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Norsampsonone E, an unprecedented decarbonyl polycyclic polyprenylated acylphloroglucinol with a homoadamantyl core from *Hypericum sampsonii*†

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Norsampsonone E (**1**), an unprecedented decarbonyl polycyclic polyprenylated acylphloroglucinol, together with one new and two known analogues (**2–4**), was isolated from the aerial parts of *Hypericum sampsonii*. Compound **1** featured an unusual homoadamantyl skeleton with the loss of C-4 carbonyl and followed by the formation of a new C–C bond between C-3 and C-5. Their structures and absolute configurations were elucidated by extensive NMR spectroscopy, single-crystal X-ray experiments, ECD calculations and CD comparison methods, and further confirmed using the single-crystal X-ray structures of biogenetically related congeners **3** and **4**. Besides, compounds **1** and **2** showed direct binding to the RXR α -LBD protein in the SPR assay with a K_D of 10.28 μ M and 31.70 μ M, respectively. Furthermore, compound **1** (5–20 μ M) showed potent RXR α transcriptional inhibitory activity in a dose dependent manner, while compound **2** (5–20 μ M) slightly enhanced RXR α transactivation.

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Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs) have been of great interest to the scientific community due to their intricate “diamond-like” architectures and large portfolio of biological activities.^{1–3} As a vast family of natural products from the *Hypericum* genus, PPAPs possess stunningly complex structures containing bicyclo[3.3.1]nonane, homoadamantyl and adamantyl cores.^{1–3} Recently, a bewildering array of PPAPs derivatives with intriguing novel skeletons were characterized by natural product researchers, which were biosynthesized from conventional PPAPs through carbon migration, rearrangement, ring breakage, carbon reduction and so on.^{4–14} Besides, driven by their fascinating and challenging structures, PPAPs have been a vibrant area in synthesis research.^{15–19}

Retinoid X receptor alpha (RXR α), a ligand-dependent transcription factor, regulates a broad spectrum of physiological functions including cell growth, differentiation, and apoptosis.²⁰ RXR α has been considered as an intriguing drug target and ligands for RXR α show promise as therapeutic agents for many diseases, especially in the treatment of cancer.²¹ Targretin, a small synthetic molecule targeting RXR α , was approved by the FDA for the treatment of cutaneous T-cell lymphoma.²² Though many ligands of RXR α have been reported, their druggability have been hampered by severe side effects.²³ Thus, discovery of novel small-molecule modulators of RXR α with high efficacy and low toxicity from natural products is an effective strategy for the development of RXR α based drugs.

Hypericum sampsonii, a rich source of complex caged PPAPs, shows powerful aid in treating many ailments such as hematemesis, enteritis, traumatic hemorrhage, swellings and cancer.²⁴ In our previous investigations on the aerial parts of *H. sampsonii*, several novel PPAPs were discovered including four new decarbonyl PPAPs norsampsons A–D with the loss of C-2 carbonyl in phloroglucinol ring of bicyclo[3.3.1]nonane skeleton.^{11,12,25–27} Besides, some of them show potent RXR α transcriptional inhibitory activities, suggesting that PPAPs derivatives may be the small-molecule modulators of RXR α . In this paper, we reported the isolation and structural elucidation of another decarbonyl PPAPs norsampsonone E (**1**) which featured an unprecedented homoadamantyl skeleton with the loss of C-4 carbonyl and followed by the formation of a new C–C bond

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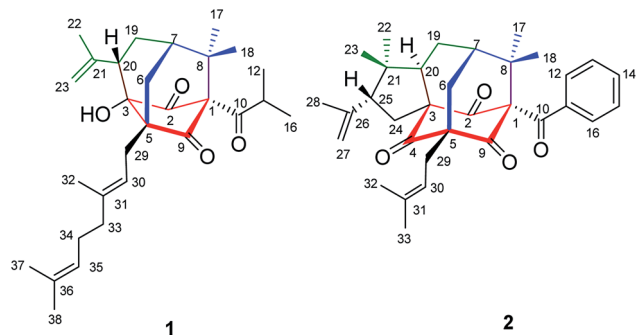


Fig. 1 Structures of compounds 1–2.

