Stereoselective Synthesis, Characterization, and Antibacterial Activities of Novel Isosteviol Derivatives with *D*-Ring Modification

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Considerable interests have been attracted by isosteviol and its derivatives because of their large variety of bioactivities. In this project, a series of novel 15- and 16-substituted isosteviol derivatives were stereoselectively prepared by means of functional interconversions in ring *D* of the tetracyclic diterpene isosteviol. All compounds synthesized were characterized by analysis of NMR, IR, HR-MS data, and the configurations of **33** and **37** were confirmed by X-ray crystallographic analysis. The antibacterial activities *in vitro* of these isosteviol derivatives were investigated; the synthetic compounds were more active against *Gram*-positive than *Gram*-negative bacteria, and were especially active against *Bacillus subtilis*. Among them, compound **27** (*MIC* = 1.56 μg/ml) exhibited the highest antibacterial activity and thus may be exploitable as a lead compound for the development of potent antibacterial agents.

Introduction. – Bacterial infections such as food poisoning, rheumatism, salmonellosis, and diarrhea are caused by multidrug-resistant *Gram*-positive and *Gram*-negative pathogens. Sixty million people are infected, and 20,000 deaths are recorded every year caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium*, and *Escherichia coli.* Amoxicillin, norfloxacin, and ciprofloxacin are the principal drugs of choice for treatment of bacterial infections, since they are effective against extraintestinal and intestinal wall infection, but these are associated with several side-effects such as nausea, metallic taste, dizziness, hypertension, *etc.* [1][2]. Therefore, there is an urgent need to discover new compounds with potent antibacterial activities for developing new drugs. Moreover, the importance of heterocyclic compounds has been recognized in this field, and it is well-known that a number of polycyclic compounds containing heterocycle fragments exhibited a wide variety of biological activities [3–9].

Isosteviol (= *ent*-16-oxobeyeran-19-oic acid; **1**) is a tetracyclic diterpenoid with a beyerane skeleton, obtained by acid hydrolysis of stevioside [10][11]. In recent years, isosteviol derivatives have attracted increasing attention because of their remarkably broad spectrum of biological activities including anti-inflammatory [12], glucocorticoid agonist [13], antihypertension [14], antitumor [15], antiproliferation [16], and inhibition of *ent*-kaurene synthase [17]. Especially, *Lin et al.* reported that isosteviol amide dimers had favorable antibacterial effects and cytotoxicity [18], which prompted us to study new isosteviol derivatives with hydrophilic functional groups to develop novel stronger antibacterial agents for therapeutic use. Some novel compounds containing OH and CH_2OH group, and heteroatom-containing frameworks fused with

isosteviol structure have been prepared in our laboratory [19]. So, hydrophilic functional groups attached to ring *D* in isosteviol skeleton may also provide some possibilities for the construction of heterocycle in the isosteviol precursor.

In view of these reports and in continuation of our previous work [20], a series of novel compounds containing indole, pyrazoline, and isoxazolidine rings fused with the isosteviol framework have been designed and synthesized. The *in vitro* antibacterial activities of these new isosteviol derivatives were investigated, which would aid in designing and synthesizing novel stronger antibacterial agents.

Results and Discussion. – All the isosteviol derivatives mentioned below were synthesized by different methods. Initial efforts were focused on structural modifications at C(15) and C(16) of isosteviol (**1**). The synthetic routes are outlined in *Scheme 1*. Treatment of isosteviol (**1**), obtained by acid hydrolysis of stevioside, with EtBr and KOH in DMSO afforded the corresponding ethyl ester **2** in 96% yield [21]. In addition, 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 [22–24]; so, indole isosteviol derivatives **5** and **6** were obtained from **1** and **2**, respectively, using AcOH saturated with gaseous HCl as catalyst *via Fischer* reaction in good yields (80 and 91%, resp.) [19][25].

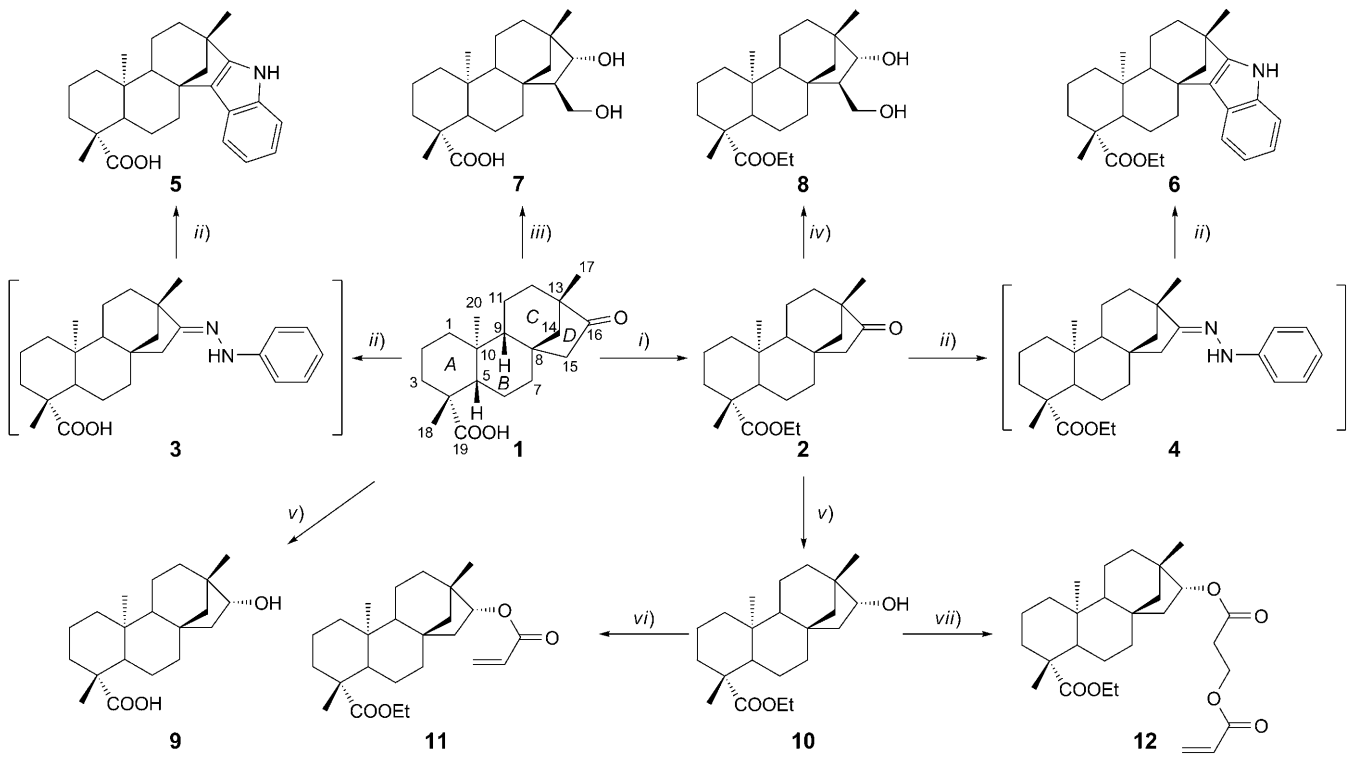
Compounds **7** and **8** were stereoselectively synthesized *via* a one-pot *Tollens*' (aldol-*Cannizzarro*) reaction in good yield (95 and 90%, resp.). The products were characterized by HR-MS, IR, and NMR, and the configuration of compound **7** was confirmed by X-ray crystallographic analysis [26]. Compounds **9** and **10** were obtained in good yields by reduction of **1** and **2**, respectively, with $NaBH_4$ in EtOH at 0° [27]. The configuration of compound **10** was established by X-ray crystallographic analysis [20].

Treatment of **10** with acrylic acid (= prop-2-enoic acid) in CH_2Cl_2 in the presence of DCC and DMAP furnished the main product **11** [19] and by-product **12**. In addition, **12** could be also obtained *via Michael* addition from **11** with acrylic acid. So, compound **11** and **12** could be selectively synthesized in CH_2Cl_2 from compound **10** in good yield (85 and 75%, resp.) by controlling the amount of acrylic acid.

Compounds **13** and **14** were selectively synthesized in the presence of Na_2CO_3 from compound **8** by controlling the amount of nicotinoyl chloride in good yield (81 and 88%, resp.), as shown in *Scheme 2*. In addition, compound **15** was obtained by selective oxidation of **8** with PCC in CH_2Cl_2. Meanwhile, treatment of 1,3-diol **8** with HNO_3/H_2SO_4 in CH_2Cl_2 gave the corresponding dinitro derivative **16** in 80% yield. Treatment of compound **8** with 4-methylphenylsulfonyl chloride (TsCl) in pyridine furnished compound **17** (75%), which was further converted to the ring-opening product **18** in 96% yield *via Grob* fragmentation of compound **17** in the presence of NaOH in MeCN [28].

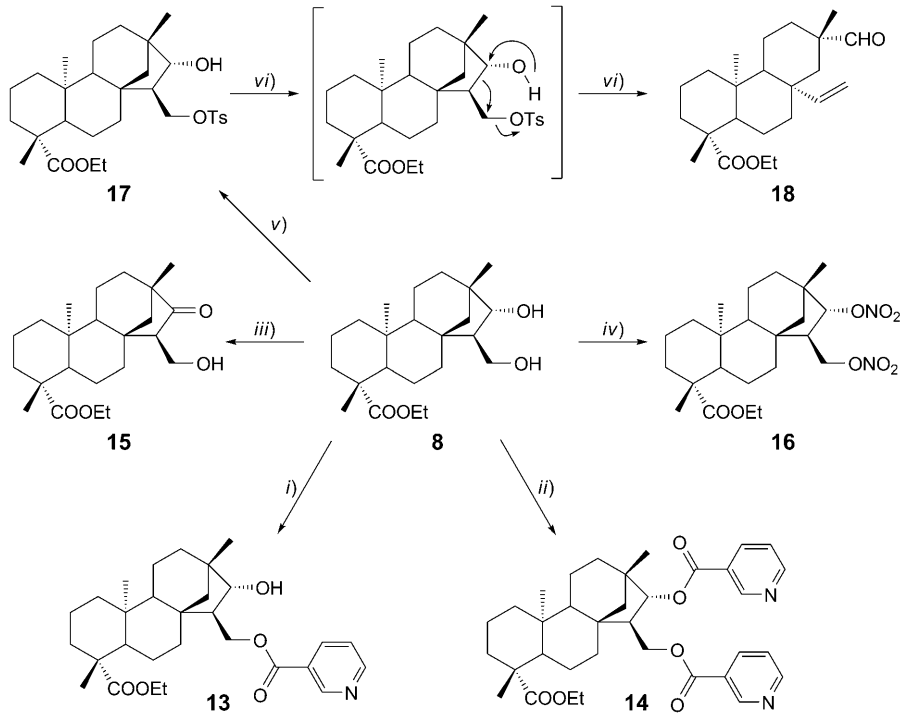
The electrophile-promoted cyclization of ω-substituted alkenes is an increasingly important method for the synthesis of tetrahydropyrans and six-membered lactones, which are essential components of a wide range of interesting, biologically active natural products [29–32]. In this regard, with compound **18** as starting material, some experiments were carried out for the structural modification and functional-group conversion at the aldehyde group in order to probe the effect of the newly introduced substituents. So, the corresponding carboxylic acid, amine, alcohol, lactone, and methyltetrahydropyran derivatives of **18** were synthesized as depicted in *Scheme 3*.

