mL) was stirred at 0 °C for 1 h. After that the reaction mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. At last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **4** (0.334 g, 96%), mp 152–153 °C; IR (KBr): 3533, 2978, 2939, 2880, 2837, 1700, 1460, 1374, 1318, 1231, 1178, 1151, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (q, *J* = 7.2 Hz, 2H), 3.85 (q, *J* = 4.8 Hz, 1H), 2.16 (d, *J* = 13.2 Hz, 1H), 1.81–1.51 (m, 11H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23–1.18 (m, 1H), 1.16 (s, 3H), 1.04–0.93 (m, 4H), 0.90 (s, 3H), 0.88–0.86 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 80.6, 59.9, 57.1, 55.8, 55.2, 43.7, 42.8, 42.0, 41.7, 39.9, 38.1, 38.0, 33.7, 29.0, 24.9, 21.7, 20.4, 18.9, 14.1, 13.3; HRMS (ESI, *m/z*) calcd for $C_{21}H_{34}O_4Na$ $[M+Na]^+$ 371.2562. Found: 371.2554.

4.3.5. Ethyl *ent*-16β-acryloxybeyeran-19-oate (5)

A mixture of the compound **4** (0.348 g, 1 mmol), acrylic acid (0.792 g, 1.1 mmol), DCC (0.412 g, 2 mmol) and DMAP (0.024 g, 0.2 mmol) was stirred at room temperature. After stirring for 12 h, the reaction mixture was filtered, and the filtrate was concentrated.

Table 2
Inhibition activities of isosteviol derivatives against α-glucosidase

Compound	α-Glucosidase[b]	Compound	α-Glucosidase[b]	Compound	α-Glucosidase[b]
1	>200	**10d**	87.2	**14a**	138.6
2	>200	**10e**	102.5	**14b**	118.4
3	156.3	**10f**	113.8	**15a**	83.2
4	132.1	**10g**	115.6	**15b**	68.2
5	>200	**10h**	143.2	**16a**	92.1
6	148.6	**10i**	>200	**16b**	88.9
7	86.2	**10j**	>200	**17a**	>200
8	NI[a]	**11a**	132.5	**17b**	91.2
9	143.2	**11b**	112.4	**18**	113.6
10a	96.5	**12a**	>200	**19a**	81.6
10b	85.4	**12b**	>200	**19b**	72.4
10c	97.2	**13**	>200	**20**	NI[a]

[a] No inhibition at 200 μM.
[b] IC_{50} (μM).

The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 6:1, v/v) to give product **5** (0.341 g, 85%). IR (KBr): 3101, 2950, 2847, 1723, 1625, 1455, 1405, 1378, 1194, 1151, 1060, 981, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 17.2 Hz, 1H), 6.13 (dd, J = 17.2, 10.4 Hz, 1H), 5.81 (d, J = 10.4 Hz, 1H), 4.80 (q, J = 4.8 Hz, 1H), 4.07 (m, 2H), 2.17 (d, J = 13.6 Hz, 1H), 1.92–1.68 (m, 7H), 1.61–1.33 (m, 7H), 1.25 (t, J = 7.2 Hz, 3H), 1.15 (s, 3H), 1.09–0.94 (m, 4H), 0.90 (s, 3H), 0.87–0.84 (m, 1H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 166.4, 130.2, 128.9, 81.7, 59.9, 57.0, 55.7, 54.8, 43.7, 42.4, 41.6, 41.5, 40.6, 39.9, 38.5, 38.0, 34.6, 28.9, 24.9, 21.7, 20.2, 18.9, 14.1, 13.2; HRMS (ESI, m/z) calcd for $C_{25}H_{39}O_4$ $[M+H]^+$ 403.2848. Found: 403.2835.

4.3.6. *ent*-15α-Hydroxymethyl-16β-hydroxybeyeran-19-oic acid (6)[22]

To a stirred solution of compound **1** (0.318 g, 1 mmol) and NaOH (0.08 g, 2 mmol) in ethanol (20 mL) was added 37% formaldehyde aqueous solution (2 mL). After stirring for 1 h at 60 °C, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O, at last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **6** (0.332 g, 95%), mp 233–235 °C; IR (KBr): 3462, 2945, 2927, 2846, 1696, 1456, 1072, 1052 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 3.83 (dd, J = 10.4, 5.2 Hz, 1H), 3.62 (d, J = 4.8 Hz, 1H), 3.50 (t, J = 9.6 Hz, 1H), 3.30 (s, 2H), 2.12–1.99 (m, 2H), 1.95–1.70 (m, 6H), 1.56–1.51 (m, 1H), 1.44–1.34 (m, 2H), 1.17 (s, 3H), 1.15–0.90 (m, 6H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 179.0, 82.3, 62.4, 57.8, 56.7, 54.5, 50.2, 43.1, 42.6, 40.5, 39.1, 38.2, 38.0, 34.9, 33.8, 29.1, 25.6, 22.3, 19.4, 19.0, 13.4; HRMS (ESI, m/z) calcd for $C_{21}H_{34}O_4Na$ $[M+Na]^+$ 373.2355. Found: 373.2358.

4.3.7. Ethyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (7)[22]

To a stirred solution of compound **2** (0.346 g, 1 mmol) and C_2H_5ONa (0.136 g, 2 mmol) in ethanol (20 mL) was added 37% formaldehyde aqueous solution (2 mL). After stirring for 3 h at 60 °C, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O, at last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **7** (0.34 g, 90%). Mp 181–182 °C; IR (KBr): 3435, 2940, 2838, 1720, 1458, 1378, 1234, 1179, 1153, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.09 (q, J = 7.2 Hz, 2H), 3.98 (dd, J = 9.7, 5.0 Hz, 1H), 3.63 (d, J = 4.7 Hz, 1H), 3.56 (t, J = 10.2 Hz, 1H), 2.16 (d, J = 13.0 Hz, 1H), 2.05 (m, 1H), 1.83–1.56 (m, 9H), 1.43–1.37 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.22–1.19 (m, 1H), 1.16 (s, 3H), 1.08–0.95 (m, 4H), 0.94 (s, 3H), 0.88–0.86 (m, 1H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 86.7, 64.9, 60.0, 57.5, 57.0, 54.2, 50.2, 43.6, 42.4, 40.8, 39.6, 38.1, 37.9, 34.8, 33.0, 28.9, 25.0, 22.1, 19.5, 18.8, 14.1, 13.2; HRMS (ESI, m/z) calcd for $C_{23}H_{38}O_4Na$ $[M+Na]^+$ 401.2668. Found: 401.2664.

