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ORIGINAL ARTICLE

Four New Phloroglucinol-Terpene Adducts from the Leaves of *Myrciaria cauliflora*

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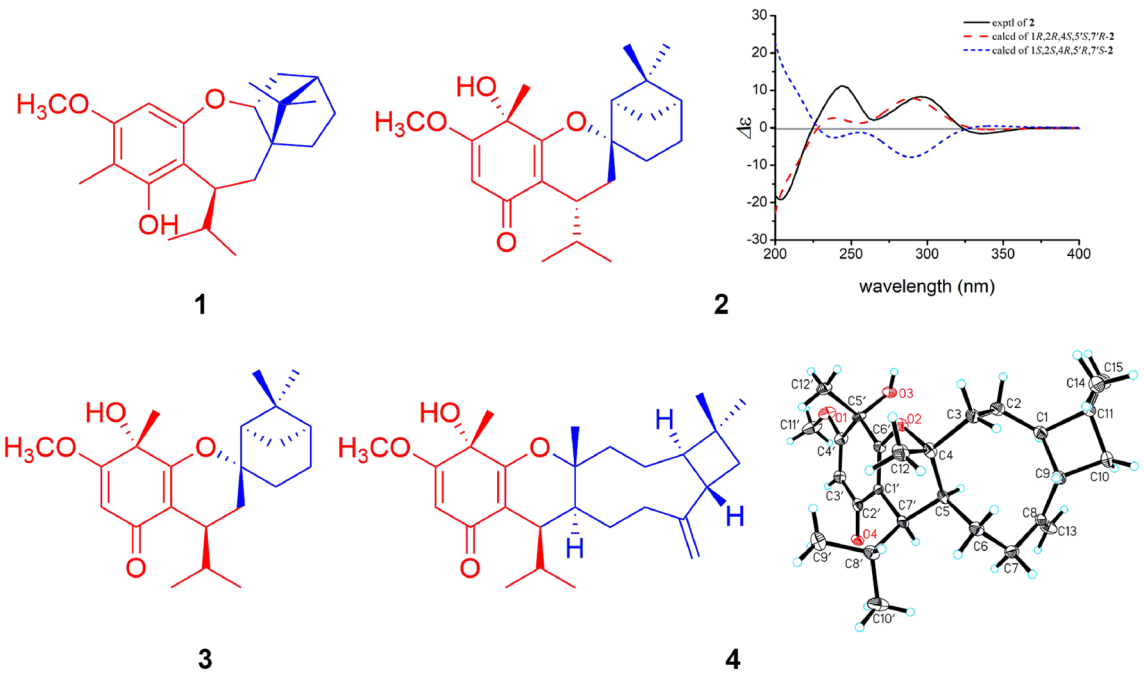
Abstract

Myrcauones A–D (**1**–**4**), four new phloroglucinol–terpene adducts were isolated from the leaves of *Myrciaria cauliflora*. Their structures with absolute configurations were elucidated by combination of spectroscopic analysis, single crystal X-ray diffraction, and electronic circular dichroism (ECD) calculations. Compound **1** was a rearranged isobutylphloroglucinol–pinene adduct featuring an unusual 2,3,4,4a,10,11-hexahydro-1*H*-3,11a-methanodibenzo[*b*,*f*]oxepin backbone. Compound **4** showed moderate antibacterial activity against Gram-positive bacteria including multiresistant strains.

Graphic Abstract



Keywords *Myrciaria cauliflora* · Phloroglucinol–terpene adducts · Antibacterial activity

1 Introduction

The plant *Myrciaria cauliflora* is an evergreen shrub and widely distributed in southern and central Brazil [1]. This plant has been traditionally used as a folk medicine to treat asthma, diarrhea, and gastrointestinal diseases [2, 3].

Ming Chen and Jia-Qing Cao contributed equally to this work.

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Extended author information available on the last page of the article

Previous phytochemical investigations on this plant only reported essential oils and flavonoids [4–6]. As a part of our efforts to search for structural unique and bioactive constituents from Myrtaceae plants [7–10], four new phloroglucinol–terpene adducts, myrcauones A–D (**1**–**4**), were isolated from the leaves of *M. cauliflora*. Their structures and absolute configurations were determined by means of 1D and 2D NMR spectroscopy, X-ray diffraction analysis, and electronic circular dichroism (ECD) calculations. Compound **1** is a rearranged isobutylphloroglucinol–pinene adduct featuring an unusual 2,3,4,4a,10,11-hexahydro-1*H*-3,11a-methanodibenzo[*b*,*f*]oxepin backbone. All isolates were evaluated for their antibacterial activities. Herein, we describe the isolation, structural elucidation, and antibacterial activities of these myrcauones A–D (**1**–**4**).