Scheme 1



i) EtBr, DMSO, KOH, r.t., 3 h; 96%. *ii*) HCl/AcOH, $PhNHNH_2$, reflux, 3 h; 80–91%. *iii*) HCHO, NaOH, EtOH, 60°, 1 h; 95%. *iv*) HCHO, EtONa, EtOH, 60°, 3 h; 90%. *v*) $NaBH_4$, EtOH, 0°, 1 h; 92–96%. *vi*) *N,N'*-Dicyclohexylcarbodiimide (DCC)/4-(dimethylamino)pyridine (DMAP), 1 equiv. acrylic acid, CH_2Cl_2, r.t., 12 h; 85%. *vii*) DCC/DMAP, 2 equiv. acrylic acid, CH_2Cl_2, r.t., 16 h; 75%.

Scheme 2

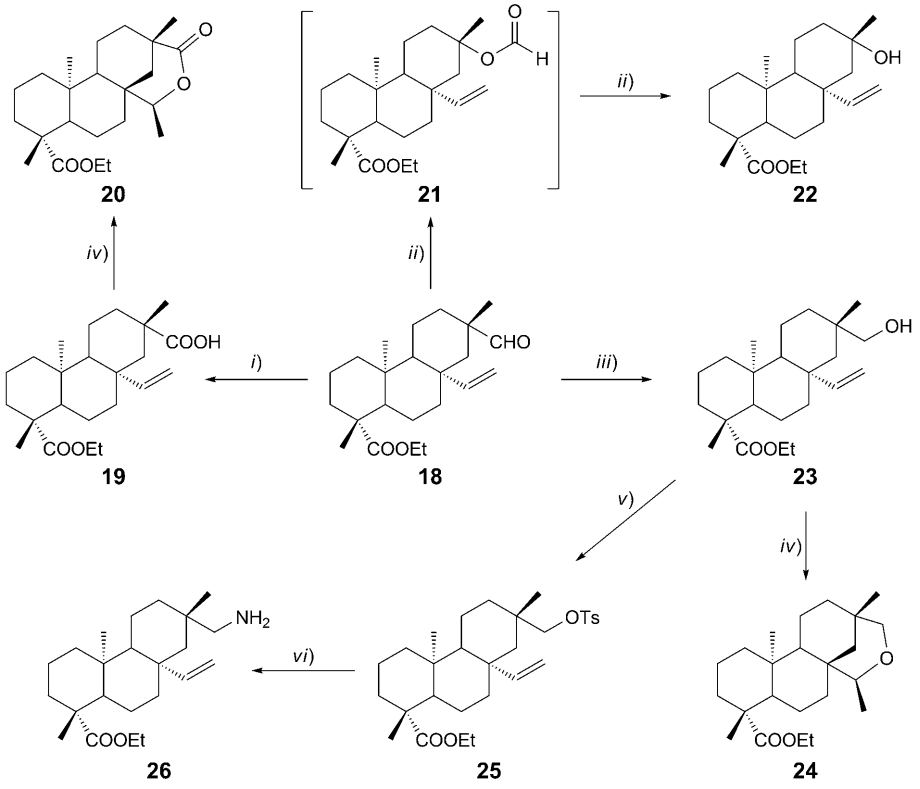


i) 1 equiv. nicotinoyl chloride, Na_2CO_3, $CHCl_3$, 60°, 1 h; 81%. *ii*) 2 equiv. nicotinoyl chloride, Na_2CO_3, $CHCl_3$, 60°, 3 h; 88%. *iii*) Pyridinium chlorochromate (PCC), CH_2Cl_2, r.t., 1 h; 82%. *iv*) HNO_3/H_2SO_4, CH_2Cl_2, 3 h; 80%. *v*) TsCl, pyridine, r.t., 18 h; 75%. *vi*) NaOH, MeCN, r.t., 3 h; 96%.

Compound **18** was oxidized with the *Jones* reagent (8N) in acetone, resulting in the carboxylic acids **19** (90%), which was further converted to the δ-lactone **20** in the presence of $BF_3 \cdot OEt_2$ in 75% yield. In the NOESY experiment of **20**, the correlation of δ(H) 4.32–4.20 (H–C(15)) with Me(20) (δ(H) 0.74) indicated that Me–C(15) was β-oriented. Treatment of **18** in presence of H_2O_2 and NaOH in MeOH *via Baeyer–Villiger* oxidation furnished compound **21** in 75% yield. Reduction of **18** with $NaBH_4$ in EtOH at 0° led to the corresponding hydroxy derivative **23** (96%), the subsequent $BF_3 \cdot OEt_2$-initiated cyclization afforded methyltetrahydropyran **24**. In the NOESY experiment of **24**, the correlation of δ(H) 3.63–3.56 (H–C(15)) with Me(20) (δ(H) 0.68) indicated that Me–C(15) was also β-oriented. Compound **23** was further converted to the tolyloxymethyl derivative **25** in 85% yield by esterification of **23** with TsCl in pyridine. Treatment of **25** with NaN_3 under basic conditions gave the corresponding azide, which was further converted to the amino derivative **26** with Ph_3P in H_2O at 65° (85%).

As shown in *Scheme 4*, reaction of **18** with $HONH_2 \cdot HCl$ in presence of $NaHCO_3$ in EtOH gave only one of the two possible geometric isomers of the corresponding aldoxime **27** (90%). Compound **27** was catalytically tautomerized with $BF_3 \cdot OEt_2$ in

Scheme 3

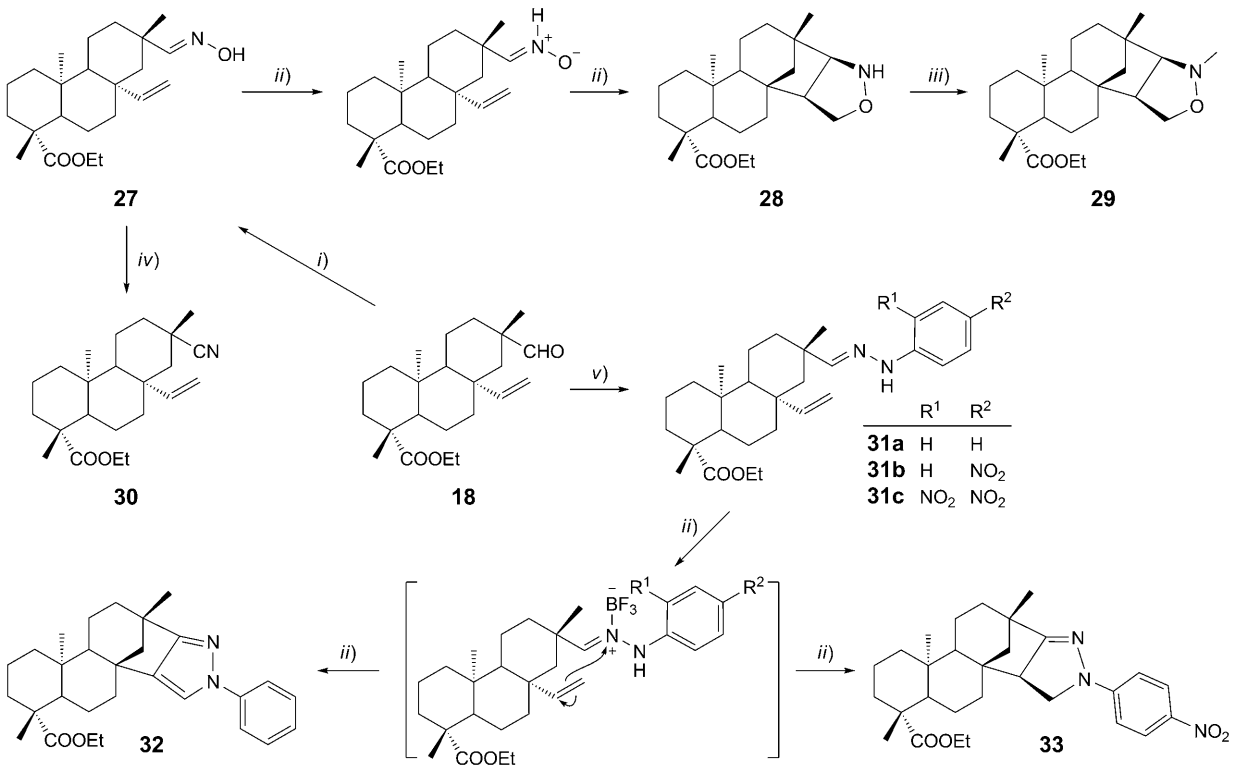


i) *Jones* reagent (8N), acetone, 0°, 2 h; 90%. *ii*) MeOH, NaOH, H_2O_2, 65°, 4 h; 75%. *iii*) $NaBH_4$, EtOH, 0°, 10 min; 96%. *iv*) $BF_3 \cdot OEt_2$, CH_2Cl_2, reflux, 30 h; 74–75%. *v*) TsCl, pyridine, r.t., 12 h; 85%. *vi*) 1. NaN_3, DMF, 80°, 3 h; 80%; 2. Ph_3P, H_2O, 65°, 3 h; 85%.

boiling toluene into its nitrone form, which then intramolecularly cyclized to the fused isoxazolidine **28** in high yield (96%) [33]. The NOESY spectrum of the product **28** indicated the α-orientation of the H-atoms at C(15) and C(16). Treatment of **28** with MeI in presence of NaH in DMF at 50° afforded *N*-methylisoxazolidine **29** in 85% yield. In addition, treatment of compound **27** with H_2SO_4 in acetone gave the dehydration product **30**.

The condensation of **18** with $PhNHNH_2$ was carried out in EtOH at 10° to give phenylhydrazone **31a**, and $BF_3 \cdot OEt_2$-induced cycloaddition of **31a** was also accomplished to give pyrazole **32** (84%) [34]. Meanwhile, the reaction of **18** with 4-nitrophenylhydrazine in EtOH at 10° gave the corresponding 4-nitrophenylhydrazone **31b**, which readily cyclized, after purification in the presence of a catalytic amount of $BF_3 \cdot OEt_2$, to afford a single 4,5-dihydro-1*H*-pyrazole **33** in 75% yield [34]. The stereostructure of **33** was confirmed through X-ray crystallographic analysis (*Fig. 1*). The 2,4-dinitrophenylhydrazone **31c** was obtained from aldehyde **18** with 2,4-dinitrophenylhydrazine in EtOH at 10°, but the 2,4-dinitrophenylhydrazone **31c**

Scheme 4



i) $HONH_2 \cdot HCl$, $NaHCO_3$, EtOH, 60°, 2 h; 97%. *ii*) Toluene, $BF_3 \cdot OEt_2$, 80°, 1 h; 84–96%. *iii*) DMF, NaH, MeI, 50°, 2 h; 85%. *iv*) H_2SO_4, acetone, 40°, 12 h; 71%. *v*) For **31a**: EtOH, AcOH, $PhNHNH_2$, 10°, 3 h; 95%; for **31b**: EtOH, AcOH, (4-nitrophenyl)hydrazine, 10°, 2 h; 85%; for **31c**: EtOH, AcOH, (2,4-dinitrophenyl)hydrazine 10°, 2 h; 81%.