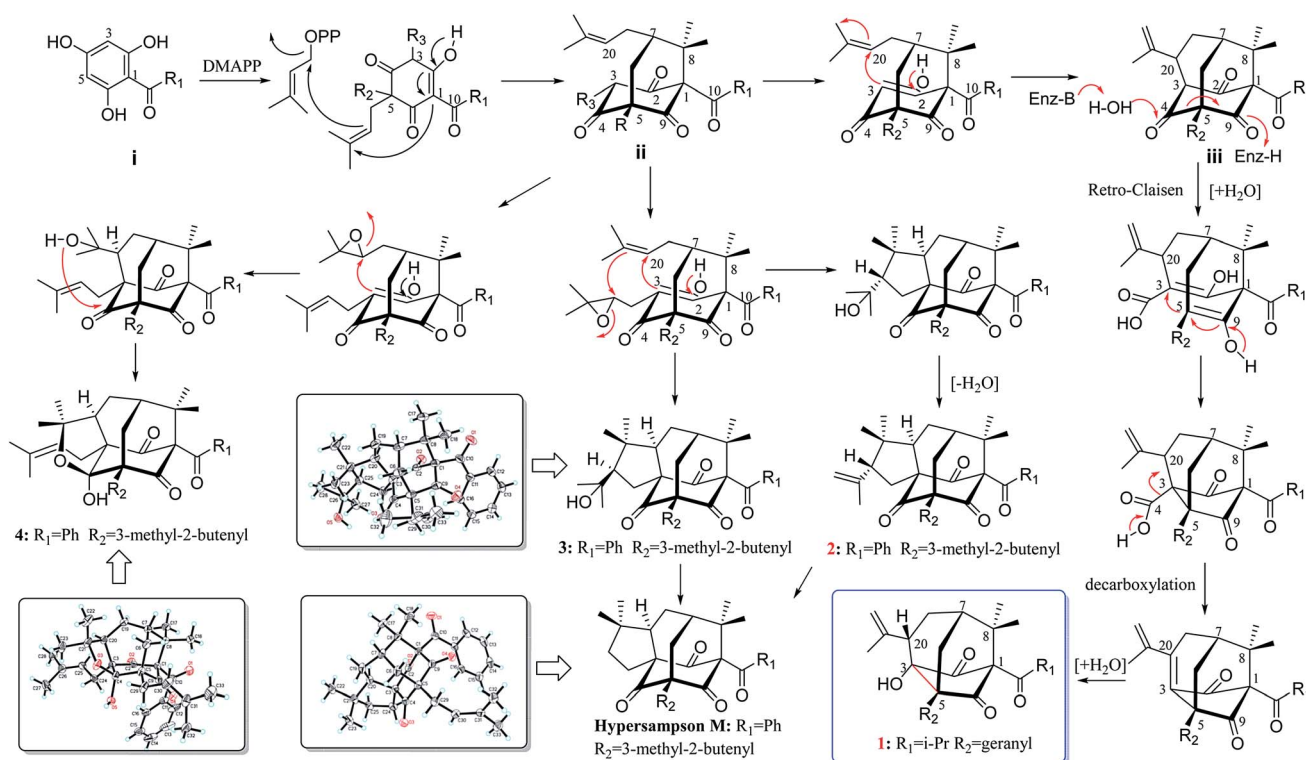
between C-3 and C-5, along with one new analogue hypersampsonone X (2) (Fig. 1). Besides, single crystal X-ray structures of hypersampsonone Q (3) (CCDC 1551384[†]) and sampsonione B (4) (CCDC 1551380[†]) was reported for the first time and further confirmed the absolute configurations of the new compounds (Scheme 1).