2 Results and Discussion

2.1 Structural Elucidation

Compound **1** was obtained as yellow gum. The molecular formula of **1** was established as $C_{22}H_{32}O_3$ by its HRESIMS data (*m*/*z* 345.2423 $[M+H]^+$, calcd for $C_{22}H_{33}O_3$: 345.2424). The UV spectrum displayed absorption maximum at 206 nm. The IR spectrum showed characteristic absorptions for hydroxyl group (3475 cm^{-1}) and aromatic ring (1611 and 1488 cm^{-1}). The ^1H NMR spectrum of **1** suggested the presence of an olefinic proton [δ_H 6.23 (1H, s, H-5′)], a hydroxyl group [δ_H 4.75 (1H, s, 2′-OH)], a methoxy group [δ_H 3.76 (3H, s, H_3-11′)], an isopropyl moiety [δ_H 1.97 (1H, m, H-8′), 0.52 (3H, d, J = 6.8 Hz, H_3-9′), and 1.03 (3H, d, J = 6.8 Hz, H_3-10′)], and three tertiary methyls [δ_H 2.06 (3H, s, H_3-12′), 0.90 (3H, s, H_3-9), and 0.79 (3H, s, H_3-8)]. The ^{13}C NMR and DEPT spectra of **1** exhibited 22 carbon signals including 7 quaternary carbons (5 olefinic ones), 5 methines (an oxygenated and an olefinic ones), 4 methylenes, and 6 methyls (an oxygenated one). The aforementioned data implied that **1** could be an isobutylphloroglucinol–monoterpene adduct (Fig. 1) [11].

A comparison of the NMR data of **1** with those of melaleucadine A [11] indicated the presence of an uncommon rearranged *β*-pinene unit (part **1a**), which was further confirmed by the two spin systems (H-2 to H-6 and H-10 to H-9′/H-10′) in its ^1H–^1H COSY spectrum (Fig. 2) and the HMBC correlations between H_3-8/H_3-9 and C-1/C-4/C-7 and between H_2-10 and C-1/C-2/C-6/C-7. In addition, the HMBC correlations between H-5′ and C-1′/C-3′/C-4′/C-6′, between H_3-12′ and C-2′/C-3′/C-4′, between H_3-11′ and C-4′, and between H-7′ and C-1′/C-2′/C-6′, allowed the establishment of an isobutylphloroglucinol moiety (part **1b**). Furthermore, the HMBC correlations between H-7′ and C-1, and between H_2-10 and C-1′ defined the connection of **1a** and **1b** via C-7′–C-10 bond. Finally, the leftover oxygen atom was