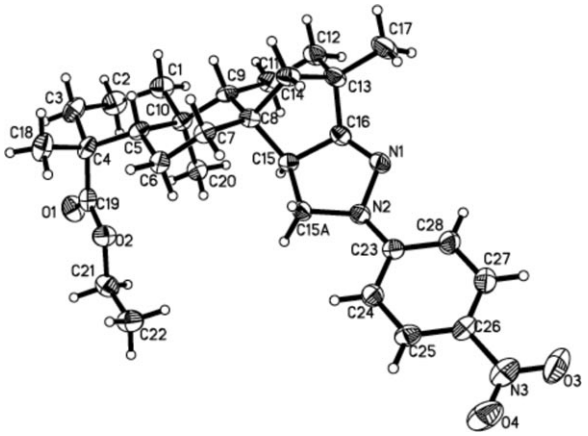


Fig. 1. *X-Ray structure of compound* **33**

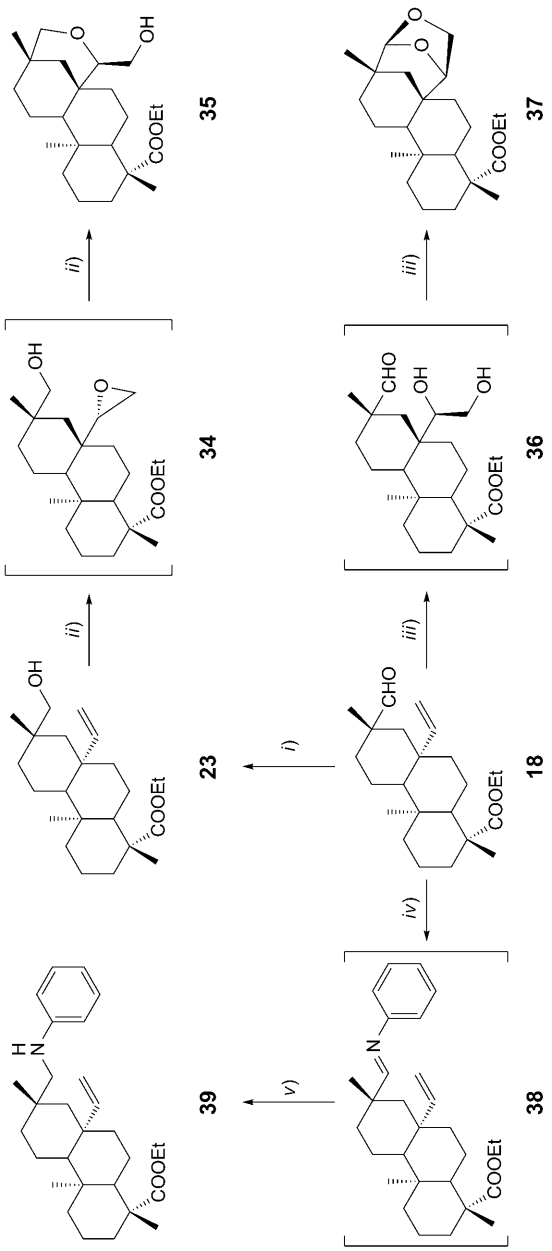
containing two electron-withdrawing NO_2 groups exhibited great stability against both thermal and *Lewis* acid-catalyzed cycloaddition.

Treatment of compound **18**, after reduction with $NaBH_4$ with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 at 0° afforded the epoxy intermediate **34**, which was then intramolecularly converted to the (hydroxymethyl)tetrahydropyran **35** (*Scheme 5*). In the NOESY experiment of compound **35**, the correlation of δ(H) 3.22 (H–C(15)) with Me(20) (δ(H) 0.66) indicated α-orientation of the H-atom at C(15). Meanwhile, treatment of compound **18** with $NaIO_4$ and NaBr in AcOH at 90° led stereoselectively to 1,2-dihydroxy derivative **36**, which was further converted to acetal **37** (84%) [35]. The configuration of compound **37** was confirmed by X-ray crystallographic analysis (*Fig. 2*). In addition, treatment of **18** with aniline in CH_2Cl_2 in the presence of molecular sieves (4 Å) afforded imino intermediate **38**, which was converted to a reduction product **39** with $NaBH_4$.

In further studies, all of the synthetic compounds were tested for their antibacterial activities against *Bacillus subtilis*, *Staphylococcus aureus*, and *Shigella flexneri* strains.

In our studies, none of the compounds exhibited antibacterial activities against *Sigella*, *Gram*-negative bacterial strains as shown in the *Table*. In general, the synthetic compounds were more active against *Gram*-positive than *Gram*-negative bacteria, and were especially active against *Bacillus subtilis*. The minimum inhibitory concentrations (*MIC*s) of these compounds against *Bacillus subtilis* CMCC(B)63501 are collected in the *Table*. Nicotinates and nitrates exhibited much higher antibacterial activities than the precursor 1,3-diol **8** (*i.e.*, **13**, **14**, **16** *vs.* **8**). In addition, the ring-opened derivatives containing OH, NH_2, and oxime groups were more potent than ring-opened product **18** (*i.e.*, **19**, **20**, **22**, **23**, **27** *vs.* **18**). Especially, compound **27** (*MIC* = 1.56 μg/ml) was the most potent of these tested compounds against *Bacillus subtilis*, which may be exploitable as a lead compound for the development of potent bacteriostat. Meanwhile, the results indicated that these isosteviol derivatives were capable of inhibiting *Staphylococcus aureus* CMCC(B)26003 with moderate activities and had no inhibiting activities against *Shigella flexneri* 626.

Scheme 5



i) $NaBH_4$, EtOH, 0°, 10 min; 96%. *ii*) *m*-CPBA, CH_2Cl_2, 0°, 5 h; 78%. *iii*) $NaIO_4$, NaBr, AcOH, 90°, 3 h; 84%. *iv*) Aniline or 4-methylaniline, CH_2Cl_2, molecular sieves (4 Å), 40°, 3 h; 84–96%. *v*) $NaBH_4$, EtOH, 0°, 10 min; 96%.

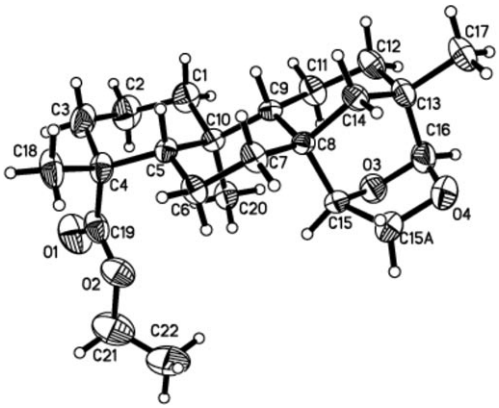


Fig. 2. *X-Ray structure of compound* **37**

Table. *Antibacterial Activities of Isosteviol Derivatives against* Bacillus subtilis, Staphylococcus aureus, *and* Shigella flexneri *Strains*

Compound	*Bacillus subtilis*	*Saphylococcus aureus*	*Sigella flexneri*
1	100[a])	>100[a]) (17%)[b])	NI[c])
2	100[a])	>100[a]) (17%)[b])	NI
5	>200[a])	>100[a]) (3%)[b])	NI
6	200[a])	>100[a]) (18%)[b])	NI
7	100[a])	>100[a]) (16%)[b])	NI
8	200[a])	>100[a]) (66%)[b])	NI
9	>200[a])	>100[a]) (15%)[b])	NI
10	>200[a])	>100[a]) (4%)[b])	NI
11	>200[a])	>100[a]) (84%)[b])	NI
12	>200[a])	>100[a]) (77%)[b])	NI
13	12.5[a])	>100[a]) (32%)[b])	NI
14	3.125[a])	>100[a]) (58%)[b])	NI
15	12.5[a])	>100[a]) (47%)[b])	NI
16	12.5[a])	>100[a]) (75%)[b])	NI
18	>200[a])	>100[a]) (15%)[b])	NI
19	12.5[a])	>100[a]) (63%)[b])	NI
20	3.125[a])	>100[a]) (52%)[b])	NI
22	12.5[a])	NI	NI
23	6.25[a])	>100[a]) (59%)[b])	NI
24	>200[a])	>100[a]) (53%)[b])	NI
26	>200[a])	NI	NI
27	1.56[a])	>100[a]) (40%)[b])	NI
28	>200[a])	100[a])	NI
29	NI	>100[a]) (5%)[b])	NI
30	NI	>100[a]) (7%)[b])	NI
32	NI	NI	NI
33	NI	>100[a]) (8%)[b])	NI
35	6.25[a])	>100[a]) (71%)[b])	NI
37	>200[a])	>100[a]) (21%)[b])	NI
39	>200[a])	NI	NI

[a]) *MIC* [μg/ml]. [b]) Inhibition [%] determined at 100 μg/ml concentration of compound. [c]) NI = No inhibition at 100 μM.

Conclusions. – In summary, a series of novel isosteviol derivatives containing OH and $HOCH_2$ groups, and heteroatom-containing frameworks have been successfully synthesized in high yields; especially some new compounds containing pyrazoline, pyrazole, and isoxazolidine rings fused with isosteviol structure were stereoselectively synthesized from compound **8** *via Grob* fragmentation and subsequent intramolecular 1,3-dipolar cycloaddition. The *in vitro* antibacterial activities of these new isosteviol derivatives were investigated, and some of them showed noteworthy activities. Among all the derivatives, compound **27** showed the highest antibacterial activity against *Bacillus subtilis*, and thus may be exploitable as potentially potent antibacterial agents for therapeutic use. Further efforts aiming at developing potent bacteriostats based on appropriately modified *D*-ring fused heterocyclic analogues are continuing in our laboratory, and they will be reported in due course.

Experimental Part

General. All reagents and solvents were obtained from commercial suppliers. All reactions were monitored by TLC. M.p.: *Beijing Keyi XT5* apparatus; not corrected. IR Spectra: as KBr pellets on a *Thermo Nicolet IR200* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker DPX-400* spectrometer at 400 and 100 MHz, resp., with TMS as internal standard. MS: *Waters Q-Tof micro* mass spectrometer. X-Ray analysis: *Rigaku RAXIS-IV*.

ent-*16β-Hydroxy-15α-(hydroxymethyl)beyeran-19-oic Acid* (=*(15β,16α)-16-Hydroxy-15-(hydroxymethyl)beyeran-18-oic Acid*; **7**) [26]. To a stirred soln. of isosteviol (**1**; 0.318 g, 1 mmol) and NaOH (0.08 g, 2 mmol) in EtOH (20 ml) was added 37% aq. HCHO soln. (2 ml). After stirring for 1 h at 60°, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give **7** (0.332 g, 95%). White powder. M.p. 233–235°. IR (KBr): 3462, 2945, 2927, 2846, 1696, 1456, 1072, 1052. ^{1}H-NMR (400 MHz, (D_6)acetone): 3.83 (*dd*, *J* = 10.4, 5.2, 1 H); 3.62 (*d*, *J* = 4.8, 1 H); 3.50 (*t*, *J* = 9.6, 1 H); 3.30 (*s*, 2 H); 2.12–1.99 (*m*, 2 H); 1.95–1.70 (*m*, 6 H); 1.56–1.51 (*m*, 1 H); 1.44–1.34 (*m*, 2 H); 1.17 (*s*, 3 H); 1.15–0.90 (*m*, 6 H); 0.88 (*s*, 3 H); 0.87 (*s*, 3 H). ^{13}C-NMR (100 MHz, (D_6)acetone): 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. HR-ESI-MS: 373.2358 ($[M+Na]^+$, $C_{21}H_{34}NaO_4^+$; calc. 373.2355).