4.3.8. Ethyl *ent*-15α-bromo-16-oxobeyeran-19-oate (8)

To a stirred solution of compound **2** (0.346 g, 1 mmol) and KOH (0.112 g, 2 mmol) in DMSO (10 mL) was added CH_3CH_2Br (2 mL), and the mixture was heated at 80 °C for 3 h. Then the mixture was poured into H_2O and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 9:1, v/v) to give product **8** (0.407 g, 96%). Mp 150–151 °C; IR (KBr): 2956, 2934, 2873, 2851, 1747, 1716, 1454, 1378, 1239, 1151, 1105, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.50 (d, J = 2.4 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.24–2.17 (m, 2H), 1.93–1.66 (m, 7H), 1.51–1.31 (m, 5H), 1.27 (t, J = 3.2 Hz, 3H), 1.19 (s, 3H), 1.18–1.15 (m, 1H), 1.09 (s, 3H), 1.04–0.87 (m, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.5, 177.8, 60.8, 57.9, 56.8, 56.6, 50.7, 49.0, 44.3, 43.7, 40.1, 39.4, 39.0, 38.5, 38.4, 29.5, 21.5, 21.4, 20.6, 19.6, 14.8, 14.3; HRMS (ESI, m/z) calcd for $C_{22}H_{34}NBrO_3$ $[M+H]^+$ 425.1691. Found: 425.1681.

4.3.9. Ethyl *ent*-15α-hydroxymethyl-16-oxobeyeran-19-oate (9)

A mixture of the compound **7** (0.378 g, 1 mmol) and PCC (0.236 g, 1.1 mmol) was stirred at room temperature for 1 h. Then the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 7:1, v/v) to give product **9** (0.308 g, 82%). Mp 155–157 °C; IR (KBr): 3534, 2958, 2857, 1735, 1721, 1462, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.10 (m, 2H), 3.90 (m, 1H), 3.70 (t, J = 10.4 Hz, 1H), 2.52 (m, 1H), 2.50 (m, 1H), 2.19 (d, J = 13.3 Hz, 1H), 1.89–1.69 (m, 8H), 1.42–1.29 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.19 (s, 3H), 1.18–1.10 (m, 2H), 0.98 (s, 3H), 0.97–0.80 (m, 2H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 226.1, 177.2, 60.4, 60.1, 57.1, 56.7, 52.9, 52.5, 48.4, 43.6, 40.5, 39.6, 38.2, 37.8, 37.0, 35.2, 28.9, 21.6, 19.8, 19.6, 18.8, 14.1, 13.3; HRMS (ESI, m/z) calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2511. Found: 399.2514.

4.3.10. General procedure for synthesis of compounds 10a–10j

A mixture of various alcohols (0.032–0.108 g, 1 mmol) and 4-methylphenylsulfonyl chloride (0.216 g, 1 mmol) in dry acetonitrile were stirred at 50 °C in the presence of K_2CO_3 (0.414 g, 3 mmol). After completion of the reaction monitored by TLC, compound **6** was added. After stirring of the mixture overnight, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. At last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica to give product **10**.

4.3.10.1. Methyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10a). Yield 93%; mp 181–182 °C; IR (KBr): 3416, 2948, 2845, 1720, 1452, 1370, 1327, 1235, 1187, 1154, 1096, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.00 (dd, J = 9.9, 5.2 Hz, 1H), 3.63 (s, 4H), 3.48 (t, J = 10.3 Hz, 1H), 2.16 (d, J = 13.2 Hz, 1H), 2.03–1.91 (m, 5H), 1.82–1.56 (m, 6H), 1.43–1.37 (m, 2H), 1.26–1.17 (m, 1H), 1.16 (s, 3H), 1.08–0.97 (m, 3H), 0.94 (s, 3H), 0.92–0.86 (m, 1H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 86.8, 64.9, 57.5, 57.0, 54.1, 51.2, 50.2, 43.6, 42.4, 40.8, 39.5, 38.1, 37.8, 34.7, 33.0, 28.8, 25.0, 22.1, 19.4, 18.8, 12.9; HRMS (ESI, m/z) calcd for $C_{22}H_{36}O_4Na$ $[M+Na]^+$ 387.2511. Found: 387.2514.

4.3.10.2. *n*-Propyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10b). Yield 90%; mp 120–121 °C; IR (KBr): 3405, 2954, 2847, 1723, 1468, 1454, 1387, 1374, 1232, 1180, 1123, 1072, 1052, 1005, 951, 722, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.98 (m, 3H), 3.63 (d, J = 4.7 Hz, 1H), 3.49 (t, J = 10.4 Hz, 1H), 2.14–2.01 (m, 4H), 1.90–1.50 (m, 9H), 1.40–1.36 (m, 2H), 1.26–1.17 (m, 1H), 1.16 (s, 3H), 1.10–0.98 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H), 0.94 (s, 3H), 0.92–0.86 (m, 1H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 86.7, 65.8, 64.9, 57.5, 57.0, 54.1, 50.2, 43.7, 42.4, 40.8, 39.5, 38.1, 37.9, 34.7, 33.0, 28.9, 25.0, 22.1, 21.8, 19.4, 18.8, 13.1, 10.7; HRMS (ESI, m/z) calcd for $C_{24}H_{40}O_4Na$ $[M+Na]^+$ 415.2824. Found: 415.2831.

4.3.10.3. *i*-Propyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10c). Yield 92%; mp 137–138 °C; IR (KBr): 3440, 2938, 2848, 1719, 1455, 1375, 1234, 1179, 1153, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.97 (m, 1H), 3.99 (dd, J = 9.9, 5.2 Hz, 1H), 3.62 (d, J = 4.6 Hz, 1H), 3.50 (t, J = 10.3 Hz, 1H), 2.15 (d,

J = 13.0 Hz, 1H), 2.00 (m, 1H), 1.82–1.56 (m, 8H), 1.43–1.37 (m, 2H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.13 (s, 3H), 1.09–0.96 (m, 6H), 0.94 (s, 3H), 0.90–0.82 (m, 1H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 86.7, 67.1, 64.9, 57.5, 56.9, 54.2, 50.2, 43.6, 42.4, 40.8, 39.6, 38.2, 37.9, 34.8, 33.0, 28.9, 25.0, 22.2, 21.7, 21.6,19.4, 18.8, 13.4; HRMS (ESI, *m/z*) calcd for $C_{24}H_{40}O_4Na$ $[M+Na]^+$ *m/z* 415.2824. Found: 415.2827.