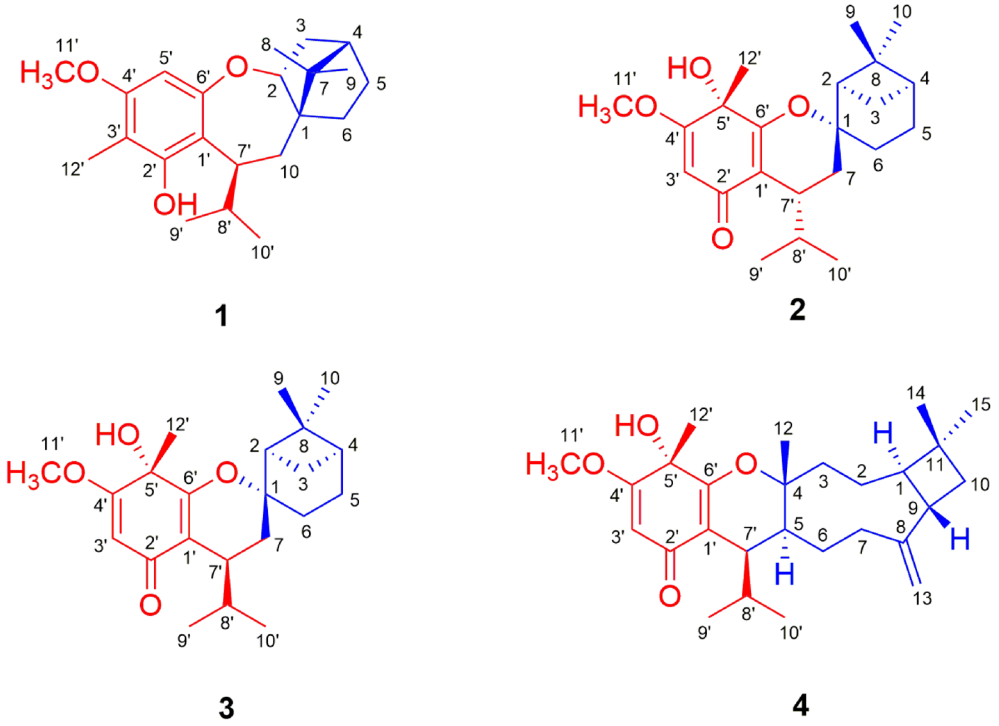

Fig. 1 Chemical structures of **1**–**4**

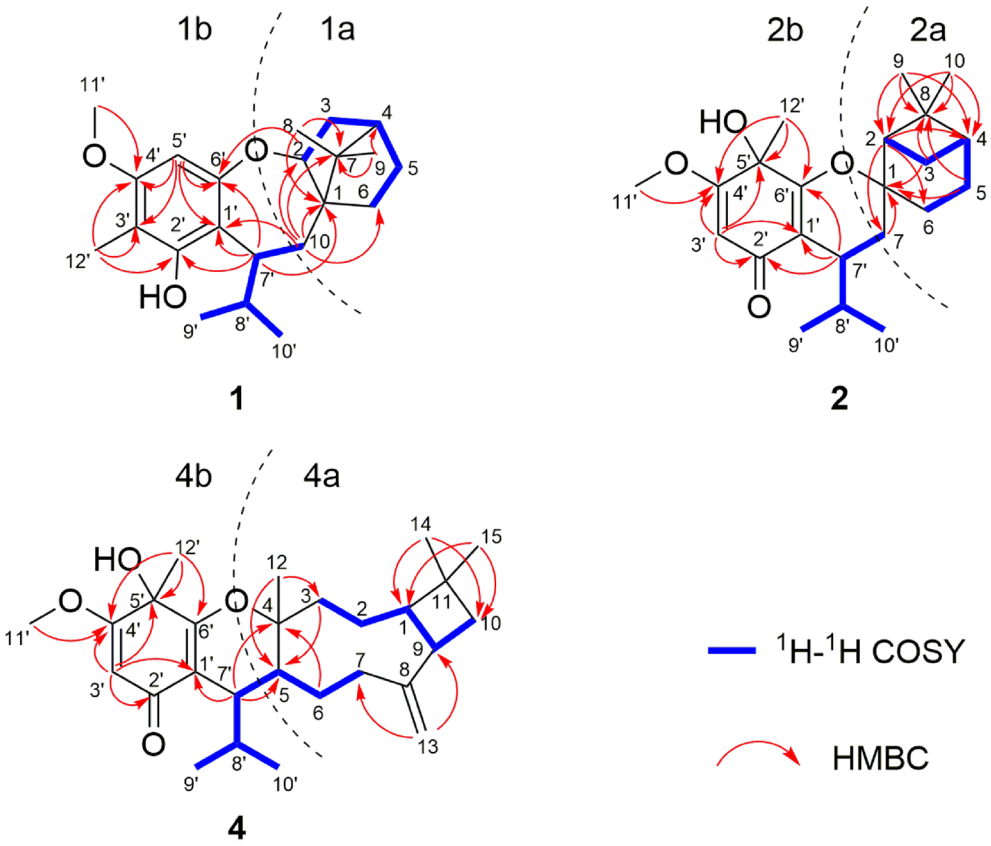

Fig. 2 Key ^{1}H–^{1}H COSY and HMBC correlations of **1**, **2**, **4**

anticipated to connect C-2 (δ_C 88.6) with C-6′ (δ_C 159.4) to form an uncommon 2,3,4,5-tetrahydrooxepine ring on the basis of the HMBC correlation between H-2 and C-6′ as well as the molecular formula information.

The relative configuration of **1** was established by a NOESY experiment (Fig. 3). The NOE correlations between H-10β and H-2/Me-8/H-8′ indicated that H-2, Me-8, and the isopropyl group (C-9′/8′/10′) were β-oriented. Meanwhile, the correlations between H-10α and H-6a/H-7′ as well as between H-6a and Me-9 suggested that Me-9 and H-7′ were α-oriented. To determine the absolute configurations of **1**, a comparison of its experimental and calculated ECD data was performed. The experimental ECD spectrum of **1** exhibited negative Cotton effects at 211 ($\Delta\varepsilon+6.2$) and 277 ($\Delta\varepsilon+0.7$) nm, and a negative one at 238 ($\Delta\varepsilon-0.5$) nm, which were similar with those in the calculated CD spectrum for 1*R*,2*R*,4*S*,7′*S*-isomer (Fig. 4). Thus, the absolute configuration of **1** was determined as 1*R*, 2*R*, 4*S*, and 7′*S*.

The molecular formula of compound **2** was determined as $C_{22}H_{32}O_4$ by its HRESIMS data (*m/z* 361.2386 $[M+H]^+$, calcd for $C_{22}H_{33}O_4$: 361.2373). The IR spectrum showed absorptions of hydroxyl (3357 cm^{-1}), carbonyl group (1656 cm^{-1}), and double bonds (1605 and 1462 cm^{-1}). The ^{1}H NMR data (Table 1) for an olefinic proton [δ_H 5.33 (1H, s, H-3′)], a methoxy group [δ_H 3.75 (3H, s, H_3-11′)], an isopropyl moiety [δ_H 2.86 (1H, m, H-8′), 0.61 (3H, d, $J=6.8$ Hz, H_3-9′), and 0.93 (3H, d, $J=6.8$ Hz, H_3-10′)], and three tertiary methyls [δ_H 1.51 (3H, s, H_3-12′), δ_H 1.23 (3H, s, H_3-9), and 0.96 (3H, s, H_3-10)] indicated that **2** could be an isobutylphloroglucinol–monoterpene adduct [12].