Ethyl ent-*16β-Hydroxy-15α-(hydroxymethyl)beyeran-19-oate* (=*Ethyl (15β,16α)-16-Hydroxy-15-(hydroxymethyl)beyeran-18-oate*; **8**) [26]. To a stirred soln. of **2** (0.346 g, 1 mmol) and EtONa (0.136 g, 2 mmol) in EtOH (20 ml) was added 37% aq. HCHO soln. (2 ml). After stirring for 3 h at 60°, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give **8** (0.34 g, 90%). White powder. M.p. 181–182°. IR (KBr): 3435, 2940, 2838, 1720, 1458, 1378, 1234, 1179, 1153,1123. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.09 (*q*, *J* = 7.2, 2 H); 3.98 (*dd*, *J* = 9.7, 5.0, 1 H); 3.63 (*d*, *J* = 4.7, 1 H); 3.56 (*t*, *J* = 10.2, 1 H); 2.16 (*d*, *J* = 13.0, 1 H); 2.06–2.04 (*m*, 1 H); 1.83–1.56 (*m*, 9 H); 1.43–1.37 (*m*, 2 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.22–1.19 (*m*, 1 H); 1.16 (*s*, 3 H); 1.08–0.95 (*m*, 4 H); 0.94 (*s*, 3 H); 0.88–0.86 (*m*, 1 H); 0.78 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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. HR-ESI-MS: 401.2664 ($[M+Na]^+$, $C_{23}H_{38}NaO_4^+$; calc. 401.2668).

ent-*16β-Hydroxybeyeran-19-oic Acid* (=*(16α)-16-Hydroxybeyeran-18-oic Acid*; **9**) [27]. A soln. of **1** (0.318 g, 1 mmol) and $NaBH_4$ (0.057 g, 1.5 mmol) in dry EtOH (10 ml) was stirred at 0° for 1 h. Then, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give **9** (0.294 g, 92%). White powder. M.p. 168–169°. IR (KBr): 3475, 2990, 2943, 2896, 2841, 1653, 1453, 1371, 1187, 1056, 998, 621. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.61–3.56 (*m*, 1 H); 2.01 (*d*, *J* = 12.8, 1 H); 1.76–1.62 (*m*, 5 H); 1.59–1.52 (*m*, 3 H); 1.45–1.41 (*m*, 2 H); 1.31–1.17 (*m*, 3 H); 1.09 (*s*, 3 H); 1.06–0.86 (*m*, 6 H); 0.82 (*s*, 3 H); 0.75 (*s*, 3 H). HR-ESI-MS: 321.2425 ($[M+H]^+$, $C_{20}H_{33}O_3^+$; calc. 321.2430).

Ethyl ent-*16β-Hydroxybeyeran-19-oate* (= *Ethyl (16α)-16-Hydroxybeyeran-18-oate*; **10**). A soln. of **2** (0.346 g, 1 mmol) and $NaBH_4$ (0.057 g, 1.5 mmol) in dry EtOH (10 ml) was stirred at 0° for 1 h. Then, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give **10** (0.334 g, 96%). White powder. M.p. 152–153°. IR (KBr): 3533, 2978, 2939, 2880, 2837, 1700, 1460, 1374, 1318, 1231, 1178, 1151, 1049. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.09 (*q*, *J* = 7.2, 2 H); 3.85 (*q*, *J* = 4.8, 1 H); 2.16 (*d*, *J* = 13.2, 1 H); 1.81–1.51 (*m*, 11 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.23–1.18 (*m*, 1 H); 1.16 (*s*, 3 H); 1.04–0.93 (*m*, 4 H); 0.90 (*s*, 3 H); 0.88–0.86 (*m*, 1 H); 0.74 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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. HR-ESI-MS: 371.2554 ($[M+Na]^+$, $C_{21}H_{34}NaO_4^+$; calc. 371.2562).

Ethyl ent-*16β-Acryloxybeyeran-19-oate* (= *Ethyl (16α)-16-[(Prop-2-enoyl)oxy]beyeran-18-oate*; **11**) [19]. A mixture of **10** (0.348 g, 1 mmol), prop-2-enoic acid (0.792 g, 1.1 mmol), DCC (0.412 g, 2 mmol), and DMAP (0.024 g, 0.2 mmol) was stirred at r.t. After stirring for 12 h, the mixture was filtered, and the filtrate was concentrated. The residue was purified by CC (SiO_2; petroleum ether (PE)/AcOEt 6:1) to give **11** (0.341 g, 85%). IR (KBr): 3101, 2950, 2847, 1723, 1625, 1455, 1405, 1378, 1194, 1151, 1060, 981, 811. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.38 (*d*, *J* = 17.2, 1 H); 6.13 (*dd*, *J* = 17.2, 10.4, 1 H); 5.81 (*d*, *J* = 10.4, 1 H); 4.80 (*q*, *J* = 4.8, 1 H); 4.15–4.06 (*m*, 2 H); 2.17 (*d*, *J* = 13.6, 1 H); 1.92–1.68 (*m*, 7 H); 1.61–1.33 (*m*, 7 H); 1.25 (*t*, *J* = 7.2, 3 H); 1.15 (*s*, 3 H); 1.09–094 (*m*, 4 H); 0.90 (*s*, 3 H); 0.87–084 (*m*, 1 H); 0.70 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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. HR-ESI-MS: 403.2835 ($[M+H]^+$, $C_{25}H_{39}O_4^+$; calc. 403.2848).

Treatment of **10** *with Prop-2-enoic Acid*. A mixture of **10** (0.348 g, 1 mmol), prop-2-enoic acid (1.584 g, 2.2 mmol), DCC (0.412 g, 2 mmol), and DMAP (0.024 g, 0.2 mmol) was stirred at r.t. After stirring for 16 h, the mixture was filtered, and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 6:1) to give *ethyl (16α)-16-({3-[(prop-2-enoyl)oxy]propanoyl}oxy)beyeran-18-oate* (**12**; 0.355 g, 75%). IR (KBr): 2948, 2848, 1728, 1634, 1456, 1407, 1388, 1180, 1117, 1058, 980, 809. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.41 (*dd*, *J* = 17.2, 1.2, 1 H); 6.09 (*dd*, *J* = 17.2, 10.4, 1 H); 5.81 (*dd*, *J* = 10.4, 1.6, 1 H); 4.78 (*q*, *J* = 4.8, 1 H); 4.44 (*t*, *J* = 6.4, 2 H); 4.15–4.04 (*m*, 2 H); 2.71 (*t*, *J* = 6.4, 2 H); 2.15 (*d*, *J* = 13.6, 1 H); 1.92–1.68 (*m*, 7 H); 1.61–1.33 (*m*, 7 H); 1.24 (*t*, *J* = 7.2, 3 H); 1.15 (*s*, 3 H); 1.04–0.92 (*m*, 4 H); 0.90 (*s*, 3 H); 0.86–0.84 (*m*, 1 H); 0.69 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.5; 170.7; 165.8; 131.1; 128.0; 82.1; 60.2; 59.9; 57.0; 55.6; 54.7; 43.6; 42.3; 41.5; 41.4; 40.5; 39.9; 38.2; 38.0; 34.6; 34.2; 28.9; 24.8; 21.6; 20.1; 18.9; 14.1; 13.2. HR-ESI-MS: 497.2868 ($[M+Na]^+$, $C_{28}H_{42}NaO_6^+$; calc. 497.2879).

Ethyl ent-*16β-Hydroxy-15α-[(nicotinoyloxy)methyl]beyeran-19-oate* (= *Ethyl (15β,16α)-16-Hydroxy-15-{[(pyridin-3-ylcarbonyl)oxy]methyl}beyeran-18-oate*; **13**). A mixture of **8** (0.378 g, 1 mmol) and nicotinoyl chloride (0.141 g, 1 mmol) in dry $CHCl_3$ (10 ml) was stirred at 60° in the presence of Na_2CO_3. After stirring for 1 h, the mixture was extracted with aq. Na_2CO_3, brine, and H_2O successively. The $CHCl_3$ phase was dried (Na_2SO_4), filtered, and concentrated to give a crude product, which was crystallized from $CHCl_3$ to give **13** (0.391 g, 81%). M.p. 88.1–88.9°. IR (KBr): 3422, 2945, 2848, 1722, 1592, 1458, 1383, 1282, 1150, 1025, 742, 702. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.26 (*s*, 1 H); 8.78 (*d*, *J* = 4.0, 1 H); 8.41–8.34 (*m*, 1 H); 7.42 (*dd*, *J* = 8.0, 4.8, 1 H); 4.68 (*dd*, *J* = 10.8, 4.8, 1 H); 4.25 (*t*, *J* = 10.8, 1 H); 4.18–4.06 (*m*, 2 H); 3.65 (*d*, *J* = 4.8, 1 H); 2.41–2.28 (*m*, 1 H); 2.25–2.13 (*m*, 1 H); 2.05 (*d*, *J* = 19.2, 1 H); 1.86–1.40 (*m*, 11 H); 1.25 (*t*, *J* = 7.2, 3 H); 1.17 (*s*, 3 H); 1.07–0.95 (*m*, 5 H); 0.94 (*s*, 3 H); 0.92–0.85 (*m*, 1 H); 0.80 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 165.3; 153.0; 150.6; 137.5; 126.4; 123.5; 85.8; 67.5; 60.0; 57.5; 57.0; 54.1; 47.3; 43.6; 42.8; 41.1; 39.6; 38.2; 37.9; 35.0; 33.1; 28.9; 25.0; 22.1; 19.5; 18.9; 14.1; 13.2. HR-ESI-MS: 484.3051 ($[M+H]^+$, $C_{29}H_{42}NO_5^+$; calc. 484.3063).

Ethyl ent-*16β-(Nicotinoyloxy)-15α-[(nicotinoyloxy)methyl]beyeran-19-oate* (= *Ethyl (15β,16α)-16-[(Pyridin-3-ylcarbonyl)oxy]-15-{[(pyridin-3-ylcarbonyl)oxy]methyl}beyeran-18-oate*; **14**). A mixture of **8** (0.378 g, 1 mmol) and nicotinoyl chloride (0.282 g, 2 mmol) in dry $CHCl_3$ (10 ml) was stirred at 60° in the presence of Na_2CO_3. After stirring for 3 h, the mixture was extracted with aq. Na_2CO_3, brine, and H_2O successively. The $CHCl_3$ phase was dried (Na_2SO_4), filtered, and concentrated to give a crude product which was crystallized from $CHCl_3$ to give **14** (0.517 g, 88%). IR (KBr): 2950, 2850, 1723, 1590, 1460, 1286, 1127, 1024, 971, 741, 702. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.12 (*d*, *J* = 18.4, 2 H); 8.76 (*s*, 1 H); 8.68 (*s*, 1 H); 8.23–8.15 (*m*, 2 H); 7.38 (*dd*, *J* = 8.0, 4.8, 1 H); 7.25 (*dd*, *J* = 8.0, 4.8, 1 H); 5.28 (*d*, *J* = 4.8,

1 H); 4.75 (*dd*, *J* = 10.8, 4.8, 1 H); 4.42–4.30 (*m*, 1 H); 4.20–4.08 (*m*, 2 H); 2.68–2.62 (*m*, 1 H); 2.19 (*d*, *J* = 12.8, 1 H); 1.91–1.71 (*m*, 10 H); 1.47–1.28 (*m*, 2 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.18 (*s*, 3 H); 1.15–1.04 (*m*, 3 H); 1.01 (*s*, 3 H); 0.99–0.87 (*m*, 2 H); 0.85 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 165.1; 164.6; 153.3; 153.1; 150.6; 150.5; 137.0; 137.0; 126.1; 125.9; 123.4; 123.1; 85.6; 66.3; 60.0; 57.4; 56.9; 54.0; 45.2; 43.6; 43.3; 41.6; 39.6; 38.2; 37.8; 34.8; 34.2; 28.8; 24.8; 22.0; 19.4; 18.8; 14.0; 13.2. HR-ESI-MS: 611.3081 ($[M+Na]^+$, $C_{35}H_{44}N_2NaO_6^+$; calc. 611.3097).

