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Isolation, Structure Elucidation, and Total Synthesis of Myrtuspirone A from *Myrtus communis*

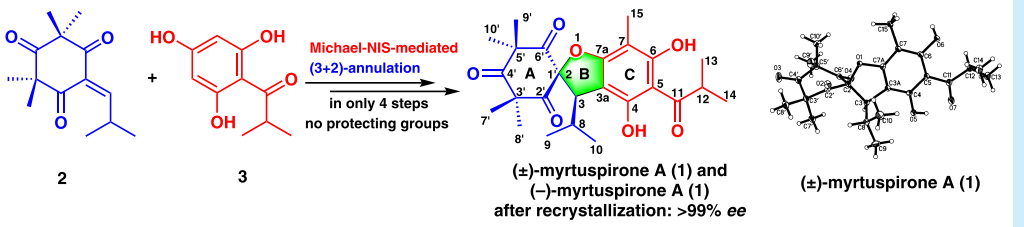
Min-Jing Cheng,[†,‡,∥] Xin-Yi Yang,[§,∥] Jia-Qing Cao,[‡] Chao Liu,[‡] Li-Ping Zhong,[†] Ying Wang,[‡] Xue-Fu You,[§] Chuang-Chuang Li,[*,†] Lei Wang,[*,‡] and Wen-Cai Ye[*,‡]

[†]Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen 518055, P.R. China

[‡]Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P.R. China

[§]Beijing Key Laboratory of Antimicrobial Agents/Laboratory of Pharmacology, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing 100050, P.R. China

Supporting Information



ABSTRACT: A pair of enantiomeric triketone–phloroglucinol hybrids, (+)- and (−)-myrtuspirone A (**1**), featuring an unprecedented 3-isopropyl-3*H*-spiro[benzofuran-2,1′-cyclohexane] backbone, were isolated from the leaves of *Myrtus communis*. The absolute configuration of each enantiomer of **1** was determined by X-ray diffraction and chemical calculations. Furthermore, the gram-scale total syntheses of (±)-**1** and (−)-**1** were conducted in four steps using a Michael-*N*-iodosuccinimide (NIS)-mediated (3 + 2)-annulation reaction. Both (+)- and (−)-**1** exhibited antibacterial activities against Gram-positive bacteria including multidrug-resistant strains.

The plants of the family Myrtaceae are well-known for producing structurally diverse phloroglucinols with various biological activities.[1] In recent years, Myrtaceous phloroglucinols have attracted substantial attention from chemists and pharmacologists.[2] Some Myrtaceous phloroglucinols with new skeletons and significant biological effects had been reported, such as antitumor phloroglucinol–sesquiterpenes,[3a] anti-inflammatory phloroglucinol–monoterpenes,[3b] antimalarial triketone–phloroglucinol–triketones,[3c] and antibacterial triketone–phloroglucinol–monoterpenes.[3d] Among these compounds, triketone–phloroglucinol hybrids consist of triketone and phloroglucinol monomers, which are biogenetically linked through a Michael addition or oxidative coupling to form densely functionalized pyran or furan rings.[4]

Myrtus communis L. (Myrtaceae), an herbal medicine with antibacterial and insecticidal effects, is native to the Mediterranean region.[5] As part of our search for structurally unique and biologically interesting natural products, we reported the isolation of several new phloroglucinol derivatives from *M. communis*.[3d,6] In a continuation of that investigation, a pair of enantiomeric triketone–phloroglucinol hybrids, (+)-**1** and (-)-**1**, with a new carbon skeleton were isolated from the leaves of *M. communis*. Structurally, myrtuspirone A (**1**) represents the first example of a triketone–phloroglucinol biogenetically constructed by a (3 + 2) annulation reaction, which forms an unprecedented 3-isopropyl-3*H*-spiro[benzofuran-2,1′-cyclohexane] backbone. The absolute configuration of each enantiomer of **1** was determined by X-ray diffraction and electronic circular dichroism (ECD) calculations. The gram scale site-selective and enantioselective total synthesis of (±)-**1** and (−)-**1** was achieved using a unique Michael–NIS-mediated (3 + 2)-annulation approach. Furthermore, both (+)-**1** and (-)-**1** exhibited antibacterial activities against Gram-positive bacteria including several multidrug-resistant strains (methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *Enterococcus faecium* (VRE)). Herein, we report the structure elucidation, total synthesis, and antibacterial activities of myrtuspirone A (**1**).