Results and discussion

Norsampsonone E (1), was isolated as a colorless oil. The HR-ESI-MS spectrum of 1 showed the molecular ion peak at m/z 455.3161 [$M + H$]⁺, corresponding to the molecular formula $C_{29}H_{42}O_4$, with 9 degrees of unsaturation. The ¹H NMR and ¹³C NMR spectra exhibited an isopropyl group [δ_C 42.6; δ_H 2.27, sept, $J = 6.4$ Hz], (δ_C 19.8; δ_H 1.06, d, $J = 6.4$ Hz), (δ_C 19.6; δ_H ,

1.02, d, $J = 6.4$ Hz)], a terminal double bond [$(\delta_C$ 118.4; δ_H 5.23, br.s, δ_H 4.95, br.s), (δ_C 142.6)], three carbonyl groups [δ_C 211.7, 211.0, 208.4], a geranyl group [δ_C 25.9, 118.7, 139.0, 16.3, 40.3, 26.6, 124.2, 131.8, 17.8, 25.9] and additional three singlet methyls [δ_C 21.9–24.5; δ_H 1.20–1.84], which accounted for six degrees of unsaturation. The remaining three degrees of unsaturation required a tricyclic core structure in 1. The above analysis indicated that compound 1 was a derivative of PPAPs. The NMR data of 1 were similar to those of sampsonione H,²⁸ except for an isobutyryl group at C-1 instead of a benzoyl group, the significant downshift of C-3 (δ_C 82.7) as well as obvious upfield shift of C-5 (δ_C 58.4) and C-20 (δ_C 42.0), together with the absence of C-4 carbonyl and C-24–25. Additionally, the HMBC correlations from H-6_{eq} to C-5/C-8/C-9/C-19, H-6_{ax} to C-3, H-20 to C-2/C-3/C-5 and those from H₃-23 to C-20/C-21/C-22 further suggested the existence of an decarboxyl homoadamantyl core structure with the loss of C-4 carbonyl and followed by the formation of a new C–C bond between C-3 and C-5. HMBC correlations from H-29 to C-3/C-5/C-6/C-9 allowed the linkage of the geranyl group to the C-5 of the core structure. By now, the gross structure was poor in one hydroxyl groups compared with the molecular formula of 1. Taking the chemical shift of C-3 (δ_C 82.7) into account, the hydroxyl group should be attached to the C-3 of the core structure (Fig. 2). Thus, the planar structure of 1 was established.

In the NOESY spectrum, the correlations of H₃-18/H-6_{ax} and H-6_{eq}/H-20 indicated the β -orientation of H-20. Therefore, the relative configuration of 1 was elucidated as shown in Fig. 2. Since compound 1 was obtained as colorless oil with low



Scheme 1 Plausible Biogenetic Pathway for 1–4.



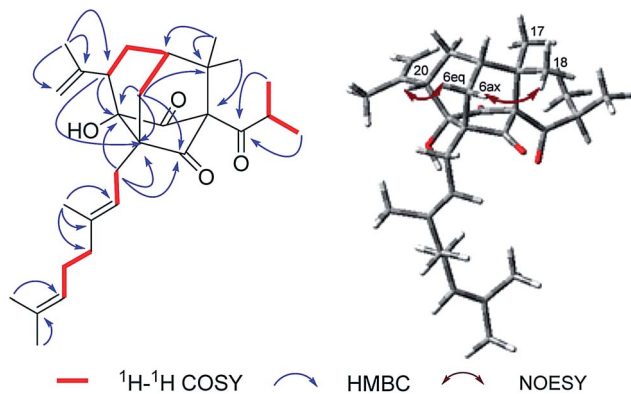


Fig. 2 Key ^1H - ^1H COSY, HMBC and NOESY correlations of **1**.

polarity, crystals suitable for single X-ray experiment were failed to be obtained. Recently, the absolute configuration of an oily PPAPs derivative hypercohin A with a hydroxyl group was successfully determined by the single X-ray crystal of its *p*-bromobenzoate ester which was much easier to crystallize.¹⁴ Thus, the *p*-bromobenzoate ester of compound **1** was try to prepared in order to obtain its single crystal X-ray structure. However, it was failed as well, which may be due to the existence of a tertiary alcohol hydroxyl instead of a secondary alcohol hydroxyl as well as the large space steric hindrance. Fortunately, the calculated electronic circular dichroism (ECD) method has demonstrated great success in determining the absolute configurations of the PPAPs type compounds.⁴⁻¹⁴ Thus, the calculated ECD method was used to determine the absolute configuration of **1**. On the basis of the above deduction of the relative configuration of **1**, a pair of enantiomers (1R,3S,5S,7S,20S)-**1a** and (1S,3R,5R,7R,20R)-**1b** were calculated for their ECD spectrum by the TDDFT [B3LYP/6-311pG(2d,3p)] method using the Gaussian 09 software package.²⁹ As a consequence, the overall pattern of the calculated ECD curve of **1a** was in agreement with the measured CD spectrum of **1** (Fig. 3). Thus, the absolute configurations of chiral carbons in **1** were assigned as 1R,3S,5S,7S,20S, which was further confirmed by its consistence with the absolute configurations of previously reported homoadamantyl PPAPs from the same plant.^{11,12,25}