4.3.10.4. *n*-Butyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10d). Yield 91%; mp 99–100 °C; IR (KBr): 3423, 2944, 2873, 2847, 1721, 1458, 1373, 1323, 1230, 1178, 1151, 1125, 1096, 1068, 1052, 983 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (m, 3H), 3.63 (m, 1H), 3.48 (t, *J* = 10.3 Hz, 1H), 2.16 (d, *J* = 13.2 Hz, 1H), 1.82–1.56 (m, 10H), 1.44–1.37 (m, 4H), 1.21–1.17 (m, 2H), 1.16 (s, 3H), 1.08–0.93 (m, 8H), 0.94 (s, 3H), 0.92–0.80 (m, 1H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 86.7, 65.0, 64.0, 57.5, 57.0, 54.2, 50.2, 43.7, 42.4, 40.8, 39.6, 38.1, 37.9, 34.8, 33.1, 30.5, 29.0, 25.0, 22.2, 19.5, 19.4, 18.9, 13.7, 13.1; HRMS (ESI, *m/z*) calcd for $C_{25}H_{42}O_4Na$ $[M+Na]^+$ 429.2981. Found: 429.2986.

4.3.10.5. *i*-Butyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10e). Yield 91%; mp 123–124 °C; IR (KBr): 3407, 2951, 2876, 2848, 1722, 1466, 1369, 1327, 1180, 1152, 1126, 1072, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (dd, *J* = 9.9, 5.2 Hz, 1H); 3.77 (m, 2H), 3.63 (d, *J* = 4.6 Hz, 1H), 3.49 (t, *J* = 10.3 Hz, 1H), 2.17 (d, *J* = 13.0 Hz, 1H), 2.05 (m, 2H), 1.93–1.60 (m, 12H), 1.40–1.18 (m, 3H), 1.17 (s, 3H), 1.08–0.99 (m, 2H), 0.97 (d, *J* = 1.6 Hz, 3H), 0.95 (d, *J* = 1.7 Hz, 3H), 0.94 (s, 3H), 0.91–0.83 (m, 1H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 86.7, 70.5, 65.0, 57.5, 57.0, 54.2, 50.3, 43.8, 42.5, 40.9, 39.6, 38.2, 37.9, 34.8, 33.1, 29.0, 27.6, 25.0, 22.2, 19.5, 19.4, 19.3, 18.9, 13.1; HRMS (ESI, *m/z*) calcd for $C_{25}H_{42}O_4Na$ $[M+Na]^+$ 429.2981. Found: 429.2981.

4.3.10.6. *t*-Butyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10f). Yield 94%; mp 156–157 °C; IR (KBr): 3431, 2940, 2848, 1721, 1685, 1458, 1391, 1368, 1323, 1254, 1148, 1126, 1054, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.62 (d, *J* = 4.6 Hz, 1H), 3.48 (t, *J* = 10.3 Hz, 1H), 2.10 (d, *J* = 13.0 Hz, 1H), 2.05 (m, 1H), 1.80–1.69 (m, 5H), 1.68–1.53 (m, 3H), 1.43 (s, 9H), 1.42–1.35 (m, 2H), 1.3–1.13 (m, 1H), 1.12 (s, 3H), 1.09–0.95 (m, 4H), 0.94 (s, 3H), 0.92–0.86 (m, 2H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 86.7, 79.8, 65.0, 57.6, 56.9, 54.2, 50.2, 44.3, 42.6, 40.9, 39.8, 38.4, 38.2, 35.0, 33.2, 29.1, 28.0, 28.0, 28.0, 25.1, 22.3, 19.5, 19.0, 13.8; HRMS (ESI, *m/z*) calcd for $C_{25}H_{42}O_4Na$ $[M+Na]^+$ 429.2981. Found: 429.2983.

4.3.10.7. *i*-Pentyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10g). Yield 89%; mp 73–74 °C; IR (KBr): 3418, 2953, 2872 2847, 1721, 1463, 1371, 1324, 1232, 1177, 1151, 1052, 1007, 963 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (m, 2H); 3.98 (d, *J* = 4.8 Hz, 1H), 3.63 (d, *J* = 4.8 Hz, 1H), 3.49 (t, *J* = 10.4 Hz, 1H), 2.15 (d, *J* = 15.2 Hz, 1H), 2.03 (m, 1H), 1.86–1.70 (m, 5H), 1.67–1.64 (m, 4H), 1.63–1.49 (m, 4H), 1.42–1.18 (m, 3H), 1.15 (s, 3H), 1.09–0.97 (m, 3H), 0.96 (s, 3H), 0.92 (d, *J* = 1.8 Hz, 6H), 0.90–0.83 (m, 1H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 86.7, 64.9, 62.7, 57.5, 57.0, 54.2, 50.2, 43.7, 42.4, 40.8, 39.6, 38.1, 37.9, 37.2 ,34.8, 33.1, 28.9, 25.2, 25.0, 22.4, 22.4, 22.1, 19.5, 18.9, 13.2; HRMS (ESI, *m/z*) calcd for $C_{26}H_{44}O_4Na$ $[M+Na]^+$ 443.3137. Found: 443.3139.

4.3.10.8. Propenyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10h). Yield 96%; mp 66–67 °C; IR (KBr): 3426, 3084, 2943, 2848, 1722, 1646, 1458, 1380, 1323, 1229, 1175, 1149, 1126, 1053, 981 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (m, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.53 (m, 2H), 3.98 (q, *J* = 4.8 Hz, 1H), 3.63 (d, *J* = 4.8 Hz, 1H), 3.48 (t, *J* = 10.4 Hz, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.01 (m, 2H), 1.90–1.77 (m, 4H), 1.76–1.55 (m, 3H), 1.43–1.20 (m, 3H), 1.18 (s, 3H) ,1.09–0.98 (m, 5H), 0.96 (s, 3H), 0.90–0.83 (m, 1H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 132.3 ,118.0, 86.6, 64.9, 64.9, 57.5, 57.1, 54.1, 50.2, 43.7, 42.5, 40.8, 39.5, 38.2, 37.9, 34.7, 33.1, 28.9, 25.0, 22.2, 19.5, 18.8, 13.2; HRMS (ESI, *m/z*) calcd for $C_{24}H_{38}O_4Na$ $[M+Na]^+$ 413.2668. Found: 413.2663.