The ^{1}H–^{1}H COSY spectrum of **2** revealed the presence of two spin systems (H-2 to H-6 and H-7 to H-9′/H-10′) (Fig. 2). Accordingly, a β-pinene unit (part **2a**) could be established by the HMBC correlations between H-2 and C-4/C-6/C-7, between H_2-3/H_2-5 and C-1/C-8, and between H_3-9/H_3-10 and C-2/C-4/C-8. Furthermore, comparison of its NMR data with those of the known compound baeckfrutone H indicated the existence of an isobutyrylphloroglucinol moiety (part **2b**), which was further confirmed by the HMBC correlations between H-3′ and C-1′/C-2′/C-4′/C-5′, between H_3-12′ and C-4′/C-5′/C-6′, between H_3-11′ and C-4′, and between H-7′ and C-1′/C-2′/C-6′ [12]. The closure mode of dihydropyran ring which connected the two fragments (**2a** and **2b**) could be deduced on the basis of the molecular formula information and the downfield chemical shift at C-1 (δ_C 85.4).

In the NOESY spectrum, the correlations between H-3b and H-2/H-4/Me-9, between H-2 and H-7′, between H-7β

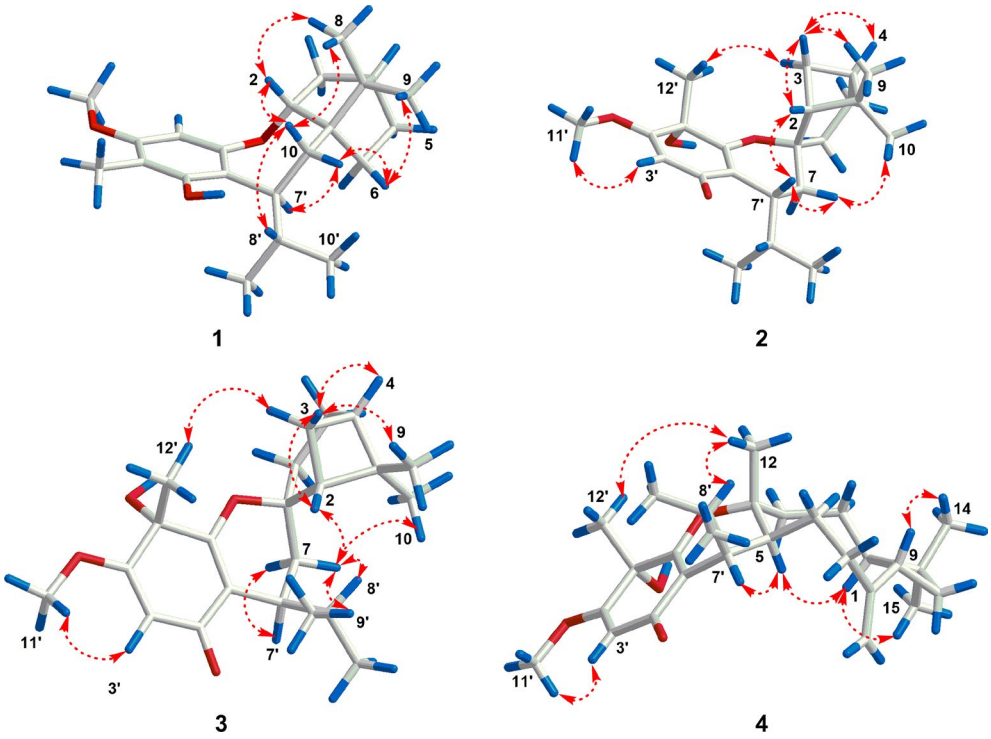

Fig. 3 Key NOESY correlations of **1**–**4**

and Me-10/H-7′, as well as between H-3a and Me-12′ indicated that these protons were all *β*-oriented (Fig. 3). The absolute configuration of **2** was determined by ECD calculation. The experimental ECD spectrum of **2** displayed positive cotton effects at 244 (+ 11.7) and 296 (+ 8.1) nm, and negative ones at 203 (− 19.8) and 337 (− 1.8) nm, which were similar to those in the calculated spectrum for 1*R*,2*R*,4*S*,5′*S*,7′*R*-**2** (Fig. 4). Thus, the absolute configuration of **2** was identified as 1*R*, 2*R*, 4*S*, 5′*S*, 7′*R*.