Hypersampsonse X (**2**) was obtained as colorless oil. Its molecular formula was assigned as $\text{C}_{33}\text{H}_{40}\text{O}_4$ on the basis of HRESIMS with a pseudo-molecular ion at $501.3016 [\text{M} + \text{H}]^+$.

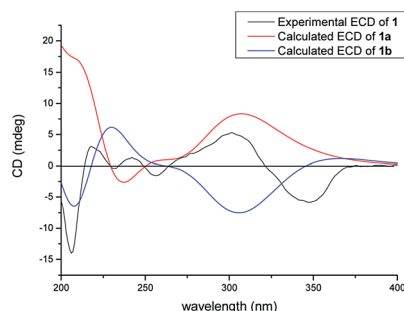


Fig. 3 Calculated and experimental ECD spectra of **1**.

The ^{13}C and DEPT NMR spectra displayed 33 carbons including a benzoyl group [δ_{C} 192.7, 135.0, 132.1, 129.1×2 , 128.2×2], three carbonyl groups [δ_{C} 205.0, 206.7, 204.2], an isopentenyl group [δ_{C} 29.7, 119.2, 134.9, 18.2, 26.2], a terminal double bond [δ_{C} 118.4, 142.6] and five methyls [δ_{C} 23.0-27.3], suggesting that **2** was a PPAP derivative possessing a homoadamantyl skeleton. Extensively comparison of the NMR data of **2** with those of hypersampsonse M¹¹ revealed that they were structurally similar except for an additional 1-methylethenyl group substituted at C-25, which can be further confirmed by the obvious downshift of C-25 (δ_{C} 55.2) and the HMBC correlations from H₃-28 to C-25/C-26/C-27 and H-25 to C-21 (Fig. 4).

The NOESY correlations of H₃-18/H-6_{ax}, H₃-17/H-20 and H-20/H₃-28 indicated the α -orientation of H-20 and the β -orientation of H-25 in **2** (Fig. 4). Moreover, crystals suitable for a single-crystal X-ray diffraction experiment were fortunately obtained, which further confirmed the structure and relative configuration of **2** (Fig. 5). The CD spectrum of compound **2** has a highly agreement with biogenetic related analogue hypersampsonse M (Fig. 6), whose absolute configuration has been unambiguously determined as 1R,3R,5S,7S,20R by the single crystal X-ray structure in our previously reported work.¹¹ Thus, the absolute configuration of **2** was determined as 1R,3R,5S,7S,20R,25R, which was consistent with the absolute configuration of hypersampsonse M.

Biosynthetically, PPAPs are probably derived from the acylphloroglucinol core structure (**i**). Prenylation of **i** would afford monocyclic polyprenylated acylphloroglucinols (MPAPs), which may be further cyclized to bicyclic polyprenylated

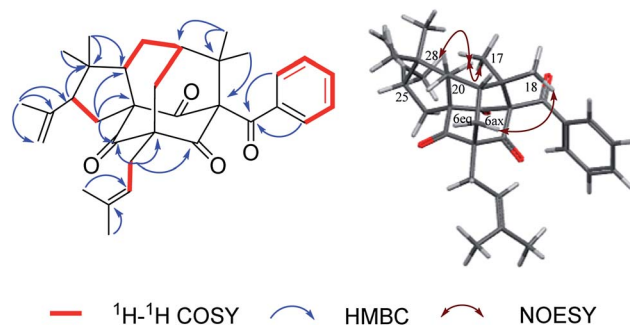


Fig. 4 Key ^1H - ^1H COSY, HMBC and NOESY correlations of **2**.