4.3.10.9. Hydroxyethyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10i). Yield 93%; mp 176–177 °C; IR (KBr): 3411, 2942, 2847, 1720, 1457, 1386, 1323, 1231, 1178, 1153, 1072, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (m, 1H), 4.04 (m, 1H), 3.98 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.82 (m, 2H), 3.54 (d, *J* = 4.3 Hz, 1H), 3.43 (t, *J* = 10.3 Hz, 1H), 2.16 (d, *J* = 13.2 Hz, 1H), 2.0 (m, 1H), 1.82–1.65 (m, 5H), 1.50–1.56 (m, 3H), 1.45–1.34 (m, 2H), 1.30–1.20 (m, 1H), 1.18 (s, 3H), 1.11–0.96 (m, 5H), 0.92 (s, 3H), 0.90–0.83 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 85.5, 65.3, 64.0, 59.7, 57.3, 56.7, 53.9, 50.2, 43.4, 42.3, 40.4, 38.2, 37.9, 37.7, 34.5, 33.1, 28.6, 25.0, 21.9, 19.2, 18.6, 12.9; HRMS (ESI, *m/z*) calcd for $C_{23}H_{38}O_5Na$ $[M+Na]^+$ 417.2617. Found: 417.2614.

4.3.10.10. Benzyl *ent*-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (10j). Yield 89%; mp 75–76 °C; IR (KBr): 3416, 3064, 3031, 2936, 2847, 1723, 1656, 1626, 1499, 1455, 1369, 1328, 1230, 1175, 1147, 1123, 1096, 1050, 1008, 751, 734, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 3.83 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.61 (d, *J* = 4.7 Hz, 1H), 3.40 (t, *J* = 10.2 Hz, 1H), 2.19 (d, *J* = 13.4 Hz, 1H), 1.93 (m, 1H), 1.90–1.49 (m, 8H), 1.42–1.34 (m, 2H), 1.22–1.13 (m, 1H), 1.18 (s, 3H), 1.08–0.95 (m, 4H), 0.93 (s, 3H), 0.92–0.82 (m, 2H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 135.9, 128.4, 128.4, 128.2, 128.0, 128.0, 86.7, 66.1, 64.8, 57.5, 57.0, 54.1, 50.2, 43.7, 42.4, 40.8, 39.5, 38.1, 37.9, 34.7, 33.0, 28.8, 25.0, 22.2, 19.4, 18.8, 13.1; HRMS (ESI, *m/z*) calcd for $C_{28}H_{40}O_4Na$ $[M+Na]^+$ 463.2824. Found: 463.2820.

4.3.11. General procedure for synthesis of compounds 11a and 11b

A mixture of compound **7** (0.378 g, 1 mmol) and Et_3N (0.202 g, 1.1 mmol) in toluene (20 mL) was stirred at 0 °C for 10 min, and RCOCl (1.1 mmol) in toluene (5 mL) was added dropwise to the solution during 1 h, then the mixture was stirred at room temperature for 1 h. It was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography on silica to give product **11**.

4.3.11.1. Ethyl *ent*-15α-acetoxymethyl-16β-hydroxybeyeran-19-oate (11a). Yield 96%; mp 90–91 °C; IR (KBr): 3445, 2945, 2849, 1740, 1721, 1458, 1384, 1368, 1238, 1181, 1151, 1127, 1051, 1031, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (dd, *J* = 10.6, 5.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.95 (t, *J* = 10.3 Hz, 1H), 3.49 (d, *J* = 4.7 Hz, 1H), 2.19–2.11 (m, 2H), 2.09 (s, 3H), 1.90–1.61 (m, 10H), 1.42–1.39 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22–0.93 (m, 6H), 0.92 (s, 3H), 0.90–0.77 (m, 2H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 171.2, 86.0, 66.8, 60.0, 57.5, 57.0, 54.0, 47.2, 43.6, 42.7, 40.9, 39.6, 38.1, 37.9, 34.8, 33.1, 28.9, 25.0, 22.0, 21.2, 19.4, 18.8, 14.1, 13.1; HRMS (ESI, *m/z*) calcd for $C_{25}H_{40}O_5Na$ $[M+Na]^+$ 443.2773. Found: 443.2774.

4.3.11.2. Ethyl *ent*-15α-benzoyloxymethyl-16β-hydroxybeyeran-19-oate (11b). Yield 85%; mp 115–117 °C; IR (KBr): δ 3427, 2926, 2882, 1719, 1601, 1456, 1275, 1152, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 8.07 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.60 (dd, *J* = 10.6, 5.4 Hz, 1H), 4.24 (t, *J* = 10.4 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.67 (d, *J* = 4.8 Hz, 1H),

2.33 (m, 1H), 2.17 (d, J = 13.6 Hz, 1H), 1.87–1.40 (m, 10H), 1.25 (t, J = 7.2 Hz, 3H), 1.17 (s, 3H), 1.15–0.99 (m, 4H), 0.94 (s, 3H), 0.92–0.83 (m, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 170.7, 131.6, 129.7, 129.3, 129.3, 129.0, 129.0, 87.1, 66.8, 61.7, 58.7, 56.2, 56.0, 50.9, 47.6, 44.2, 40.3, 39.5, 38.2, 37.1, 36.2, 34.5, 28.8, 25.4, 20.0, 19.2, 18.3, 14.1, 13.1; HRMS (ESI, *m/z*) calcd for $C_{30}H_{42}O_5Na$ $[M+Na]^+$ 505.2930. Found: 505.2931.

4.3.12. General procedure for synthesis of compounds 12a–12b

A mixture of the compound **11** (1 mmol) and PDC (0.412 g, 2 mmol) in CH_2Cl_2 was stirred at room temperature for 3 h, then the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica to give product **12**.

4.3.12.1. Ethyl *ent*-15α-acetoxymethyl-16-oxobeyeran-19-oate (12a). Yield 91%; IR (KBr): 2954, 2851, 1745, 1722, 1460, 1381, 1236, 1180, 1152, 1124, 1097, 1032, 959, 604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (dd, J = 11.3, 5.9 Hz, 1H), 4.22 (dd, J = 11.3, 3.7 Hz, 1H), 4.10 (m, 2H), 2.62 (m, 1H), 2.17 (d, J = 13.4 Hz, 1H), 2.03 (s, 3H), 1.86–1.71 (m, 8H), 1.51–1.26 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.24–1.20 (m, 2H), 1.19 (s, 3H), 1.14–0.98 (m, 2H), 0.97 (s, 3H), 0.95–0.74 (m, 2H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 221.8, 177.1, 170.5, 62.1, 59.9, 56.9, 56.8, 52.8, 50.9, 48.0, 43.5, 40.6, 39.6, 38.2, 37.8, 37.1, 35.4, 28.8, 21.4, 20.9, 19.7, 19.5, 18.8, 14.1, 13.3; HRMS (ESI, *m/z*) calcd for $C_{25}H_{38}O_5Na$ $[M+Na]^+$ 441.2617. Found: 441.2612.