Compound **3** possessed the same molecular formula as **2** on the basis of its HRESIMS data (*m*/*z* 361.2391 $[M+H]^+$, calcd for $C_{22}H_{33}O_4$, 361.2373). Analyses of the NMR data of **3** and comparison with those of **2** indicated that these two compounds had the same planar structure but differed in their relative configurations. The downfield chemical shifts of C-2 (from δ_C 45.2 to 53.0) and C-7 (from δ_C 32.7 to 33.7), as well as the upfield chemical shifts of C-6 (from δ_C 30.8 to 27.4), C-7′ (from δ_C 33.6 to 32.2) revealed that **3** was a C-7′ epimer of **2**. This deduction was confirmed by the NOE correlations between H-3b and H-2/H-4/Me-9, between H-2 and H-7*β*, between H-7*β* and H-8′/Me-9′/Me-10, between H-3a and Me-12′, and between H-7*α* and H-7′ (Fig. 3). Finally, the agreement of the ECD curve of **3** with those of the calculated 1*R*,2*R*,4*S*,5′*S*,7′*S*-**3** (Fig. 4) allowed the assignment its absolute configuration.

Compound **4** was obtained as colorless blocks. Its molecular formula was determined to be $C_{27}H_{40}O_4$ by its HRESIMS data at *m*/*z* 429.2996 $[M+H]^+$ (calcd for $C_{27}H_{41}O_4$: 429.2999). Comparison of the NMR data of **4** with those of **3** suggested that they had the same isobutyrylphloroglucinol moiety (part **4b**) (Fig. 2). The remaining NMR signals for 15 carbons implied the presence of a sesquiterpene moiety. The spin systems (from H-3 to H-10 and from H-7 to H-9′/H-10′) established by the ^1H–^1H COSY spectrum as well as the HMBC correlations between H_3-14/ H_3-15 and C-1/C-10, between H_2-13 and C-7/C-9, and between H_3-12 and C-3/C-5 indicated the presence of a caryophyllene unit (part **4a**) (Fig. 2), which was further confirmed by comparison of the NMR data of **4** with those of myrtucommulone K [10]. Furthermore, the HMBC correlations between H-7′ and C-4/C-5/C-1′ indicated the connection of parts **4a** and **4b** via a C-5 and C-7′ bond. Finally, the closure mode of dihydropyran ring which connected the two fragments (**4a** and **4b**) could be deduced on the basis of the molecular formula information and the downfield chemical shift at C-4 (δ_C 85.8).

In the NOESY spectrum, the correlations between H-5 and H-1/H-7′, between H-1 and Me-15, between H-9 and Me-14, as well as between Me-12 and H-8′/Me-12′ suggested that the relative configurations of C-1, C-4, C-5, C-9, and C-7′ were identical to those of myrtucommulone K (Fig. 3). Additionally, the structure and absolute configuration of **4** was unambiguously determined by X-ray crystallographic analysis using Cu K*α* radiation with the Flack