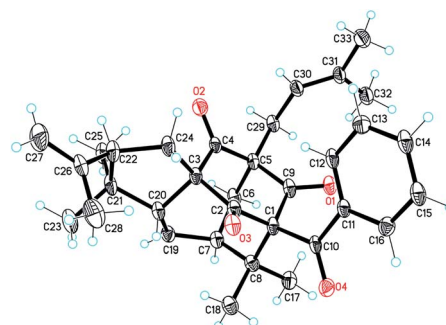


Fig. 5 The single X-ray crystal structure of **2**. (CCDC 1551387†).



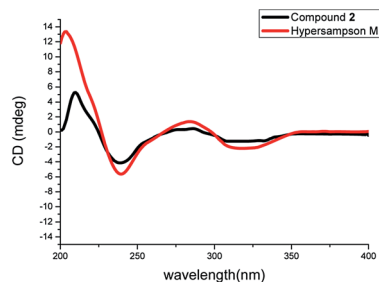


Fig. 6 The comparison of the CD spectra of **2** and hypersampson M.

acylphloroglucinols (BPAPs) type metabolites. The BPAPs type intermediate **ii** undergoes the cyclization of C-3 and C-20 to yield the homoadamantyl (**iii**) core structure.³⁰ Norsampson E (**1**) could be considered as the homoadamantyl type PPAPs with the loss of C-4 carbonyl in the phloroglucinol ring and followed by the formation of a new C-C bond between C-3 and C-5. The plausible biogenetic pathway of **1** was proposed to be generated from **iii** through the Retro-Claisen and decarboxylation

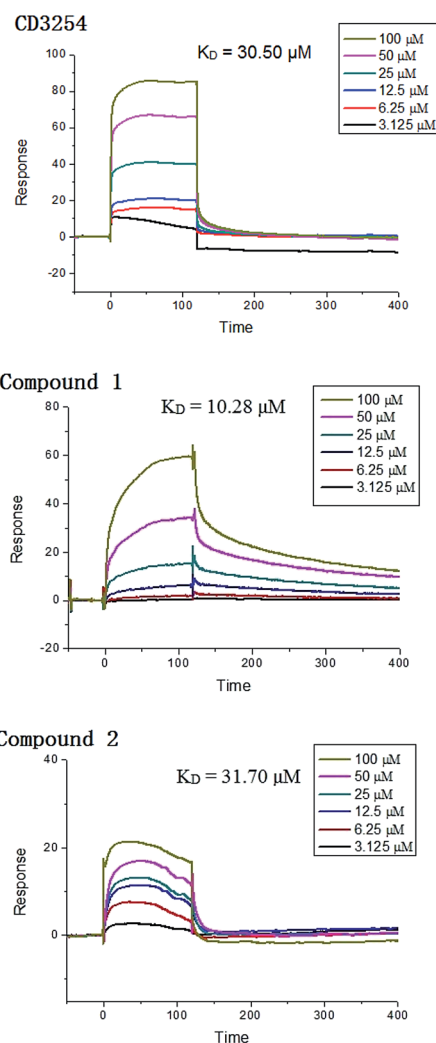


Fig. 7 SPR results of CD3254, compound **1** and **2** binding to RXR α -LBD.

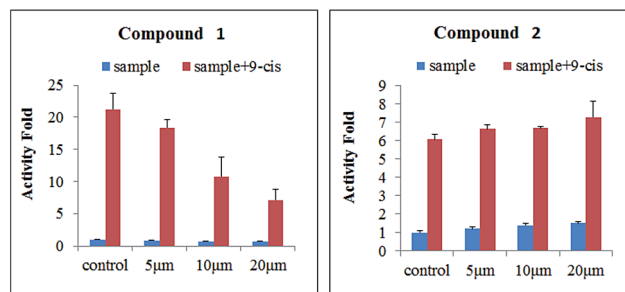


Fig. 8 Effects of compounds **1–2** (5, 10, and 20 μ M) on the transcriptional activities of RXR α .

reactions (Scheme 1). Compounds **2–4** was probably biosynthesized from the same precursor **ii** by epoxidation, intramolecular cyclization, and dehydration reactions (Scheme 1).^{25,30}