4.3.12.2. Ethyl *ent*-15α-benzoyloxymethyl-16-oxobeyeran-19-oate (12b). Yield 71%; mp 103–105 °C; IR (KBr): 2928, 2854, 1744, 1722, 1462, 1376, 1296 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.64 (dd, J = 11.4, 5.0 Hz, 1H), 4.53 (dd, J = 11.4, 3.2 Hz, 1H), 4.09 (m, 2H), 2.73 (m, 1H), 2.22 (d, J = 13.6 Hz, 1H) 2.00–1.70 (m, 8H), 1.46–1.28 (m, 10H), 1.25 (t, J = 7.2 Hz, 3H), 1.05 (s, 3H), 1.02–0.93 (m, 2H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.6, 176.4, 165.7, 133.7, 129.5, 129.2, 129.2, 129.0, 129.0, 62.7, 59.7, 56.2, 56.1, 52.2, 50.9, 47.7, 43.2, 40.3, 39.1, 37.9, 37.4, 36.6, 35.1, 28.6, 21.4, 20.0, 19.3, 18.7, 14.1, 13.1; HRMS (ESI, *m/z*) calcd for $C_{30}H_{40}O_5Na$ $[M+Na]^+$ 503.2773. Found: 503.2775.

4.3.13. Ethyl *ent*-15-methylene-16-oxobeyeran-19-oate (13)

A mixture of the compound **12** (1 mmol) and DBU (0.228 g, 1.5 mmol) in pyridine (15 mL) was stirred at 80 °C for 6 h, then the reaction mixture was poured into water and acidified to pH 6 with 1 M hydrochloric acid. The aqueous layer was extracted with $CHCl_3$ and the filtrate was concentrated. The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 10:1, v/v) to give product **13**. Yield 85%; mp 109–111 °C; IR (KBr): 3478, 2954, 2927, 2853, 1727, 1631, 1456, 1378, 1233, 1177, 1151, 1110, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H), 5.39 (s, 1H), 4.03 (m, 2H), 2.07–2.02 (m, 2H), 1.93–1.87 (m, 1H), 1.72–1.46 (m, 7H), 1.37–1.17 (m, 6H), 1.16 (s, 3H), 1.14–1.00 (m, 3H), 0.92 (s, 3H), 0.90–0.70 (m, 2H), 0.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.8, 177.2, 154.5, 115.8, 60.0, 56.8, 56.6, 54.6, 54.2, 53.4, 48.4, 46.7, 43.7, 41.5, 39.4, 38.0, 37.3, 28.9, 21.7, 20.3, 19.6, 14.1, 12.4; HRMS (ESI, *m/z*) calcd for $C_{23}H_{34}O_3Na$ $[M+Na]^+$ 381.2406. Found: 381.2407.

4.3.14. General procedure for synthesis of compounds 14a and 14b

A mixture of compound **1**or **2** (1 mmol) and *m*-CPBA (0.258 g, 1.5 mmol) in CH_2Cl_2 was stirred at 0 °C for 5 h, then the reaction mixture was poured into water and neutralized with $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2 and the filtrate was concentrated. The residue was purified by column chromatography on silica to give product **14**.

4.3.14.1. Lactone of isosteviol (14a)[27]. Yield 60%; mp 270–271 °C; IR (KBr): 3438, 2949, 2925, 2847, 1721, 1693, 1454, 1372, 1243, 1156, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (dd, J = 18.6, 2.5 Hz, 1H), 2.18 (d, J = 13.4 Hz, 1H), 2.07–1.79 (m, 5H), 1.71 (br d, J = 13.4 Hz, 1H), 1.61–1.37 (m, 7H), 1.34 (s, 3H), 1.25 (s, 3H), 1.23–0.97 (m, 5H), 0.87 (s, 3H); HRMS (ESI, *m/z*) calcd for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ 357.2042. Found: 357.2068.

4.3.14.2. Lactone of isosteviol ethyl ester (14b). Yield 71%; mp 153–154 °C; IR (KBr): 2958, 2925, 1715, 1474, 1446, 1377, 1239, 1146, 1020, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (m, 2H), 3.10 (dd, J = 18.8, 2.6 Hz, 1H), 2.17 (d, J = 13.2 Hz, 1H), 2. 04 (d, J = 18.8 Hz, 1H), 1.99–1.54 (m, 9H), 1.46–1.37 (m, 3H), 1.34 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.17 (s, 3H), 1.09–0.82 (m, 5H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 172.7, 80.3, 60.1, 57.2, 55.8, 47.7, 43.7, 43.6, 41.2, 39.9, 38.6, 38.4, 37.8, 34.9, 28.7, 28.2, 19.5, 18.8, 18.5, 14.1, 13.6; HRMS (ESI, *m/z*) calcd for $C_{22}H_{34}O_4Na$ $[M+Na]^+$ 385.2355. Found: 385.2355.

4.3.15. General procedure for synthesis of compounds 15a and 15b

A mixture of compound **1**or **2** (1 mmol) and phenylhydrazine (1.1 mmol) in acetic acid (20 mL), saturated with gaseous HCl at 20 °C, was quickly warmed to boiling. When all solids were dissolved refluxing was continued for 5 min. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica to give product **15**.

4.3.15.1. Indole derivative of isosteviol (15a). Yield 80%; mp 154–156 °C; IR (KB): 3366, 3060, 2936, 2846, 1694, 1610, 1448, 1356, 1260, 1225, 1180, 1150, 1021, 970, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.05 (m, 1H), 7.01 (m, 1H), 2.58 (m, 1H), 2.21–1.77 (m, 6H), 1.66–1.35 (m, 5H), 1.33 (s, 3H), 1.28 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.19–0.56 (m, 3H), 0.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 148.9, 138.7, 124.3, 119.3, 118.8, 118.3, 118.2, 111.5, 66.9, 56.4, 53.4, 44.9, 43.0, 39.6, 37.8, 37.1, 34.8, 30.5, 29.1, 28.8, 23.1, 22.2, 20.9, 18.9, 13.1; HRMS (ESI, *m/z*) calcd for $C_{26}H_{33}NO_2Na$ $[M+Na]^+$ 414.2409. Found: 414.2426.