Ethyl ent-*15α-(Hydroxymethyl)-16-oxobeyeran-19-oate* (= *Ethyl (15β)-15-(Hydroxymethyl)-16-oxobeyeran-18-oate*; **15**) [10]. A mixture of **8** (0.378 g, 1 mmol) and PCC (0.236 g, 1.1 mmol) was stirred at r.t. for 1 h. Then, the mixture was filtered, and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 7:1) to give **15** (0.308 g, 82%). M.p. 155–157°. IR (KBr): 3534, 2958, 2857, 1735, 1721, 1462, 1151. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.16–4.08 (*m*, 2 H); 3.95–3.88 (*m*, 1 H); 3.70 (*t*, *J* = 10.4, 1 H); 2.56–2.18 (*m*, 1 H); 2.54–2.48 (*m*, 1 H); 2.19 (*d*, *J* = 13.3, 1 H); 1.89–1.69 (*m*, 8 H); 1.42–1.29 (*m*, 4 H); 1.27 (*t*, *J* = 7.2, 3 H); 1.19 (*s*, 3 H); 1.18–1.10 (*m*, 2 H); 0.98 (*s*, 3 H); 0.97–0.80 (*m*, 2 H); 0.75 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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. HR-ESI-MS: 399.2514 ($[M+Na]^+$, $C_{23}H_{36}NaO_4^+$; calc. 399.2511).

Ethyl (15β,16α)-16-(Nitrooxy)-15-[(nitrooxy)methyl]beyeran-18-oate (**16**). To a stirred soln. of **8** (0.378 g, 1 mmol) in CH_2Cl_2 (20 ml) at 0° was added a mixture of HNO_3 (0.13 ml) and H_2SO_4 (0.49 ml) for 15 min. After stirring at r.t. for 3 h, the mixture was extracted with CH_2Cl_2 and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 6:1) to give **16** (0.374 g, 80%). M.p. 120.7–122.2°. IR (KBr): 2943, 2852, 1721, 1625, 1467, 1384, 1279, 1180, 977, 853. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.01 (*d*, *J* = 4.8, 1 H); 4.75 (*dd*, *J* = 10.8, 5.2, 1 H); 4.49–4.37 (*m*, 1 H); 4.10 (*q*, *J* = 7.2, 2 H); 2.56–2.48 (*m*, 1 H); 2.19–2.15 (*m*, 1 H); 1.88–1.56 (*m*, 7 H); 1.45–1.28 (*m*, 4 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.15–1.04 (*m*, 3 H); 1.02 (*s*, 3 H); 0.99–0.83 (*m*, 3 H); 0.74 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 92.5; 73.2; 60.1; 57.1; 56.6; 53.8; 43.5; 43.4; 42.8; 41.7; 39.4; 38.1; 37.8; 34.8; 33.6; 28.8; 24.8; 21.7; 19.1; 18.7; 14.0; 13.0. ESI-HR-MS: 491.2372 ($[M+Na]^+$, $C_{23}H_{36}N_2NaO_8^+$: calc. 491.2369).

Ethyl ent-*16β-Hydroxy-15α-{[(4-toluenesulfonyl)oxy]methyl}beyeran-19-oate* (= *Ethyl (15β,16α)-16-Hydroxy-15-({[(4-methylphenyl)sulfonyl]oxy}methyl)beyeran-18-oate*; **17**). A mixture of **8** (0.378 g, 1 mmol) and TsCl (0.238 g, 1.1 mmol) in pyridine (5 ml) was stirred at r.t. for 18 h. Then, the mixture was filtered, and the filtrate was extracted with CH_2Cl_2 and aq. HCl soln. (5M). The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 4:1) to give **17** (0.399 g, 75%). IR (KBr): 3541, 2950, 2928, 2851, 1718, 1598, 1458, 1361, 1177, 1151, 1097, 1020, 948, 924, 816, 779, 665, 555. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (*d*, *J* = 8.2, 2 H); 7.37 (*d*, *J* = 8.2, 2 H); 4.32 (*dd*, *J* = 9.8, 3.6, 1 H); 4.07 (*q*, *J* = 7.1, 2 H); 3.96 (*t*, *J* = 9.8, 1 H); 3.47 (*d*, *J* = 7.5, 1 H); 3.46 (*s*, 3 H); 2.37–2.30 (*m*, 1 H); 2.22–2.14 (*m*, 2 H); 1.80–1.28 (*m*, 8 H); 1.23 (*t*, *J* = 7.1, 3 H); 1.19–1.11 (*m*, 1 H); 1.16 (*s*, 3 H); 1.10–0.93 (*m*, 5 H); 0.88 (*s*, 3 H); 0.86–0.79 (*m*, 3 H); 0.67 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.2; 144.8; 132.9; 129.8; 129.8; 127.7; 127.7; 84.9; 72.8; 59.9; 57.4; 56.8; 53.8; 47.6; 43.5; 42.8; 40.9; 39.5; 38.0; 37.8; 34.6; 33.0; 28.8; 24.8; 21.9; 21.6; 19.3; 18.7; 14.0; 12.9. HR-ESI-MS: 555.2742 ($[M+Na]^+$, $C_{30}H_{44}NaO_6S^+$; calc. 555.2757).

Product **18** *of Ring Opening*. A mixture of **17** (0.532 g, 1 mmol) and NaOH (0.048 g, 1.1 mmol) in dry MeCN (5 ml) was stirred at r.t. for 3 h. Then, the mixture was filtered, the filtrate was concentrated, and the residue was extracted with CH_2Cl_2 and H_2O. Then, the org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was crystallized from $CHCl_3$ to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-formyl-13-methylpodocarpan-15-oate* (**18**; 0.345 g, 96%). M.p. 116.5–117.8°. IR (KBr): 3072, 2937, 2796, 2704, 1716, 1458, 1384, 1238, 1183, 1029, 912, 704. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.27 (*d*, *J* = 1.6, 1 H); 5.95 (*dd*, *J* = 17.6, 10.8, 1 H); 5.12 (*d*, *J* = 10.0, 1 H); 5.08 (*d*, *J* = 3.2, 1 H); 4.06–3.95 (*m*, 2 H); 2.32–2.24 (*m*, 1 H); 2.16–2.10 (*m*, 2 H); 1.88–1.39 (*m*, 9 H); 1.26 (*d*, *J* = 13.2, 1 H); 1.20 (*t*, *J* = 7.2, 3 H); 1.14 (*s*, 3 H); 1.10–0.89 (*m*, 5 H); 0.88 (*s*, 3 H); 0.58 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 205.2; 177.3; 142.5; 113.6; 59.9; 57.7; 57.5; 55.2; 46.1; 43.7; 40.8; 40.1; 39.6; 38.1; 38.0; 32.3; 28.7; 24.6; 20.0; 19.1; 17.4; 14.0; 13.2. HR-ESI-MS: 383.2560 ($[M+Na]^+$, $C_{23}H_{36}NaO_3^+$; calc. 383.2562).

Oxidation of **18**. A mixture of **18** (0.360 g, 1 mmol) and *Jones* reagent (8N) in dry acetone (5 ml) was stirred at 0° for 2 h. Then, the mixture was concentrated, and the residue was extracted with CH_2Cl_2 and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 2:1) to give *(5β,8α,9β,10α,13α)-8-ethenyl-15-ethoxy-13-methyl-15-oxopodocarpane-13-carboxylic acid* (**19**; 0.338 g, 90%). M.p. 160.2–161.8°. IR (KBr): 3423, 3084, 2941, 2856, 1722, 1695, 1629, 1462, 1403, 1239, 1183, 1150, 1027, 896. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.11 (*dd*, *J* = 17.6, 10.8, 1 H); 5.05 (*d*, *J* = 17.6, 1 H); 5.01 (*d*, *J* = 11.2, 1 H); 4.08–4.02 (*m*, 2 H); 2.35 (*d*, *J* = 22.0, 1 H); 2.21–2.06 (*m*, 3 H); 1.96–1.39 (*m*, 9 H); 1.24 (*t*, *J* = 7.2, 3 H); 1.17 (*s*, 3 H); 1.13 (*s*, 3 H); 1.10–0.84 (*m*, 5 H); 0.62 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 184.6; 177.3; 140.8; 112.4; 59.8; 58.4; 57.8; 55.3; 45.6; 43.7; 41.0; 40.8; 39.75; 38.2; 38.0; 36.0; 30.0; 28.7; 19.8; 19.1; 18.0; 13.9; 13.4. HR-ESI-MS: 377.2710 ($[M+H]^+$, $C_{23}H_{37}O_4^+$; calc. 377.2692).

Cyclization of **19**. Compound **19** (0.376 g, 1 mmol) was dissolved in CH_2Cl_2 (5 ml), and $BF_3 \cdot OEt_2$ (48% soln. in Et_2O, 0.47 ml, 1.5 mmol) was added dropwise during stirring of the mixture under reflux for 30 h. The soln. was then diluted with H_2O and extracted with CH_2Cl_2, and the combined org. phases were dried (Na_2SO_4), the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 5:1) to give *ethyl (3S,6S,6aS,8aS,9R,12aS,12bS)-dodecahydro-3,6,9,12a-tetramethyl-4-oxo-2*H*-3,6a-methanonaphtho[2,1-c]oxocine-9(6*H*)-carboxylate* (**20**; 0.278 g, 74%). M.p. 118.2–119.6°. IR (KBr): 2957, 2913, 2843, 1714, 1451, 1381, 1238, 1172, 1025. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.32–4.20 (*m*, 1 H); 4.15–4.02 (*m*, 2 H); 2.19 (*d*, *J* = 18.4, 1 H); 2.09–1.54 (*m*, 9 H); 1.46–1.37 (*m*, 3 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.17 (*s*, 3 H); 1.14 (*s*, 3 H); 1.10 (*d*, *J* = 2.8, 3 H); 1.09–0.82 (*m*, 5 H); 0.74 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.0; 175.4; 85.6; 60.5; 57.1; 55.5; 48.7; 44.7; 43.6; 41.8; 39.9; 38.6; 38.4; 37.8; 34.9; 33.6; 28.7; 28.2; 25.6; 19.5; 18.8; 14.5; 13.4. HR-ESI-MS: 399.2534 ($[M+Na]^+$, $C_{23}H_{36}NaO_4^+$; calc. 399.2511).