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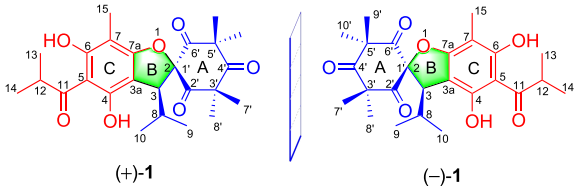

Myrtuspirone A (**1**) was obtained as colorless crystals. The molecular formula of **1** was deduced as $C_{25}H_{32}O_7$ from the quasimolecular ion at m/z 445.2224 $[M + H]^+$ (calcd for $C_{25}H_{33}O_7$ 445.2221) in its HRESIMS. The UV spectrum of **1** displayed absorption maxima at 226 and 290 nm. The IR spectrum showed characteristic absorption bands for the aromatic ring (1589, 1456 cm^{-1}), hydroxyl group (3461 cm^{-1}), and carbonyl groups (1709, 1631 cm^{-1}). The ^1H NMR spectrum of **1** suggested the presence of five tertiary methyl groups [δ_H 1.89 (3H, s), 1.46 (3H, s), 1.35 (3H, s), 1.31 (3H, s), 1.23 (3H, s)], an isopropyl unit [δ_H 1.00 (3H, d, J = 7.0 Hz), 0.53 (3H, d, J = 6.6 Hz)], an isobutyryl moiety [δ_H 3.92 (1H, septet, J = 6.7 Hz), 1.10 (3H, d, J = 6.7 Hz), 1.10 (3H, d, J = 6.7 Hz)], and a methine group [δ_H 4.22 (1H, d, J = 2.5 Hz)]. The ^{13}C NMR and DEPT spectra of **1** exhibited 25 carbon signals, including those for a benzene ring (δ_C 163.0, 161.1, 155.1, 106.1, 103.8, 98.5), an oxygenated spiro carbon (δ_C 98.7), and four carbonyl groups (δ_C 210.7, 208.1, 202.8, 202.2) (Table S1). The above data suggested that **1** could be a triketone−phloroglucinol hybrid.

A comparison of the NMR data of **1** with those of the known compound 6-methylisomyrtucommulone B[7] indicated that **1** comprises an isobutyl syncarpic acid moiety (**1a**) and an isobutyrylphloroglucinol unit (**1b**) (Figure 1). The $^1H-^1H$

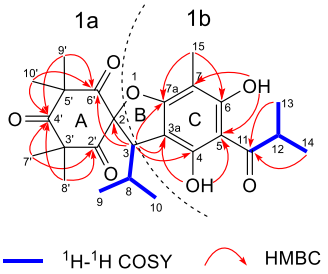

Figure 1. Key $^1H-^1H$ COSY and HMBC correlations of **1**.

COSY spin system from H-3 to H-9/H-10 together with the HMBC correlations between H-3 and C-2/C-6′/C-3a/C-4/C-7a as well as between H-15 and C-6/C-7a suggested that **1a** and **1b** were connected via C-2−O−C-7a and C-3−C-3a bonds, forming a dihydrofuran ring (ring B) and a spiro carbon (C-2) (Figure 1). Thus, the planar structure of **1** was determined. The complete structure of **1** was further determined by X-ray diffraction analysis (Figure 2). The space group $P2_1/c$ of the crystal, together with the lack of optical activity or Cotton effects, indicated that **1** was a racemate. Chiral separation of **1** by HPLC led to the isolation of two enantiomers, (+)-**1** and (−)-**1** (Figure S1).

To determine the absolute configurations of (+)-**1** and (−)-**1**, the experimental CD spectra and the calculated ones using the time-dependent DFT method of each enantiomer were compared. The measured CD spectrum of (+)-**1** showed positive Cotton effects at 311 ($\Delta\varepsilon$ +27.0) and 232 ($\Delta\varepsilon$ +4.9) nm as well as negative effects at 285 ($\Delta\varepsilon$ −20.6) and 214 ($\Delta\varepsilon$ −13.7) nm, which were consistent with the calculated CD spectrum of the 3*S* isomer (Figure 3). In contrast, the CD

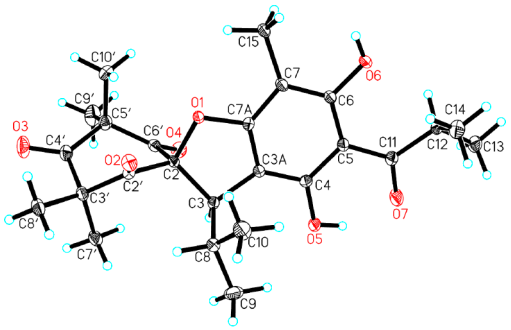

Figure 2. X-ray ORTEP drawing of **1**.