4.3.15.2. Indole derivative of isosteviol ethyl ester (15b). Yield 91%; mp 165–167 °C; IR (KBr): 3381, 3048, 2944, 2839, 1720, 1608, 1446, 1374, 1230, 1149, 1091, 1022, 744, 513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (m, 1H), 7.67 (m, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.06 (m, 2H), 4.17 (m, 2H), 2.43 (m, 1H), 2.19–1.78 (m, 5H), 1.73–1.53 (m, 7H), 1.40 (t, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.19–0.71 (m, 5H), 0.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 148.6, 138.8, 124.9, 121.0, 119.7, 119.6, 119.5, 111.6, 67.3, 60.1, 57.1, 54.0, 45.4, 44.0, 40.5, 40.4, 38.4, 37.5, 37.3, 35.1, 28.9, 23.5, 22.3, 21.4, 19.2, 14.1, 13.4; HRMS (ESI, *m/z*) calcd for $C_{28}H_{37}NO_2Na$ $[M+Na]^+$ 442.2722. Found: 442.2723.

4.3.16. General procedure for synthesis of compounds 16a and 16b

A mixture of compound **1**or **2** (1 mmol) and hydroxylamine hydrochloride (0.103 g, 1.5 mmol) in C_2H_5OH was stirred in presence of $NaHCO_3$ at 60 °C for 2 h, then the reaction mixture was concentrated under vacuum, and extracted with CH_2Cl_2 and H_2O. At last the organic layer was washed with saturated NaCl aqueous

solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **16**.

4.3.16.1. *ent*-16-Hydroximinobeyeran-19-oic acid (16a)[27]. Yield 90%; mp 103–104 °C; IR (KBr): 3425, 3118, 2942, 2847, 1694, 1471, 1454, 1417, 1387, 1250, 1215, 1188, 1153, 946, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.17 (d, J = 9.5 Hz, 1H), 2.13 (d, J = 15.1 Hz, 1H), 2.05–1.68 (m, 4H), 1.65 (d, J = 1.4 Hz, 3H), 1.62–1.29 (m, 7H), 1.23 (s, 3H), 1.14–1.18 (m, 3H), 0.96 (s, 3H), 0.87 (s, 3H), 0.86–0.78 (m, 1H); HRMS (ESI, *m/z*) calcd for $C_{20}H_{32}NO_3$ $[M+H]^+$ 334.2382. Found: 334.2387.

4.3.16.2. Ethyl *ent*-16-hydroximinobeyeran-19-oate (16b). Yield 95%; mp 42–44 °C; IR (KBr): 3306, 2939, 2847, 1723, 1450, 1377, 1320, 1299, 1233, 1179, 1152, 1097, 1028, 929, 849, 792, 722, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (m, 2H), 2.97 (d, J = 18.6 Hz, 1H), 2.17 (d, J = 13.3 Hz, 1H), 2.00 (d, J = 18.6 Hz, 1H), 1.89–1.57 (m, 7H), 1.48–1.39 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.23–1.20 (m, 2H), 1.18 (s, 3H), 1.10 (s, 3H), 1.09–0.84 (m, 4H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 170.4, 59.9, 57.0, 56.2, 54.8, 43.7, 43.6, 40.8, 40.5, 39.8, 39.3, 38.0, 37.9, 36.7, 28.8, 22.0, 21.6, 20.3, 18.8, 14.1, 13.2; HRMS (ESI, *m/z*) calcd for $C_{22}H_{35}NO_3Na$ $[M+Na]^+$ 384.2515. Found: 384.2512.

4.3.17. General procedure for synthesis of compounds 17 and 18

Compound **16a** or **16b** (1 mmol) was dissolved in C_2H_5OH or THF (30 mL) followed by addition of Ni (0.5 mmol) in catalytic hydrogenation flask. The reaction proceeded 4 h under 3 atm hydrogen at 40 °C. Then the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica to give products **17** and **18**.

4.3.17.1. *ent*-16-Aminobeyeran-19-oic acid (17a). Yield 82%; mp 367–368 °C; IR (KBr): 3428, 2940, 2846, 2678, 1689, 1616, 1546, 1464, 1398 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 3.48 (m, 1H), 2.17 (d, J = 13.3 Hz, 1H), 1.99–1.57 (m, 8H), 1.48–1.39 (m, 5H), 1.27 (s, 3H), 1.23–1.10 (m, 4H), 1.08 (s, 3H), 1.07–0.88 (m, 3H), 0.87 (s, 3H); HRMS (ESI, *m/z*) calcd for $C_{20}H_{34}NO_2$ $[M+H]^+$ 320.2590. Found: 320.2576.

4.3.17.2. Ethyl *ent*-16-aminobeyeran-19-oate (17b). Yield 88%; mp 89–91 °C; IR (KBr): 3353, 2939, 2845, 1722, 1661, 1451, 1374, 1231, 1177, 1151, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (q, J = 7.2 Hz, 2H), 2.89 (dd, J = 11.2, 6.0 Hz, 1H), 2.15 (d, J = 13.2 Hz, 1H), 1.85–1.51 (m, 9H), 1.40–1.31 (m, 6H), 1.26 (t, J = 7.2 Hz, 3H), 1.16 (s, 3H), 1.04–0.85 (m, 4H), 0.84 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 61.0, 59.8, 57.1, 56.5, 55.6, 43.6, 42.9, 41.8, 41.4, 40.0, 39.9, 37.9, 34.2, 33.3, 28.9, 24.8, 21.7, 20.5, 18.8, 14.0, 13.3; HRMS (ESI, *m/z*) calcd for $C_{22}H_{38}NO_2$ $[M+H]^+$ 348.2903. Found: 348.2904.

4.3.17.3. Ethyl *ent*-16-aminoethylbeyeran-19-oate (18). Yield 86%; mp 61–63 °C; IR (KBr): 3433, 2936, 2844, 1723, 1454, 1377, 1231, 1177, 1147, 1027, 973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (m, 2H), 2.73–2.61 (m, 3H), 2.15 (d, J = 13.2 Hz, 1H), 1.82–1.77 (m, 2H), 1.68–1.50 (m, 8H), 1.36–1.32 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.16 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H), 1.04–0.94 (m, 5H), 0.91 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 67.0, 59.8, 57.2, 57.0, 55.9, 43.6, 43.6, 42.1, 41.8, 41.4, 40.0, 39.9, 38.0, 38.0, 34.0, 28.9, 25.7, 21.7, 20.7, 18.9, 15.6, 14.1, 13.4; HRMS (ESI, *m/z*) calcd for $C_{24}H_{42}NO_2$ $[M+H]^+$ 376.3216. Found: 376.3215.

4.3.18. General procedure for synthesis of compounds 19 and 20

A mixture of the compound **16** (1 mmol) and $BF_3{\cdot}OEt_2$ (30 mL) in toluene was stirred at 100 °C for 12 h, then the reaction mixture was concentrated under vacuum , and extracted with CH_2Cl_2 and H_2O. At last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica to give products **19** and **20**.