Surface plasmon resonance (SPR) technology has been widely used to monitor the kinetics of protein/protein and ligand/protein interactions, which has been successfully used to study the interactions between ligands and nuclear receptor-RXR α .²³ Compounds **1–2** were evaluated for their binding affinity toward RXR α -LBD (ligand-binding domain) by SPR assay, which indicated that these two compounds had direct interaction towards RXR α -LBD with concentration-dependent SPR signals. As a positive control, the interaction between the known ligand CD3254 and RXR α was also investigated, which show directed interaction in a fast association and fast dissociation process ($K_D = 30.50 \mu\text{M}$) (Fig. 7). However, compound **1** could bind to RXR α -LBD in a particularly slow association and slow dissociation mode with a K_D of $10.28 \mu\text{M}$, calculated by the kinetic analysis, while compound **2** was similar to CD3254 in a faster association and dissociation mode with a K_D of $31.70 \mu\text{M}$ by steady-state binding analysis (Fig. 7). Besides, dual luciferase reporter gene assay was used to investigate the effects of compounds on RXR α transcriptional activity. As a result, compound **1** (5–20 μM) showed potent RXR α transcriptional-inhibitory activity in a dose dependent manner, while compound **2** (5–20 μM) slightly enhanced RXR α transactivation (Fig. 8). The above analysis indicated that compounds **1–2** might bind to RXR α with different mode of action, which needs further investigation.

Conclusions

Up to now, several new skeleton PPAPs with the ring breakage or carbon reduction of phloroglucinol ring have been reported, including norsampsons A–D with the loss of C-2 carbonyl of the normal BPAPs, hyphenrones A–D formed by cleavage of the C-1/C-9 bond of the normal BPAPs, and hypersubone A represents the first seco-adamantyl PPAP by the cleavage of the C-1/C-9 bond of normal adamantane. However, there were no reports about the ring breakage or carbon reduction of normal homoadamantyl PPAPs. To the best of our knowledge, norsampson E (**1**) stands for the first example of decarbonyl homoadamantyl PPAPs, which not only enriched the structural diversity of



PPAPs, but also shed new light on the synthesis of this type compounds. Furthermore, the proposed plausible biogenetic pathways for 1–2 enriched the awareness of biosynthesis of homoadamantyl PPAPs. Besides, the SPR assay and RXR α transcriptional activity results indicated that compounds 1–2 might be the small-molecule modulators of RXR α and could be considered as potential lead compounds for RXR α based drugs with different mode of action, which were worthy of further investigation.

Experimental

General experimental procedures

Optical rotations were measured on a Jasco P-1020 polarimeter with a 1 cm cell at room temperature. UV spectra were recorded on a JASCO V-550 UV/Vis spectrometer. IR spectra were obtained using a JASCO FT/IR-480 plus spectrometer. CD spectra were measured on a Jasco J-810 spectropolarimeter at room temperature. HR-ESI-MS spectra were acquired using a Waters Synapt G2 mass spectrometer. The NMR spectra were measured with a Bruker AV-300/400/600 spectrometer at room temperature. Silica gel (200–300 mesh, Qingdao Marine Chemical Ltd., China), octadecylsilanized (ODS) silica gel (YMC Ltd., Japan) were used for open column chromatography (CC). TLC was performed on precoated silica gel plates (SGF254, 0.2 mm, Yantai Chemical Industry Research Institute, China). The semi-preparative HPLC was carried out on a Shimadzu LC-6AD Liquid Chromatography system with a SPD-20A Detector (Shimadzu, Japan) using a reversed-phase C18 column (5 μ m, 10 \times 250 mm; YMC, Japan).

Plant material

The aerial parts of *Hypericum sampsonii* were collected from Wuming, Guangxi Province, China, in June, 2014, and authenticated by Professor Songji Wei (Guangxi University of Traditional Chinese Medicine, Guangxi, China).