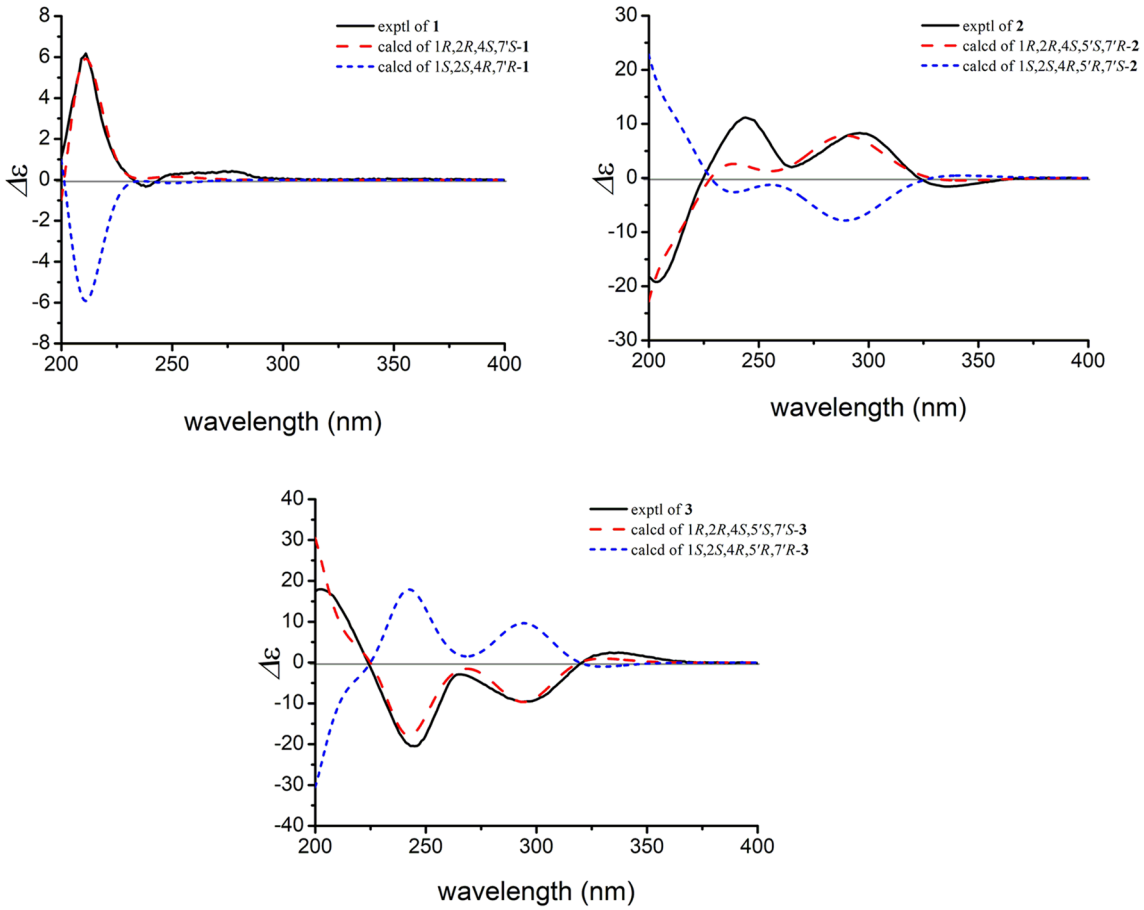

Fig. 4 Calculated and experimental ECD spectra of **1**–**3**

parameter [0.08 (13)] (Fig. 5). Hence, the absolute configuration of **4** was defined as 1*R*, 4*R*, 5*S*, 9*S*, 5′*S* and 7′*R*.

2.2 Bioactivity Evaluation

The antibacterial activities of compounds **1**–**4** against Gram-positive strains *Staphylococcus aureus* ATCC 43300 (MRSA), *S. aureus* ATCC 700699 (VISA), *S. aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212 and Gram-negative strains *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were measured by broth microdilution method. As a result, compound **4** exhibited moderate antibacterial activity against all Gram-positive strains with MIC value of 32 μg/mL (Table 2).

3 Experimental

3.1 General Methods

Melting points were obtained on a Buchi melting point B-545 apparatus (Buchi Instrument, Switzerland) and are uncorrected. Optical rotations were measured on a JASCO P-2000 digital polarimeter (Jasco Co., Ltd., Tokyo, Japan) at room temperature. IR spectra were determined on a JASCO FT/IR-4600 plus Fourier transform infrared spectrometer (Jasco Co., Ltd., Tokyo, Japan) using KBr pellets. UV spectra were recorded on a JASCO V-550 UV/Vis spectrophotometer (Jasco Co., Ltd., Tokyo, Japan). CD spectra were obtained on a ChirascanqCD (Applied Photophysics Ltd., Surrey, UK). HRESIMS spectra were acquired on an Agilent 6210 LC/MSD TOF mass spectrometer (Agilent Technologies, CA, USA). NMR spectra were measured on Bruker AV-500 or AV-400 spectrometers (Bruker, Switzerland) with TMS as internal standard, and chemical shifts were denoted in δ values (ppm). X-ray crystallographic analyses were carried out on an Agilent Gemini S Ultra CCD diffractometer with Cu Kα radiation ($\lambda = 1.54178$ Å). Silica gel (200–300

Table 1 ^{1}H and ^{13}C NMR data of **1–4** in $CDCl_3$ (δ in ppm, J in Hz)

Nos.	**1**[a]		**2**[b]		**3**[b]		**4**[a]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	–	52.5	–	85.4	–	84.7	1.53	58.1
2	3.85 (ddd 10.8, 4.8, 2.4)	88.6	2.22 (t, 5.2)	45.2	2.10 (t, 5.2)	53.0	1.56	23.6
3	α 1.21 (dd 13.6, 4.4)	35.7	a 1.53	26.4	a 1.67 (brd, 10.2)	26.5	α 1.48	46.0
	β 2.28 m		b 2.12		b 2.33		β 2.06	
4	1.62	44.3	1.96	40.8	1.98	40.6	–	85.8
5	a 1.34 (td 10.6, 3.2)	29.1	a 1.99	24.7	1.87	25.2	1.74	39.9
	b 1.76 m		b 1.89					
6	a 2.39 m	25.6	a 2.23	30.8	a 2.33	27.4	α 1.74	23.9
	b 1.64		b 1.89		b 1.87		β 1.69	
7	-	49.0	α 1.66 (dd, 14.0, 12.4)	32.7	α 1.90 (dd, 13.6, 6.8)	33.7	α 2.36	35.6
			β 2.07 (dd, 14.0, 6.4)		β 1.38 (dd, 13.6, 12.0)		β 2.18	
8	0.79 (s)	19.0	–	38.4	–	38.4	–	151.1
9	0.90 (s)	20.5	1.23 (s)	27.7	1.31 (s)	27.7	2.43	41.3
10	α 1.94 (dd 14.4, 3.6)	28.1	0.96 (s)	23.2	0.99 (s)	23.6	α 1.71 (t 10.4)	36.5
	β 1.44 (dd 14.4, 4.4)						β 1.57	
11							–	34.7
12							1.36 (s)	22.8
13							a 4.88 (s)	111.2
							b 4.90 (s)	
14							0.96 (s)	21.8
15							0.93 (s)	29.8
1′	–	115.9	–	111.1	–	112.4	–	113.0
2′	–	153.7	–	186.7	–	186.6	–	186.2
3′	–	105.4	5.33 (s)	100.0	5.35 (s)	100.2	5.37 (s)	99.7
4′	–	156.0	–	170.9	–	170.8	–	170.7
5′	6.23 (s)	97.2	–	70.0	–	69.8	–	69.3
6′	–	159.4	–	164.9	–	163.9	–	164.3
7′	3.09 (dt 11.2, 4.0)	42.3	2.59 (ddd, 12.0, 6.4, 4.4)	33.6	2.73 (ddd, 11.2, 6.8, 4.0)	32.2	2.66 dd (4.0, 3.2)	34.1
8′	1.97 (m)	32.0	2.86 (m)	26.3	2.92 (m)	26.2	2.07 (m)	26.0
9′	0.52 d (6.8)	21.8	0.61 (d, 6.8)	15.8	0.59 (d, 6.8)	15.6	0.65 d (6.8)	19.9
10′	1.03 (d 6.8)	22.8	0.93 (d, 6.8)	20.7	0.92 (d, 6.8)	20.6	1.13 d (6.8)	26.4
11′	3.76 (s)	55.6	3.75 (s)	56.2	3.76 (s)	56.2	3.76 (s)	56.2
12′	2.06 (s)	8.4	1.51 (s)	27.3	1.57 (s)	26.7	1.60 (s)	26.8
2′-OH	4.75 (s)							