Treatment of **18** *with* H_2O_2. Compound **18** (0.360 g, 1 mmol) was dissolved in MeOH (5 ml), and then NaOH (0.080 g, 2 mmol) and H_2O_2 (40%, 0.5 ml) were added. After stirring at 65° for 4 h, the mixture was concentrated, and the residue was extracted with CH_2Cl_2 and H_2O. Then, the org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 3:1) to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-hydroxy-13-methylpodocarpan-15-oate* (**22**; 0.261 g, 75%). M.p. 80.1–81.2°. IR (KBr): 3426, 3080, 2933, 2872, 2843, 1718, 1626, 1453, 1388, 1183, 1153, 1031, 905. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.54 (*dd*, *J* = 17.6, 10.8, 1 H); 5.11 (*d*, *J* = 11.2, 1 H); 5.06 (*d*, *J* = 17.6, 1 H); 4.12–4.02 (*m*, 2 H); 2.18–2.08 (*m*, 2 H); 1.96–1.39 (*m*, 11 H); 1.24 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.13 (*s*, 3 H); 1.10–0.86 (*m*, 5 H); 0.70 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 144.1; 111.7; 70.3; 59.9; 58.2; 58.1; 57.7; 43.7; 40.9; 40.5; 40.1; 39.7; 38.1; 38.1; 31.8; 28.7; 19.6; 19.1; 16.7; 14.0; 13.5. HR-ESI-MS: 371.2561 ($[M+Na]^+$, $C_{22}H_{36}NaO_3^+$; calc. 371.2562).

Reduction of **18**. A mixture of **18** (0.360 g, 1 mmol) and $NaBH_4$ (0.057 g, 1.5 mmol) in dry EtOH (10 ml) was stirred at 0° for 10 min. Then, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-(hydroxymethyl)-13-methylpodocarpan-15-oate* as a white powder (**23**; 0.337 g, 96%). M.p. 115.1–116.7°. IR (KBr): 3441, 3069, 2952, 2922, 2847, 1715, 1450, 1381, 1190, 1153. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.51 (*dd*, *J* = 17.6, 10.8, 1 H); 5.13 (*d*, *J* = 17.6, 1 H); 5.08 (*d*, *J* = 11.2, 1 H); 4.12–4.02 (*m*, 2 H); 3.56 (*d*, *J* = 12, 1 H); 3.08 (*d*, *J* = 12, 1 H); 2.14–2.06 (*m*, 2 H); 1.84–1.39 (*m*, 11 H); 1.22 (*t*, *J* = 7.2, 3 H); 1.15 (*s*, 3 H); 1.13–0.85 (*m*, 5 H); 0.84 (*s*, 3 H); 0.66 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 145.2; 110.7; 67.7; 59.6; 58.1; 57.4; 53.1; 43.4; 41.6; 40.5; 39.2; 37.8; 36.4; 34.9; 30.7; 29.0; 28.4; 19.7; 18.8; 17.0; 13.7; 13.3. HR-ESI-MS: 385.2709 ($[M+Na]^+$, $C_{23}H_{38}NaO_3^+$; calc. 385.2719).

Cyclization of **23**. Compound **23** (0.362 g, 1 mmol) was dissolved in CH_2Cl_2 (5 ml), and $BF_3 \cdot OEt_2$ (48% soln. in Et_2O; 0.47 ml, 1.5 mmol) was added dropwise during stirring of the mixture under reflux for 30 h. The soln. was then diluted with H_2O and extracted with CH_2Cl_2, and the combined org. phases were dried (Na_2SO_4), and then the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 5:1) to give *ethyl (3S,6S,6aS,8aS,9R,12aS,12bS)-dodecahydro-3,6,9,12a-tetramethyl-2*H*-3,6a-methanonaphtho[2,1-c]oxocine-9(6*H*)-carboxylate* (**24**; 0.271 g, 75%). M.p. 158.2–159.7°. IR (KBr): 2958, 2921, 2845, 1699, 1626, 1466, 1448, 1239, 1190, 1153, 921, 623. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.11–4.01 (*m*, 2 H); 3.76 (*d*, *J* = 11.2, 1 H); 3.63–3.56 (*m*, 1 H); 3.18 (*d*, *J* = 11.2, 1 H); 2.18–1.89 (*m*, 3 H); 1.82–1.31 (*m*, 11 H); 1.22 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.08 (*d*, *J* = 6.8, 3 H); 1.05–0.83 (*m*, 4 H); 0.81 (*s*,

3 H); 0.68 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 76.5; 71.7; 59.4; 57.8; 56.4; 53.3; 44.4; 42.6; 40.5; 39.8; 37.9; 36.1; 35.2; 31.7; 29.4; 28.4; 22.3; 19.7; 18.9; 17.5; 14.8; 14.3. HR-ESI-MS: 385.2731 ($[M+Na]^+$, $C_{23}H_{38}NaO_3^+$; calc. 385.2719).

Treatment of **23** *with TsCl.* A mixture of **23** (0.362 g, 1 mmol) and TsCl (0.238 g, 1.1 mmol) in pyridine (5 ml) was stirred at r.t. for 12 h. Then, the mixture was filtered, and the filtrate was extracted with CH_2Cl_2 and aq. HCl soln. (5M). The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 5:1) to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-methyl-13-({[(4-methylphenyl)sulfonyl]oxy}methyl)podocarpan-15-oate* (**25**; 0.438 g, 85%). IR (KBr): 3076, 2933, 2872, 2849, 1720, 1598, 1455, 1363, 1180, 959, 844, 666. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 8.0, 2 H); 7.34 (*d*, *J* = 8.0, 2 H); 6.07 (*dd*, *J* = 17.6, 10.8, 1 H); 4.99–4.93 (*m*, 2 H); 4.12–4.01 (*m*, 2 H); 3.95 (*d*, *J* = 9.6, 1 H); 3.57 (*d*, *J* = 9.2, 1 H); 2.92 (*d*, *J* = 28.0, 1 H); 2.44 (*s*, 3 H); 2.13 (*d*, *J* = 13.2, 1 H); 1.99 (*d*, *J* = 13.2, 1 H); 1.83–1.39 (*m*, 11 H); 1.25 (*t*, *J* = 7.2, 3 H); 1.12 (*s*, 3 H); 1.08–0.93 (*m*, 6 H); 0.81 (*s*, 3 H); 0.59 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 144.5; 143.0; 133.0; 130.2; 129.7; 127.9; 127.0; 112.5; 59.9; 58.4; 57.6; 54.9; 43.6; 42.1; 40.4; 39.5; 38.0; 37.9; 35.2; 34.6; 29.7; 28.7; 28.2; 21.6; 19.9; 19.0; 16.9; 14.0; 13.5. HR-ESI-MS: 539.2802 ($[M+Na]^+$, $C_{30}H_{44}NaO_5S^+$; calc. 539.2807).

Treatment of **25** *with* NaN_3. A mixture of **25** (0.516 g, 1 mmol) and NaN_3 (0.130 g, 2 mmol) in DMF (5 ml) was stirred at 80° for 3 h. Then, the mixture was extracted with CH_2Cl_2 and H_2O. The org. layer was concentrated, and the residue was dissolved in THF (5 ml), and then the Ph_3P (0.524 g, 2 mmol) and H_2O (0.05 ml) were added. After stirring at 65° for 3 h, the mixture was concentrated, and the aq. HCl soln. (0.5M) was added to attain pH < 3. The H_2O layer was extracted with Et_2O, the org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the filtrate was concentrated. The residue was purified by CC (SiO_2; PE/AcOEt 1:1) to give *ethyl (5β,8α,9β,10α,13α)-13-(aminomethyl)-8-ethenyl-13-methylpodocarpan-15-oate* (**26**; 0.245 g, 68%). IR (KBr): 3356, 3075, 2948, 2921, 2845, 1721, 1456, 1381, 1191, 1081. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.28 (*dd*, *J* = 17.6, 10.8, 1 H); 5.10 (*d*, *J* = 17.6, 1 H); 5.07 (*d*, *J* = 11.2, 1 H); 4.06–3.96 (*m*, 2 H); 3.26 (*d*, *J* = 10.8, 1 H); 2.88 (*d*, *J* = 10.8, 1 H); 2.18–1.74 (*m*, 4 H); 1.70–1.31 (*m*, 9 H); 1.25 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.13–0.83 (*m*, 5 H); 0.78 (*s*, 3 H); 0.67 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.4; 146.1; 111.7; 62.7; 59.8; 58.4; 57.1; 54.1; 42.4; 41.1; 39.8; 39.2; 36.8; 35.4; 34.4; 31.2; 29.4; 27.1; 20.2; 18.7; 17.4; 14.3; 13.1. HR-ESI-MS: 362.3041 ($[M+H]^+$, $C_{23}H_{40}NO_2^+$; calc. 362.3059).

Treatment of **18** *with* $HONH_2 \cdot HCl$. A mixture of **18** (0.360 g, 1 mmol) and $HONH_2 \cdot HCl$ (0.103 g, 1.5 mmol) in EtOH was stirred in presence of $NaHCO_3$ at 60° for 2 h. Then, the mixture was concentrated under vacuum, and extracted with CH_2Cl_2 and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-[(*E*)-(hydroxyimino)methyl]-13-methylpodocarpan-15-oate* (**27**; 0.363 g, 97%). White powder. M.p. 148.5–149.6°. IR (KBr): 3439, 3070, 2954, 2921, 2855, 1699, 1627, 1448, 1377, 1239, 1190, 1153, 1025, 943, 628. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (*s*, 1 H); 6.10 (*dd*, *J* = 17.6, 10.8, 1 H); 5.05 (*d*, *J* = 10.8, 1 H); 4.98 (*d*, *J* = 17.6, 1 H); 4.09–4.02 (*m*, 2 H); 2.24 (*dd*, *J* = 13.2, 9.6, 1 H); 2.15–2.09 (*m*, 2 H); 1.89–1.40 (*m*, 7 H); 1.26 (*d*, *J* = 13.2, 1 H); 1.20 (*t*, *J* = 7.2, 3 H); 1.14 (*s*, 3 H); 1.10–0.97 (*m*, 5 H); 0.94 (*s*, 3 H); 0.93–0.83 (*m*, 2 H); 0.61 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.4; 159.3; 143.5; 111.2; 59.8; 58.4; 58.2; 57.7; 43.7; 40.9; 39.8; 39.6; 38.1; 38.0; 36.7; 35.4; 29.8; 28.7; 19.8; 19.0; 17.1; 13.9; 13.3. HR-ESI-MS: 376.2848 ($[M+H]^+$, $C_{23}H_{38}NO_3^+$; calc. 376.2852).