Extraction and isolation

The air-dried aerial parts of *H. sampsonii* (20 kg) were extracted by supercritical fluid of carbon dioxide. The crude extract (443.7 g) was partitioned with petroleum ether against MeOH–H₂O (90 : 10). The petroleum ether soluble extract (200.4 g) was separated by chromatography on a silica gel column (3.5 \times 13.2 cm; cyclohexane to ethyl acetate, 100 : 0 \rightarrow 0 : 100) to afford eleven fractions (Fr. 1–Fr. 11). Fr. 2 was further purified by column chromatography (silica gel CC, 3.5 \times 13.2 cm; petroleum ether to acetone, 100 : 0 \rightarrow 0 : 100) to yield six fractions (Fr. 2.1–Fr. 2.6). Fr. 2.4 (6.7 g) was further subjected to ODS column chromatography eluted with MeOH–H₂O (70 : 30 \rightarrow 100 : 0) and purified by semi-preparative HPLC on ODS column with 80% ACN–H₂O to afford compound 1 (26.3 mg) and compound 2 (6.9 mg). Fr. 2 (8.3 g) was subjected to ODS column chromatography eluted with MeOH–H₂O (60 : 40 \rightarrow 100 : 0) to obtained nine fractions (Fr. 2.1–Fr. 2.9). Fr. 2.5 (138.5 mg) was purified by semi-preparative HPLC on ODS column with 75% ACN–H₂O to

afford compound 4 (9.6 mg). Fr. 8 (23.7 g) was subjected to ODS column chromatography eluted with MeOH–H₂O (60 : 40 \rightarrow 100 : 0) to obtained ten fractions (Fr. 8.1–Fr. 8.10). Fr. 8.9 (6.9 g) was further subjected to a silica gel column using petroleum ether to acetone gradient elution to yield 11 fractions (Fr. 8.9.1–8.9.11). Fr. 8.9.6 (297.4 mg) was purified by preparative HPLC on ODS column with 75% MeOH–H₂O to yield compounds 3 (7.8 mg).

Norsampson E (1). Colorless oil; $[\alpha]_D^{23}$ –63.0 (c 0.30, CHCl₃); UV (CH₃OH) λ_{\max} (log ϵ) 201 (4.32) nm; IR (KBr) ν_{\max} 3415, 2922, 2866, 1727, 1635, 1456, 1372, 1247, 1224, 1067 cm⁻¹; CD (CH₃OH) λ_{\max} ($\Delta\epsilon$) 327 (–1.14), 254 (0.10) nm; HR-ESI-MS m/z 455.3161 [M + H]⁺ (calcd for C₂₉H₄₃O₄, 455.3161). ¹H (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) data, see Table 1.

Table 1 ¹H NMR and ¹³C NMR data for 1–2 (CDCl₃)

No.	1 ^a		2 ^b	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	85.6		81.0	
2	211.0		205.0	
3	82.7		74.1	
4			206.7	
5	58.4		69.1	
6 _{ax}	35.8	1.97, dd (13.6, 4.0)	43.2	2.54, m
6 _{eq}		2.20, dd (13.6, 2.0)		1.89, m
7	41.7	1.69, m	44.1	2.12, m
8	50.0		51.0	
9	211.7		204.2	
10	208.4		192.7	
11	42.6	2.27, sept (6.4)	135.0	
12	19.8	1.06, d (6.4)	129.1	7.12, br.d (7.4)
13			128.2	7.39, br.t (7.4)
14			132.2	7.24, br.t (7.4)
15			128.2	7.39, br.t (7.4)
16	19.6	1.02, d (6.4)	129.1	7.12, br.d (7.4)
17	21.9	1.20, s	23.0	1.41, s
18	24.5	1.26, s	25.4	1.45, s
19	26.3	1.88, br.s	29.2	2.28, m
20	42.0	2.70, br.t (10.0)	57.4	2.03, br. d (8.4)
21	142.6		44.5	
22	22.1	1.84, s	27.1	0.87, s
23	118.4	5.23, br.s 4.96, br.s	27.3	0.94, s
24			34.6	2.65, m
25			55.2	3.16, m
26			145.4	
27			112.0	4.91, br.s 4.84, br.s
28			24.1	1.80, s
29	25.9	2.41, m	29.7	2.55, m
30	118.7	5.30, br.t (7.6)	119.2	5.06, br.t (10.8)
31	139.0		134.9	
32	16.3	1.63, s	18.2	1.66, s
33	40.3	2.01, m	26.2	1.66, s
34	26.6	2.08, m		
35	124.2	5.06, br.t (6.8)		
36	131.8			
37	17.8	1.58, s		
38	25.9	1.64, s		

^a Recorded at 100 M for ¹³C and 400 M for ¹H. ^b Recorded at 150 M for ¹³C and 600 M for ¹H.