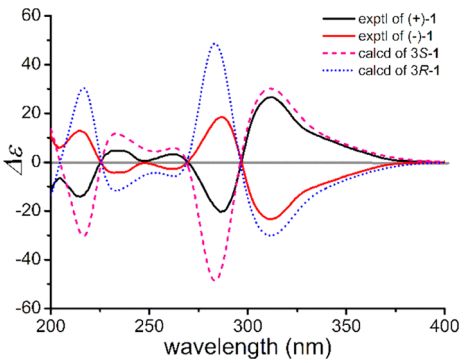

Figure 3. Calculated and experimental ECD spectra of (+)-**1** and (−)-**1**.

spectrum of (−)-**1** displayed the opposite Cotton effects at the same wavelengths, which corresponded to the 3*R* isomer (Figure 3). On the basis of the above evidence, the absolute configurations of (+)-**1** and (−)-**1** were established to be 3*S* and 3*R*, respectively.

Myrtuspirone A (**1**) represents the first example of an unusual spirodihydrobenzofuran triketone. Some natural products with a spirodihydrobenzofuran unit had been reported to exhibit different biological activities,[8] and thus, they have attracted considerable interest from the synthetic community.[9] Therefore, an enantioselective total synthesis of **1** was conducted. Biogenetically, compound **1** is composed of simple building blocks, **2** and **3** (Figure 4). With this in mind, it was envisioned that **1** could be prepared from **2** and **3** via a (3 + 2) annulation reaction followed by methylation.

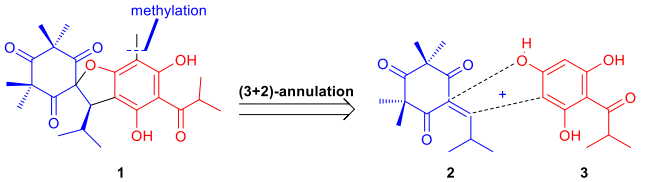

Figure 4. Retrosynthetic analysis of myrtuspirone A (**1**).

The key step in this current strategy was the (3 + 2) annulation reaction to install the dihydrofuran ring. At the outset of this investigation, we tested **2** and **3**[3d] in the presence of oxidants in MeCN at 80 °C (Table 1, entries 1−4).[3e] Disappointingly, neither the desired product **5** nor the undesired regioisomer **7** were obtained. The reason could be that the two carbonyl groups on the A ring make the carbocation unstable, which make this (3 + 2) annulation

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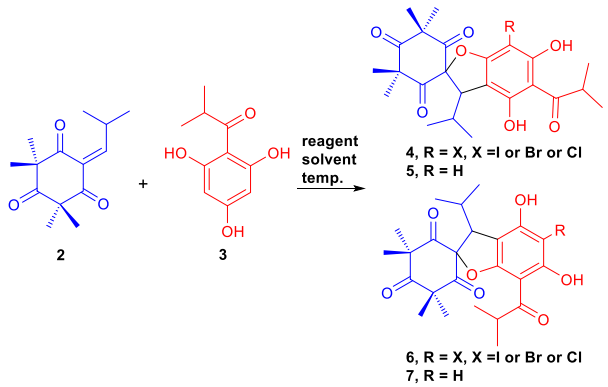
Table 1. Optimization of the Reaction Conditions