4.3.18.1. Lactam of isosteviol (19a)[37]. Mp 98–100 °C; IR (KBr): 3389, 3213, 2927, 2849, 1713, 1632, 1466, 1396, 1261, 1226, 1171, 1153, 991, 971, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 1H), 3.00 (d, J = 18.4 Hz, 1H), 2.18 (d, J = 13.2 Hz, 1H), 2.03 (d, J = 18.8 Hz, 1H), 1.96–1.77 (m, 4H), 1.70–1.57 (m, 3H), 1.50–1.38 (m, 2H), 1.30–1.25 (m, 4H), 1.22 (s, 3H), 1.20 (s, 3H), 1.08–0.89 (m, 3H), 0.88 (s, 3H), 0.86–0.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.3, 176.6, 58.5, 57.9, 52.8, 50.2, 49.3, 45.2, 44.7, 41.1, 40.9, 40.6, 39.1, 39.0, 36.2, 29.3, 28.5, 20.9, 20.1, 19.9; HRMS (ESI, *m/z*) calcd for $C_{20}H_{31}NO_3Na$ $[M+Na]^+$ 356.2202. Found: 356.2199.

4.3.18.2. Lactam of isosteviol ethyl ester (19b). Mp 65–67 °C; IR (KBr): 3430, 3199, 2946, 2847, 1722, 1661, 1471, 1328, 1233, 1149, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 1H), 4.09 (m, 2H), 2.90 (d, J = 18.4 Hz, 1H), 2.16 (d, J = 13.2 Hz, 1H), 1.94 (d, J = 18.3 Hz, 1H), 1.90–1.75 (m, 4H), 1.63–1.46 (m, 3H), 1.41–1.27 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.09–0.84 (m, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 173.9, 60.0, 57.4, 56.7, 51.7, 49.3, 44.2, 43.6, 40.2, 39.6, 39.5, 37.9, 37.8, 35.1, 28.8, 28.6, 19.7, 18.8, 18.7, 14.1, 13.7; HRMS (ESI, *m/z*) calcd for $C_{22}H_{33}NO_2Na$ $[M+Na]^+$ 366.2409. Found: 366.2403.

4.3.18.3. Mixture of compounds 20a and 20b. A mixture of **20a** and **20b** isomers (3:1 determined by ^1H NMR); IR (KBr): 3002, 2950, 2922, 2858, 2239, 1717, 1454, 1377, 1227, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.36 (s, 1H), 4.09 (m, 2H), 2.76–1.74 (m, 10H), 1.66 (s, 3H), 1.60–1.34 (m, 5H), 1.26 (t, J = 7.2 Hz, 3H), 1.19 (s, 3H), 1.17–0.71 (m, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): for **20a**: δ 177.1, 131.2, 119.8, 119.0, 60.1, 57.1, 51.7, 48.4, 45.7, 43.6, 39.7, 39.0, 37.7, 37.3, 35.2, 28.7, 23.3, 22.1, 20.0, 19.7, 18.9, 14.1, 13.5; HRMS (ESI, *m/z*) calcd for $C_{22}H_{35}NO_3Na$ $[M+Na]^+$ 384.2515. Found: 384.2514.

4.4. X-ray crystallographic analysis

X-ray crystal data of compounds **4**, **6**, **10f**, **12b** and **14b** were collected by a Rigaku AFC5R diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by the direct method and refined with a full-matrix least squares method.

4.4.1. Crystal data for compound 4

$C_{22}H_{36}O_3$, M = 348.51, orthorhombic, space group $P2_12_12_1$, a = 7.5578(4), b = 15.1297(8), c = 17.2037(10), V = 1967.20(19) $Å^3$, Z = 4, μ(Mo-Kα) = 0.076 cm^{-1}, $F(000)$ = 768, D_c = 1.177 g/cm^3, crystal dimensions: 0.41 × 0.23 × 0.12 mm, A total of 15,181 reflections (3650 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 51°, and 2948 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.048 and 0.112, respectively. The maximum and minimum peaks in the difference map were 0.368 and −0.244 e $Å^{-3}$, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 654209.

4.4.2. Crystal data for compound 6

$C_{22}H_{38}O_5$, M = 382.52, monoclinic, space group $P2_1$, a = 2.151(2), b = 7.3549(15), c = 12.764(3), V = 1039.7(4) $Å^3$, Z = 2, μ(Mo-Kα) = 0.084 cm^{-1}, $F(000)$ = 420, D_c = 1.222 g/cm^3, crystal dimensions:

$0.22 \times 0.20 \times 0.20$ mm, A total of 2705 reflections (2641 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 49°, and 1883 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0603 and 0.1475, respectively. The maximum and minimum peaks in the difference map were 0.720 and −0.407 e Å^{-3}, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 257291.

4.4.3. Crystal data for compound 10f

$C_{25}H_{42}O_4$, $M = 406.59$, orthorhombic, space group $P2_12_12_1$, $a = 7.8760(16)$, $b = 20.434(4)$, $c = 29.280(6)$, $V = 4712.3(16)$ Å^3, $Z = 8$, μ(Mo-Kα) = 0.075 cm^{-1}, $F(000) = 1792$, $D_c = 1.146$ g/cm^3, crystal dimensions: $0.20 \times 0.18 \times 0.17$ mm, A total of 12,546 reflections (7189 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 50°, and 5249 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0709 and 0.1778, respectively. The maximum and minimum peaks in the difference map were 0.767 and −0.733 e Å^{-3}, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 705071.

4.4.4. Crystal data for compound 12b

$C_{30}H_{40}O_5$, $M = 480.62$, orthorhombic, space group $P2_12_12_1$, $a = 7.6199(15)$, $b = 12.413(3)$, $c = 27.789(6)$, $V = 2628.5(9)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.081 cm^{-1}, $F(000) = 1040$, $D_c = 1.215$ g/cm^3, crystal dimensions: $0.30 \times 0.20 \times 0.20$ mm, a total of 9122 reflections (3197 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 55°, and 2328 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0588 and 0.1251, respectively. The maximum and minimum peaks in the difference map were 0.279 and −0.217 e Å^{-3}, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 257292.

4.4.5. Crystal data for compound 14b

$C_{22}H_{34}O_4$, $M = 362.49$, orthorhombic, space group $P2_12_12_1$, $a = 6.9969(14)$, $b = 12.671(3)$, $c = 23.212(5)$, $V = 2057.9(7)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.079 cm^{-1}, $F(000) = 792$, $D_c = 1.170$ g/cm^3, crystal dimensions: $0.20 \times 0.17 \times 0.17$ mm, a total of 6421 reflections (2165 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 51°, and 1884 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0576 and 0.1475, respectively. The maximum and minimum peaks in the difference map were 0.241 and −0.203 e Å^{-3}, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 705070.