Cyclization of **27**. To a soln. of **27** (0.375 g, 1 mmol) in toluene (5 ml), 48% $BF_3 \cdot OEt_2$ (48% soln. in Et_2O, 0.05 ml, 0.17 mmol) was added dropwise, and the mixture was heated under N_2 for 2 h at 118°. H_2O (10 ml) was added to the mixture, which was then neutralized with $NaHCO_3$, and the org. phase was separated and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by CC (PE/AcOEt 2:1) to give *ethyl (3*S*,3a*S*,6a*S*,6b*S*,8a*S*,9*R*,12a*S*,12b*S*)-hexadecahydro-3,9,12a-trimethyl-3,6b-methanonaphtho[2′,1′:3,4]cyclohepta[1,2-c][1,2]oxazole-9-carboxylate* (**28**; 0.356 g, 95%). White powder. M.p. 136.5–138.1°. IR (KBr): 3026, 2956, 2934, 2872, 2855, 1704, 1467, 1382, 1238, 1178, 1149, 1052, 1029, 976, 859. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.16–4.04 (*m*, 2 H); 3.84–3.78 (*m*, 1 H); 3.74–3.70 (*m*, 1 H); 3.30 (*d*, *J* = 7.2, 1 H); 2.90 (*q*, *J* = 6.4, 1 H); 2.17 (*d*, *J* = 13.2, 1 H); 1.83–1.43 (*m*, 8 H); 1.36–1.28 (*m*, 4 H); 1.25 (*t*, *J* = 7.2, 3 H); 1.17 (*s*, 3 H); 1.10 (*dd*, *J* = 12.0, 2.0, 1 H); 1.09–0.97 (*m*, 2 H); 0.95 (*s*, 3 H); 0.93–0.80 (*m*, 2 H); 0.79 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 73.0; 72.7; 59.9; 57.6; 56.3; 52.0;

51.1; 44.9; 43.6; 40.3; 39.9; 39.2; 38.2; 37.8; 35.5; 28.9; 21.7; 21.5; 19.2; 18.9; 14.1; 13.7. HR-ESI-MS: 376.2835 ($[M+H]^+$, $C_{23}H_{38}NO_3^+$; calc. 376.2852).

Treatment of **28** *with MeI*. To a soln. of **28** (0.375 g, 1 mmol) and NaH (0.026 g, 1.1 mmol) in DMF (5 ml), MeI (0.156 g, 1.1 mmol) was added dropwise, and the mixture was heated at 50° for 2 h. The mixture was filtered, and the filtrate was concentrated. The residue was extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by CC (SiO_2; PE/AcOEt 6:1) to give *ethyl (3*S*,3a*S*,6a*S*,6b*S*,8a*S*,9*R*,12a*S*,12b*S*)-hexadecahydro-3,4,9,12a-tetramethyl-3,6b-methanonaphtho[2′,1′:3,4]cyclohepta[1,2-*c*][1,2]oxazole-9-carboxylate* (**29**; 0.330 g, 85%). M.p. 158.6–159.9°. IR (KBr): 2957, 2941, 2859, 1714, 1458, 1384, 1239, 1181, 1150, 1039, 978. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.11–4.02 (*m*, 2 H); 3.92 (*dd*, *J* = 8.4, 8.0, 1 H), 3.58 (*dd*, *J* = 8.4, 3.6, 1 H); 3.13 (*d*, *J* = 7.2, 1 H); 2.92–2.85 (*m*, 1 H); 2.78 (*s*, 3 H); 2.17 (*d*, *J* = 12.4, 1 H); 1.83–1.43 (*m*, 8 H); 1.36–1.28 (*m*, 3 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.12–0.97 (*m*, 3 H); 0.89 (*s*, 3 H); 0.87–0.77 (*m*, 3 H); 0.75 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.5; 79.5; 71.6; 59.8; 57.6; 56.3; 53.2; 52.0; 44.9; 43.6; 41.3; 39.8; 39.2; 38.5; 38.2; 37.6; 34.5; 28.4; 21.9; 20.7; 19.8; 19.2; 13.9; 13.1. HR-ESI-MS: 412.2814 ($[M+Na]^+$, $C_{24}H_{39}NNaO_3^+$; calc. 412.2828).

Treatment of **27** *with* H_2SO_4. To a soln. of **27** (0.375 g, 1 mmol) in acetone (5 ml), a mixture of H_2SO_4 (0.09 ml) and acetone (5 ml) was added dropwise, and the mixture was heated under N_2 for 2 h at 40°. H_2O (10 ml) was added to the mixture, which was then neutralized with $NaHCO_3$, and the org. phase was separated and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by CC (PE/AcOEt 4:1) to give *ethyl (5β,8α,9β,10α,13α)-13-cyano-8-ethenyl-13-methylpodocarpan-15-oate* (**30**; 0.253 g, 71%). White powder. M.p. 124.5–126.1°. IR (KBr): 3097, 2978, 2937, 2852, 2226, 1725, 1634, 1452, 1379, 1225, 1148, 1014, 902, 772. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.54 (*dd*, *J* = 17.6, 10.8, 1 H); 5.19 (*d*, *J* = 10.8, 1 H); 5.12 (*d*, *J* = 17.6, 1 H); 4.12–4.01 (*m*, 2 H); 2.22–2.16 (*m*, 3 H); 1.76–1.33 (*m*, 10 H); 1.29 (*s*, 3 H); 1.22 (*t*, *J* = 7.2, 3 H); 1.15 (*s*, 3 H); 1.11–0.85 (*m*, 5 H); 0.84 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.2; 141.4; 125.5; 112.3; 59.9; 58.1; 57.8; 57.6; 55.2; 52.9; 43.7; 40.5; 39.7; 39.6; 38.0; 31.5; 29.6; 28.6; 26.2; 19.6; 18.0; 13.9; 13.5. HR-ESI-MS: 380.2558 ($[M+Na]^+$, $C_{23}H_{35}NNaO_2^+$; calc. 380.2566).

Treatment of **18** *with* $PhNHNH_2$. To a soln. of **18** (0.360 g, 1 mmol) in EtOH (10 ml), $PhNHNH_2$ (0.10 ml, 1.00 mmol) and 2 drops of glacial AcOH were added. The mixture was stirred for 2 h at r.t. The soln. was then poured into H_2O (10 ml), and the white precipitate was filtered, washed with H_2O, and dried. The product was recrystallized from $CHCl_3$/light PE to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-methyl-13-[(*E*)-(2-phenylhydrazinylidene)methyl]podocarpan-15-oate* (**31a**; 0.427 g, 95%). M.p. 132.1–133.7°. IR (KBr): 3297, 3134, 2949, 2925, 1720, 1698, 1601, 1510, 1452, 1396, 1256, 1185, 1114, 749. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.22 (*t*, *J* = 8.0, 2 H); 6.98 (*d*, *J* = 8.0, 2 H); 6.79 (*t*, *J* = 7.2, 1 H); 6.66 (*s*, 1 H); 6.08 (*dd*, *J* = 17.6, 11.2, 1 H); 4.94 (*s*, 1 H); 4.91 (*d*, *J* = 4.4, 1 H); 4.06–3.88 (*m*, 2 H); 2.49 (*dd*, *J* = 12.8, 2.0, 1 H); 2.14–2.10 (*m*, 2 H); 1.91–1.44 (*m*, 8 H); 1.33–1.26 (*m*, 2 H); 1.20 (*t*, *J* = 7.2, 3 H); 1.14 (*s*, 3 H); 1.12–0.96 (*m*, 5 H); 0.93 (*s*, 3 H); 0.89–0.84 (*m*, 1 H); 0.56 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.9; 154.6.0; 146.3; 140.7; 129.6; 129.6; 120.7; 118.5; 118.5; 112.3; 61.9; 59.9; 58.1; 53.7; 43.8; 43.4; 40.2; 40.1; 38.3; 37.9; 37.8; 36.6; 29.1; 22.5; 21.8; 21.3; 19.0; 14.1; 12.5. HR-ESI-MS: 473.3138 ($[M+Na]^+$, $C_{29}H_{42}N_2NaO_2^+$; calc. 473.3144).

Treatment of **18** *with 4-Nitrophenylhydrazine.* To a soln. of **18** (0.360 g, 1 mmol) in EtOH (10 ml), 4-nitrophenylhydrazine (0.154 g, 1.00 mmol), and 2 drops of glacial AcOH were added. The mixture was stirred for 2 h at r.t. The soln. was then poured into H_2O (10 ml), and the white precipitate was filtered, washed with H_2O, and dried. The product was recrystallized from $CHCl_3$/light PE to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-methyl-13-{(*E*)-[2-(4-nitrophenyl)hydrazinylidene]methyl}podocarpan-15-oate* (**31b**; 0.420 g, 85%). M.p. 205.6–206.9°. IR (KBr): 3312, 3088, 2944, 2847, 1702, 1593, 1319, 1270, 1167, 1104, 906, 841. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.14 (*d*, *J* = 9.2, 2 H); 7.61 (*s*, 1 H); 6.97 (*d*, *J* = 9.2, 2 H); 6.81 (*s*, 1 H); 6.02 (*dd*, *J* = 18.0, 10.8, 1 H); 4.98 (*s*, 1 H); 4.94 (*d*, *J* = 3.2, 1 H); 4.06–3.98 (*m*, 2 H); 2.51–2.44 (*m*, 1 H); 2.12 (*t*, *J* = 12.4, 2 H); 1.86–1.31 (*m*, 9 H); 1.18 (*t*, *J* = 7.2, 3 H); 1.14 (*s*, 3 H); 1.12–0.83 (*m*, 4 H); 0.96 (*s*, 3 H); 0.92–0.83 (*m*, 4 H); 0.57 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 153.0; 150.3; 144.3; 139.4; 126.2; 126.2; 111.0; 111.0; 110.8; 59.8; 58.5; 58.1; 57.7; 43.7; 40.9; 39.9; 39.6; 38.1; 37.3; 35.3; 29.8; 29.6; 28.7; 19.8; 19.0; 17.1; 13.9; 13.4. HR-ESI-MS: 518.2996 ($[M+Na]^+$, $C_{29}H_{39}N_3NaO_4^+$; calc. 518.2995).

Cyclization of **31a**. To a soln. of **31a** (0.450 g, 1 mmol) in toluene (5 ml), 48% $BF_3 \cdot OEt_2$ (48% soln. in Et_2O, 0.05 ml, 0.17 mmol) was added dropwise, and the mixture was heated under a N_2 atmosphere for 2 h at 118°. H_2O (10 ml) was added to the mixture, which was then neutralized with $NaHCO_3$, and the org. phase was separated and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by CC (PE/AcOEt 2:1) to give *ethyl (3*S*,6b*S*,8a*S*,9*R*,12a*S*,12b*S*)-1,3,5,7,8,8a,9,10,11,12,12a,12b-dodecahydro-3,9,12a-trimethyl-5-phenyl-2*H*-3,6b-methanonaphtho[2′,1′:3,4]cyclohepta[1,2-*c*]pyrazole-9-carboxylate* (**32**; 0.374 g, 84%). White powder. M.p. 61.9–63.4°. IR (KBr): 3113, 2949, 2847, 1720, 1598, 1572, 1506, 1381, 1150, 1033, 948, 756, 690. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.61 (*d*, *J* = 8.0, 2 H); 7.50 (*s*, 1 H); 7.39 (*t*, *J* = 8.0, 2 H); 7.17 (*t*, *J* = 7.2, 1 H); 4.20–4.08 (*m*, 2 H); 2.19 (*d*, *J* = 13.6, 1 H); 2.06–1.92 (*m*, 4 H); 1.77–1.40 (*m*, 9 H); 1.35 (*s*, 3 H); 1.30 (*t*, *J* = 7.2, 3 H); 1.23 (*s*, 3 H); 1.20–0.86 (*m*, 4 H); 0.59 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 167.0; 140.9; 130.7; 129.2; 129.2; 125.0; 120.7; 118.5; 118.5; 65.3; 59.9; 57.1; 53.5; 43.8; 43.4; 40.2; 40.1; 38.3; 37.9; 37.8; 36.6; 29.1; 22.5; 21.8; 21.3; 19.0; 14.1; 12.5. HR-ESI-MS: 447.3009 ($[M+H]^+$, $C_{29}H_{39}N_2O_2^+$; calc. 447.3012).