Overlapped signals were reported without designating multiplicity

[a]Recorded at 500 (^{1}H) and 125 (^{13}C) MHz

[b]Recorded at 400 (^{1}H) and 100 (^{13}C) MHz

mesh; Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China), Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden), and reversed-phase C_{18} silica gel (YMC, Kyoto, Japan) were used for column chromatography (CC). Preparative HPLC was carried out on an Agilent 1260 Chromatograph equipped with a G1311C pump and a G1315D photodiode array detector (Agilent Technologies, CA, USA) with a semi-preparative C_{18} reversed-phase column (Cosmosil, 10 mm × 250 mm, 5 μm). All solvents used in CC and HPLC were of analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China) and chromatographic grade (Fisher Scientific, New Jersey, USA), respectively.

3.2 Plant Material

The leaves of *M. cauliflora* were collected from Nanning city, Guangxi Province of People's Republic of China, in July of 2018. A voucher specimen (No. 2018070607) identified by Professor Guang-Xiong Zhou (Jinan University) was

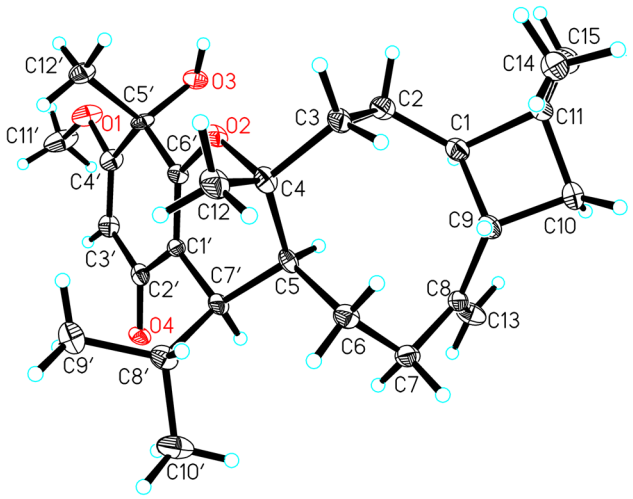

Fig. 5 X-ray ORTEP drawing of **4**

deposited in the Institute of Traditional Chinese Medicine and Natural Products, Jinan University, Guangzhou, People's Republic of China.

3.3 Extraction and isolation

The air-dried leaves of *M. cauliflora* (15 kg) were powdered and extracted with 95% EtOH (v/v, 50 L) at room temperature. The extract (2.2 kg) was suspended in H_2O and extracted with petroleum ether (PE, b.p. 60–90 °C). The PE extract (673.2 g) was subjected to a silica gel column chromatography using cyclohexane–EtOAc (100:0 → 0:100, v/v) as eluent to afford 10 fractions (Frs. A–J). Fr. G (48.3 g) was further separated by silica gel column using a gradient cyclohexane–EtOAc (100:0 → 0:100, v/v) to give 8 subfractions (Frs. G1–G8). Subfraction G5 (10.7 g) was chromatographed on Sephadex LH-20 (CH_2Cl_2/MeOH, 1:1, v/v) to obtain three subfractions (Frs. G5A–G5C). Subfraction G5B (7.3 g) was subjected to ODS column using MeOH/H_2O (50:50 → 100:0, v/v) and further purified by semi-preparative reversed-phase HPLC (MeOH/H_2O, 70:30, v/v, 3 mL/min) to afford **1** (12.5 mg, t_R 41.8 min), **3** (11.3 mg, t_R 33.7 min) and **4** (15.7 mg, t_R 49.3 min). Subfraction G6 (5.3 g) was separated on Sephadex LH-20 (CH_2Cl_2/MeOH, 1:1, v/v) to obtain **2** (7.3 mg).