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References and notes

1. Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeucki, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. J. *Antibiotics* **1984**, *37*, 1301.
2. Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heineke, E. W.; Ducep, J. B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
3. Fujisawa, T.; Ikegami, H.; Inoue, K.; Kawabata, Y.; Ogihara, T. *Metabolism* **2005**, *54*, 387.
4. Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920.
5. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.
6. Shimizu, H.; Tsuchie, H.; Yoshida, K.; Morikawa, S.; Tsuruoka, T.; Yamamoto, H.; Ushijima, H.; Kitamura, T. *AIDS* **1990**, *4*, 975.
7. Sou, S.; Takahashi, H.; Yamasaki, R.; Kagechika, H.; Endo, Y.; Hashimoto, Y. *Chem. Pharm. Bull.* **2001**, *49*, 791.
8. Liu, Y.; Zou, L.; Ma, L.; Chen, W. H.; Wang, B.; Xu, Z. L. *Bioorg. Med. Chem.* **2006**, *14*, 5683.
9. Pandey, J.; Dwivedi, N.; Singh, N.; Srivastava, A. K.; Tamarkarb, A.; Tripathi, R. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1321.
10. Look, G. C.; Fotsh, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182.
11. Kinghorn, A. D.; Soejarto, D. D.; Nanayakkara, N. P. D.; Compadre, C. M.; Makapugay, H. C.; Hovanec-Brown, J. M.; Medon, P. J.; Kamath, S. K. *J. Nat. Prod.* **1984**, *47*, 439.
12. Melis, M. S. *J. Nat. Prod.* **1992**, *55*, 688.
13. Liu, J. C.; Kao, P. F.; Hsieh, M. H.; Chen, Y. J.; Chan, P. *Acta Cardiol. Sin.* **2001**, *17*, 133.
14. Yasukawa, K.; Kitanaka, S.; Seo, S. *Biol. Pharm. Bull.* **2002**, *25*, 1488.
15. Chang, S. F.; Yang, L. M.; Lo, C. H.; Liaw, J. H.; Wang, L. H.; Li, S. J. *J. Nat. Prod.* **2008**, *71*, 87.
16. Wong, K. L.; Lin, J. W.; Liu, J. C.; Yang, H. Y.; Kao, P. F.; Chen, C. H.; Loh, S. H.; Chiu, W. T.; Cheng, T. H.; Lin, J. G.; Hong, H. J. *Pharmacology* **2006**, *76*, 163.
17. Xu, D. Y.; Zhang, S. J.; David, J. R.; Wang, J. P. *Clin. Exp. Pharmacol. Physiol.* **2007**, *34*, 488.
18. Roy, A.; Roberts, F. G.; Wilderman, P. R.; Zhou, K.; Peters, R. J.; Coates, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 12453.
19. Ma, J.; Ma, Z.; Wang, J.; Milne, R. W.; Xu, D.; Davey, A. K.; Evans, A. M. *Diabetes Obes. Metab.* **2007**, *9*, 597.
20. Liu, X. F.; Huang, X.; Xu, H. S. *Wuhandaxue Xuebao (Ziran Kexueban)* **1994**, *2*, 74.
21. Al'fonsov, V. A.; Bakaleinik, G. A.; Gubaidullin, A. T.; Kataev, V. E.; Kovylyaeva, G. I. *Russ. J. Gen. Chem.* **2000**, *70*, 953.
22. Tao, J. C.; Tian, G. Q.; Zhang, Y. B.; Fu, Y. Q.; Dai, G. F.; Wu, Y. *Chin. Chem. Lett.* **2005**, *16*, 1441.
23. Alfonsov, V. A.; Andreeva, O. V.; Bakaleynik, G. A.; Beskrovny, D. V.; Kataev, V. E.; Galina, I. K.; Litvinov, I. A.; Militsina, O. I.; Strobykina, I. Y. *Mendeleev Commun.* **2003**, *13*, 234.
24. Goldsmith, D. J.; Joines, R. C. *Tetrahedron Lett.* **1965**, *25*, 2047.
25. Zhao, Y.; Niu, X. M.; Qian, L. P.; Liu, Z. Y.; Zhao, Q. S.; Sun, H. D. *Eur. J. Med. Chem.* **2007**, *42*, 494.
26. Yang, H. M.; Shin, H. R.; Cho, S. H.; Bang, S. C.; Song, G. Y.; Ju, J. H.; Kim, M. K.; Lee, S. H.; Ryu, J. C.; Kim, Y.; Jung, S. H. *Bioorg. Med. Chem.* **2007**, *15*, 104.
27. Coates, R. M.; Bertram, E. F. *J. Org. Chem.* **1971**, *36*, 2625.
28. Terauchi, T.; Asai, N.; Doko, T.; Taguchi, R.; Takenaka, O.; Sakurai, H.; Yonaga, M.; Kimura, T.; Kajiwara, A.; Niidome, T.; Kume, T.; Akaikeb, A.; Sugimoto, H. *Bioorg. Med. Chem.* **2007**, *15*, 7098.
29. Kumar, V.; Rani, N.; Aggarwal, P.; Sanna, V. K.; Singh, A. T.; Jaggi, M.; Joshi, N.; Sharma, P. K.; Irchhaiya, R.; Burman, A. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5058.
30. Smith, T. A.; Thatcher, L. N.; Coop, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5175.
31. Barbieri, V.; Ferlin, M. G. *Tetrahedron Lett.* **2006**, *47*, 8289.
32. Nenajdenko, V. G.; Zakurdaev, E. P.; Prusov, E. V.; Balenkova, E. S. *Tetrahedron* **2004**, *60*, 11719.
33. Donoruma, L. G.; Heldt, V. Z.. In *Organic Reactions*; Wiley: New York, 1960; Vol. 11, p 30.
34. Smith, S. In *Molecular Rearrangements*; Mayo, P., Ed.; Interscience: New York, 1962; p 483. Part I.
35. Wang, C. D.; Rath, N. P.; Covey, D. F. *Tetrahedron Lett.* **2006**, *47*, 7837.
36. Oliveira, B. H.; Santos, M. C.; Leal, P. C. *Phytochemistry* **1999**, *51*, 737.
37. Militsina, O. I.; Kovyljaeva, G. I.; Bakaleynik, G. A.; Strobykina, I. Y.; Kataev, V. E.; Alfonsov, V. A.; Dmitry, R. Z.; Beskrovny, D. V.; Litvinov, I. A. *Mendeleev Commun.* **2005**, *15*, 27.