Hypersampsonone X (2). Colorless oil; $[\alpha]_D^{23} +27.1$ (c 0.50, CHCl_3); UV (CH_3OH) λ_{max} ($\log \epsilon$) 206 (3.91), 246 (3.56) nm; IR (KBr) ν_{max} 2922, 2975, 2361, 1736, 1698, 1677, 1457, 1377, 1224, 683 cm^{-1} ; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 327 (−12.3), 280 (0.14), 244 (−16.7) nm; HR-ESI-MS m/z 501.3016 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{33}\text{H}_{41}\text{O}_4$, 501.2981). ^1H (600 MHz, CDCl_3) and ^{13}C NMR (150 MHz, CDCl_3) data, see Table 1.

Quantum chemical ECD calculation method

In theoretical calculations, the geometry of the molecules was optimized with Gaussian 09 package²⁹ at B3LYP/6-31G(d) computational level. The minimum nature of the structure was confirmed by frequency calculations at the same computational level. Then ECD calculations were carried out in the methanol solvent medium using time-dependent density functional theory (TDDFT) with B3LYP functional and DGDZVP basis set.

X-ray crystallographic analysis of 2, 3, and 4

Crystal data for hypersampsonone X (2). $\text{C}_{33}\text{H}_{40}\text{O}_4$ ($M = 500.65$): orthorhombic, space group $P2_12_12_1$, $a = 7.7835(6)$ Å, $b = 12.1558(8)$ Å, $c = 28.405(3)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 2687.6(4)$ Å³, $Z = 4$, $T = 100.00(10)$ K, $\mu(\text{Cu K}\alpha) = 0.626$ mm^{-1} , $D_{\text{calc}} = 1.237$ g cm^{-3} , 19 267 measured reflections, 5321 independent reflections [$R_{\text{int}} = 0.1215$]. The final R_1 was 0.0977 and wR_2 was 0.2371 [$I > 2\sigma(I)$]. The goodness of fit on F^2 was 1.069 (CCDC 1551387†).

Crystal data for hypersampsonone Q (3). $\text{C}_{33}\text{H}_{42}\text{O}_5$ ($M = 518.66$): orthorhombic, space group $P2_12_12_1$, $a = 14.15822(19)$ Å, $b = 17.0208(3)$ Å, $c = 24.2524(4)$ Å, $\beta = 99^\circ$, $V = 5844.45(16)$ Å³, $Z = 8$, $T = 150.05(10)$ K, $\mu(\text{Cu K}\alpha) = 0.618$ mm^{-1} , $D_{\text{calc}} = 1.179$ g mm^{-3} , 20 563 measured reflections, 8816 independent reflections [$R_{\text{int}} = 0.0304$]. The final R_1 was 0.0398 and wR_2 was 0.1032 [$I > 2\sigma(I)$]. The goodness of fit on F^2 was 1.043. Flack parameter = −0.04(8) (CCDC 1551384†).

Crystal data for sampsonone B (4). $\text{C}_{33}\text{H}_{42}\text{O}_5$ ($M = 518.67$): orthorhombic, space group $P2_12_12_1$, $a = 9.8352(5)$ Å, $b = 11.5100(7)$ Å, $c = 49.946(3)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 5654.1(6)$ Å³, $Z = 8$, $T = 150.05(10)$ K, $\mu(\text{Cu K}\alpha) = 0.639$ mm^{-1} , $D_{\text{calc}} = 1.219$ mg mm^{-3} , 35 128 measured reflections, 9014 independent reflections [$R_{\text{int}} = 0.0710$]. The final R_1 was 0.042 and wR_2 was 0.0833 [$I > 2\sigma(I)$]. The goodness of fit on F^2 was 1.016. Flack parameter = 0.18(16) (CCDC 1551380†).

Acknowledgements

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