Cyclization of **31b**. To a soln. of **31b** (0.450 g, 1 mmol) in toluene (5 ml), 48% $BF_3 \cdot OEt_2$ (48% soln. in Et_2O, 0.05 ml, 0.17 mmol) was added dropwise, and the mixture was heated under N_2 for 2 h at 118°. H_2O (10 ml) was added to the mixture, which was then neutralized with $NaHCO_3$, and the org. phase was separated and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by CC (PE/AcOEt 2:1) to give *ethyl (3*S*,6a*R*,6b*S*,8a*S*,9*R*,12a*S*,12b*S*)-1,3,5,6,6a,7,8,8a,9,10,11,12,12a,12b-tetradecahydro-3,9,12a-trimethyl-5-(4-nitrophenyl)-2*H*-3,6b-methanonaphtho[2′,1′:3,4]cyclohepta[1,2-*c*]pyrazole-9-carboxylate* (**33**; 0.406 g, 75%). White powder. M.p. 186.8–188.7°. IR (KBr): 3298, 3110, 2951, 2849, 1720, 1619, 1590, 1516, 1333, 1275, 1140, 920. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.92 (*s*, 1 H); 9.11 (*d*, *J* = 2.4, 1 H); 8.29 (*d*, *J* = 9.6, 1 H); 7.91 (*d*, *J* = 9.6, 1 H); 7.45 (*s*, 1 H); 4.11–4.02 (*m*, 2 H); 2.41–2.33 (*m*, 1 H); 2.01–1.62 (*m*, 9 H); 1.56–1.28 (*m*, 6 H); 1.23 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.06 (*s*, 3 H); 1.04–0.83 (*m*, 4 H); 0.71 (*t*, *J* = 7.2, 3 H); 0.69 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.2; 158.9; 145.2; 137.6; 129.9; 128.7; 123.5; 116.4; 59.8; 59.5; 58.1; 49.1; 43.7; 40.5; 38.7; 38.4; 38.0; 38.0; 37.7; 36.4; 30.5; 28.7; 20.8; 19.3; 19.1; 17.4; 14.8; 14.0; 7.7. HR-ESI-MS: 565.3013 ($[M+Na]^+$, $C_{29}H_{42}N_4NaO_6^+$; calc. 565.3002).

Treatment of **23** *with* m-*CPBA*. A mixture of **23** (0.362 g, 1 mmol) and *m*-CPBA (0.258 g, 1.5 mmol) in $CHCl_3$ (5 ml) was stirred at 0° for 5 h, and then the mixture was poured into H_2O and neutralized with aq. $NaHCO_3$ soln. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by CC (SiO_2; PE/AcOEt 2:1) to give *ethyl (3*S*,6*R*,6a*S*,8a*S*,9*R*,12a*S*,12b*S*)-dodecahydro-6-(hydroxymethyl)-3,9,12a-trimethyl-2*H*-3,6a-methanonaphtho[2,1-*c*]oxocine-9(6*H*)-carboxylate* (**35**; 0.293 g, 78%). M.p. 85.5–86.7°. IR (KBr): 3576, 2982, 2928, 2846, 1716, 1459, 1380, 1328, 1235, 1179, 1149, 1023, 969. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.16–4.04 (*m*, 2 H); 3.87 (*d*, *J* = 8.4, 2 H); 3.71 (*d*, *J* = 9.2, 1 H); 3.28 (*dd*, *J* = 10.4, 2.2, 1 H); 3.22 (*d*, *J* = 8.0, 1 H); 2.14 (*d*, *J* = 13.6, 1 H); 2.09–2.04 (*m*, 1 H); 1.87–1.34 (*m*, 9 H); 1.27 (*t*, *J* = 7.2, 3 H); 1.24–1.15 (*m*, 2 H); 1.14 (*s*, 3 H); 1.08–0.80 (*m*, 5 H); 0.72 (*s*, 3 H); 0.66 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 89.9; 79.8; 64.7; 59.9; 59.6; 58.1; 57.2; 43.6; 40.5; 39.7; 38.6; 38.0; 36.7; 36.2; 31.9; 28.6; 25.5; 22.3; 21.0; 19.3; 14.1; 14.0. HR-ESI-MS: 399.2502 ($[M+Na]^+$, $C_{23}H_{36}NaO_4^+$; calc. 399.2511).

Cyclization of Compound **18**. A mixture of **18** (0.360 g, 1 mmol), $NaIO_4$ (0.319 g, 1.5 mmol), and NaBr (0.153 g, 1.5 mmol) in glacial AcOH (10 ml) was stirred at 70° for 8 h, then, the mixture was concentrated under vacuum, and extracted with H_2O and $CHCl_3$. The org. layer was washed with aq. $Na_2S_2O_4$ soln. and sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by CC (SiO_2; PE/AcOEt 4:1) to give *ethyl (3*S*,4*S*,7*R*,7a*S*,9a*S*,10*R*,13a*S*,13b*S*)-tetradecahydro-3,10,13a-trimethyl-2*H*-4,7-epoxy-3,7a-methanonaphtho[2,1-*d*]oxonine-10-carboxylate* (**37**; 0.245 g, 65%). M.p. 83.3–84.5°. IR (KBr): 2945, 2929, 1725, 1464, 1377, 1226, 1156, 989. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.95 (*s*, 1 H); 4.74–4.66 (*m*, 1 H); 4.14–4.06 (*m*, 2 H); 3.87 (*d*, *J* = 7.2, 1 H); 3.55–3.51 (*m*, 1 H); 2.18–2.13 (*m*, 2 H); 1.88–1.44 (*m*, 11 H); 1.26 (*t*, *J* = 7.2, 3 H); 1.16 (*s*, 3 H); 1.15–1.11 (*m*, 5 H); 0.91 (*s*, 3 H); 0.76 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.2; 108.1; 78.8; 65.7; 60.0; 57.9; 57.9; 44.6; 43.7; 39.6; 38.1; 37.9; 37.2; 36.7; 35.0; 29.7; 28.8; 24.6; 21.6; 19.7; 19.1; 14.1; 13.3. HR-ESI-MS: 379.2840 ($[M+H]^+$, $C_{23}H_{39}O_4^+$; calc. 379.2848).

Reduction of **38**. A mixture of **38** (0.435 g, 1 mmol) and $NaBH_4$ (0.057 g, 1.5 mmol) in dry EtOH (10 ml) was stirred at 0° for 1 h. Then, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated

under vacuum. The residue was purified by CC (SiO_2; PE/AcOEt 4:1) to give *ethyl (5β,8α,9β,10α,13α)-8-ethenyl-13-methyl-13-[(phenylamino)methyl]podocarpan-15-oate* (**39**; 0.419 g, 96%). M.p. 57.5–59.1°. IR (KBr): 3422, 3063, 2938, 2843, 1721, 1595, 1486, 1452, 1379, 1149, 1093, 963, 754, 691. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (*t*, *J* = 8.0, 2 H); 6.65 (*t*, *J* = 7.2, 1 H); 6.56 (*d*, *J* = 7.6, 2 H); 6.40 (*dd*, *J* = 17.6, 11.2, 1 H); 5.10 (*d*, *J* = 17.6, 1 H); 5.01 (*d*, *J* = 11.2, 1 H); 4.12–4.01 (*m*, 2 H); 2.98–2.92 (*m*, 2 H); 2.17–2.11 (*m*, 2 H); 1.87–1.41 (*m*, 10 H); 1.21 (*t*, *J* = 7.2, 3 H); 1.15 (*s*, 3 H); 1.12–0.87 (*m*, 6 H); 0.85 (*s*, 3 H); 0.65 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.4; 149.2; 144.0; 129.1; 129.1; 116.8; 113.1; 113.1; 111.0; 59.8; 58.8; 57.8; 54.8; 51.0; 43.7; 41.6; 40.8; 39.6; 38.5; 38.1; 34.6; 30.2; 29.6; 28.7; 19.9; 19.1; 17.3; 14.0; 13.6. HR-ESI-MS: 438.3374 ($[M+H]^+$, $C_{29}H_{44}NO_2^+$; calc. 438.3372).

Antibacterial Activity Assay. The bacteria strains were *Staphylococcus aureus* CMCC(B)26003, *Bacillus subtilis* CMCC(B)63501, and *Shigella flexneri* 626. All tested bacteria strains were purchased from Henan Provincial Institute of Food and Drug Control except *Shigella flexneri* 626, a multidrug-resistant strain separated from clinical studies. For the determination of the antibacterial susceptility, yeast extract (*Oxoid*, USA), tryptone (*Oxoid*, USA), and *Mueller–Hinton* Broth (*MHB*, *Beijing Aoboxing*, China) were used.

Minimum Inhibitory Concentration (*MIC*) *Measurements.* Each tested compound was dissolved in DMSO before serial two-fold dilution into the desired testing concentration ranges using sterile liquid medium. DMSO was used for solvent control test, and the final concentration of DMSO was 2% in all the tested samples. The seed was cultured in *Shigella flexneri* 626 in *MHB* culture medium and others in *Luria–Bertani* (*LB*) culture medium, until containing 10^9 colony forming units (cfu) per ml. All media, sterilized by autoclave at 121° for 20 min, were used to dilute microorganism in the exponential-growth phase, until the final concentration of microorganism was 10^5 cfu/ml in the 96-well plates, and then inoculated to the 96-well plates and mixed with the compound to be tested. Every microplate had a negative control and a blank without bacterium, and a sample blank. The *MIC* value was defined as the lowest concentration of tested compounds, allowing no visible growth of test-strain bacteria after an incubation at 37° for 6 h. Absorbance was measured by *ELISA* reader (*Bio-Tek Instruments*, *Microplate Autoreader*, *power waveX*) at 450 nm.

X-Ray Crystallographic Analysis. X-Ray crystal data of compounds **33** and **37** were collected by a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å). The structure was solved by the direct methods and refined with a full-matrix least-squares method.

Crystal Data for Compound **33**. $C_{30}H_{39}N_2O_4$, M_r 491.63, orthorhombic, space group $P2_12_12_1$, a = 7.6600(15), b = 21.257(4), c = 32.780(7), V = 5337.6(18) Å^3, Z = 8, μ(MoK_α) = 0.081 cm^{-1}, $F(000)$ = 2120, D_c = 1.224 g/cm^3, crystal dimensions: 0.20 × 0.18 × 0.17 mm. A total of 15417 reflections (5091 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 55°, and 4289 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0619 and 0.1381, resp. The maximum and minimum peaks in the difference map were 0.195 and −0.232 e Å^{-3}, resp. The data have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-714716.

Crystal Data for Compound **37**. $C_{23}H_{36}O_4$, M_r 376.52, orthorhombic, space group $P2_12_12_1$, a = 8.9274(18), b = 9.1642(18), c = 25.500(5), V = 2086.2(7) Å^3, Z = 4, μ(MoK_α) = 0.080 cm^{-1}, $F(000)$ = 824, D_c = 1.199 g/cm^3, crystal dimensions: 0.20 × 0.18 × 0.17 mm. A total of 6333 reflections (2147 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 51°, and 1891 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0680 and 0.1666, resp. The maximum and minimum peaks in the difference map were 0.257 and −0.259 e Å^{-3}, resp. The data have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-705231.

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