Compound 1 yellow gum (CH_3OH); $[\alpha]_D^{25} = +119$ ($c = 0.50$, MeOH); UV (MeOH) λ_{max} (log ε) 206 (3.73) nm; IR (KBr) ν_{max} 3475, 2977, 2954, 2876, 1611, 1584, 1488, 1445, 1415, 1385, 1307, 1236, 1199, 1132, 1084, 1035, 1014, 982, 904, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; HRESIMS *m/z* 345.2423 $[M+H]^+$ (calcd for $C_{22}H_{33}O_3$: 345.2424); ECD (MeCN, $\Delta\varepsilon$) 211 (+6.2), 238 (−0.5), 277 (+0.7) nm.

Compound 2 yellow oil (CH_3OH); $[\alpha]_D^{25} = +59$ ($c = 0.50$, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.85), 245 (3.92), 296 (3.50) nm; IR (KBr) ν_{max} 3357, 2957, 2933, 2871, 1656, 1605, 1462, 1385, 1353, 1236, 1137, 1092, 998, 983, 893, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HRESIMS *m/z* 361.2386 $[M+H]^+$ (calcd for $C_{22}H_{33}O_4$: 361.2373); ECD (MeCN, $\Delta\varepsilon$) 203 (−19.8), 244 (+11.7), 296 (+8.1), 337 (−1.8) nm.

Compound 3 yellow oil (CH_3OH); $[\alpha]_D^{25} = -63$ ($c = 0.50$, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.71), 245 (3.77), 297 (3.32) nm; IR (KBr) ν_{max} 3359, 2958, 2924, 2871, 1656, 1603, 1463, 1388, 1372, 1259, 1232, 1136, 1089, 989, 899, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HRESIMS *m/z* 361.2391 $[M+H]^+$ (calcd for $C_{22}H_{33}O_4$: 361.2373); ECD (MeCN, $\Delta\varepsilon$) 203 (+18.0), 245 (−20.5), 293 (−9.6), 333 (+2.5) nm.

Compound 4 colorless blocks (CH_3OH); m.p. 162–163 ℃; $[\alpha]_D^{25} = -42$ ($c = 0.50$, MeOH); UV (MeOH) λ_{max} (log ε) 205 (3.86), 247 (3.87), 310 (3.44) nm; IR (KBr) ν_{max} 3336, 2957, 2870, 1663, 1615, 1462, 1386, 1364, 1284, 1259, 1233, 1176, 1140, 999, 941, 886, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; HRESIMS *m/z* 429.2996 $[M+H]^+$ (calcd for $C_{27}H_{41}O_4$: 429.2999).

Table 2 Antibacterial activities of compounds **1**–**4** (MIC, μg/mL)

Microorganism	1	2	3	4	Ciprofloxacin[a]	Vancomycin[a]
S. aureus ATCC 43300 (MRSA)	> 128	> 128	> 128	32	–[b]	1
S. aureus ATCC 700699 (VISA)	> 128	> 128	> 128	32	–	8
S. aureus ATCC 25923	> 128	> 128	> 128	32	–	1
E. faecalis ATCC 29212	> 128	> 128	> 128	32	–	2
P. aeruginosa ATCC 27853	> 128	> 128	> 128	> 512	0.25	–
E. coli ATCC 25922	> 128	> 128	> 128	> 128	< 0.0625	–
K. pneumoniae ATCC 700603	> 128	> 128	> 128	> 128	0.5	–

[a]As positive controls

[b]NA

3.4 X-Ray Analysis

Crystal data for 4 $C_{27}H_{40}O_4$, monoclinic, space group $P2_1$, $a = 10.2148$ (3) Å, $b = 24.2552$ (4) Å, $c = 20.4139$ (5) Å, $\alpha = 90°$, $\beta = 97.254$ (2)°, $\gamma = 90°$, $V = 5017.3$ (2) Å^3, $T = 293$ (2) K, $Z = 2$, $D_{calcd} = 1.135$ g cm^{-3}, $F(000) = 1872$, 20761 reflections measured ($2.18° \leq \theta \leq 73.86°$), 13408 unique ($R_{int} = 0.0389$, $R_{sigma} = 0.0574$) which were used in all calculations. The final R_1 was 0.0916 [$I > 2\sigma(I)$] and wR_2 was 0.2884 (all data). CCDC-1998470 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

3.5 Antibacterial Activity Assay

Staphylococcus aureus ATCC 43300 (methicillin-resistant *S. aureus*, MRSA), *S. aureus* ATCC 700699 (vancomycin-intermediate *S. aureus*, VISA), *S. aureus* ATCC 25923, *E. faecalis* ATCC 29212, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were standard isolates from ATCC (Manassas, VA, USA). The MIC values were measured using a previously reported method [7]. Ciprofloxacin and vancomycin were used as positive controls.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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