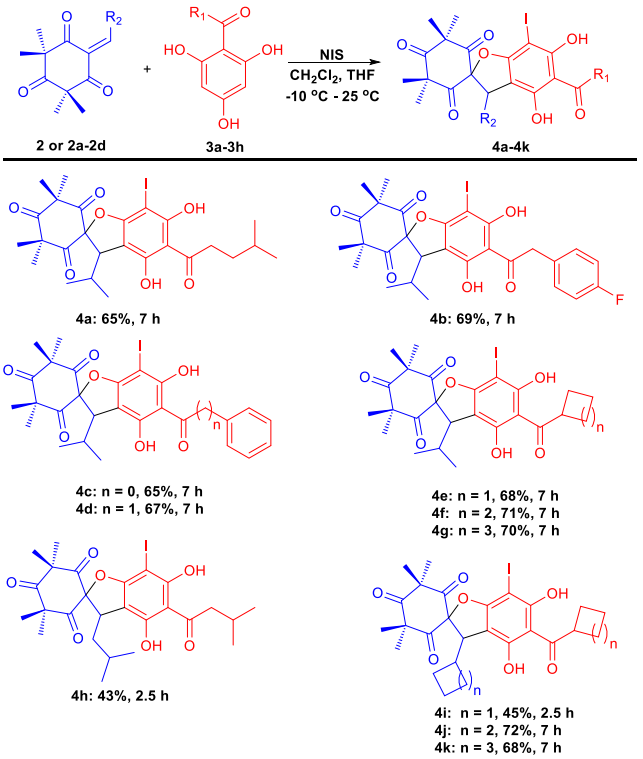
entry	reagent	temp (°C)	solvent	yield (%) of 4[c]	yield (%) of 5[c]
1[a]	$Cu(OAc)_2$ (2 equiv)	80	MeCN	0	0
2[a]	Ag_2CO_3 (2 equiv)	80	MeCN	0	0
3[a]	CAN (2 equiv)	80	MeCN	0	0
4[a]	$Mn(OAc)_3$ (2 equiv)	80	MeCN	0	0
5[b]	NIS (2.5 equiv)	−10 to +25	DCM	38	trace
6[b]	NBS (2.5 equiv)	−10 to +25	DCM	trace	6
7[b]	NCS (2.5 equiv)	−10 to +25	DCM	trace	20
8[b]	I_2 (3 equiv)	−10 to +25	DCM	trace	11
9[b]	NIS (2.5 equiv)	−10 to +25	toluene	36	trace
10[b]	NIS (2.5 equiv)	−10 to +25	DCM/THF	63	trace

[a]The reactions in entries 1−4 were carried out with **3** (0.2 mmol), **2** (0.3 mmol), and MeCN (2 mL) at 80 °C. [b]The reactions in entries 5−10 were carried out with **3** (0.2 mmol), **2** (0.3 mmol), and CH_2Cl_2 (1 mL) at 25 °C for 6 h, followed by THF (5 mL) and NIS (2.5 equiv) at −10 °C for 1 h. [c]Isolated yield.

reaction more difficult.[3e] Next, **2** was treated with **3** in CH_2Cl_2 at 25 °C, followed by NIS (2.5 equiv) at −10 °C in one pot (Table 1, entry 5). To our delight, the reaction proceeded smoothly to provide **4** in 38% yield. However, the yield dramatically decreased when the NBS, NCS, or I_2 was used instead (Table 1, entries 6−8). Then, the reaction conditions were further optimized by changing the solvents. Ultimately, we found that treating **2** with **3** in CH_2Cl_2, followed by THF and NIS (2.5 equiv) in one pot (Table 1, entry 10), was the optimal method, and the substrate underwent regioselective (3 + 2)-annulation to give **4** in 63% yield without the formation of side products **6** and **7** (see the Supporting Information).

To further investigate the synthetic utility of this optimized reaction, we examined the substrate scope of various substituted triketones and phloroglucinols. As shown in Scheme 1, different substituents on substrates **2** or **2a−d** (see the Supporting Information for details) were tolerated in the (3 + 2)-annulation reaction with different substrates **3a−h**, and the reactions gave the corresponding products **4a−k** in moderate to good isolated yields (43−72%) (see the Supporting Information for details). Hence, our method has broad generality for the synthesis of spirodihydrobenzofuran triketone derivatives. Notably, some products (**4h**, **4i**) were

Scheme 1. Substrate Scope of the Michael-NIS-Mediated (3 + 2)-Annulation Reaction[a,b]



[a]Unless otherwise noted, the reactions were carried out with **2**, **2a−d** (0.3 mmol), and **3a−h** (0.2 mmol) in CH_2Cl_2 (1 mL) at 25 °C for 1.5−6 h, followed by THF (5 mL) and NIS (2.5 equiv) at −10 °C for 1 h. [b]Isolated yield (%).

isolated in lower yields because the amount of byproduct generated from the double-Michael addition increased.[3d]

Having established a reliable method for constructing the spirodihydrobenzofuran backbone, we turned our attention to the synthesis of myrtuspirone A (**1**). The synthesis commenced with a gram-scale reaction using substrates **2** and **3**, and desired product **4** (most likely via intermediate **9**) was obtained in 63% yield on a 2.0 g scale (Scheme 2). Subsequently, product **4** underwent one transformation; upon treatment of **4** with $ZnMe_2$ in THF, Negishi coupling product (±)-myrtuspirone A (**1**) was generated in 65% yield. Furthermore, inspired and encouraged by our previous work,[3d] we treated compound **2** with **3** in the presence of catalyst (*S*)-C**1** in PhMe at −70 °C for 6 days,[3d,10] followed by THF and NIS (2.5 equiv) in the same pot. Rewardingly, spiro-compound (−)-**4** was obtained in 55% yield on a 1.0 g scale (Scheme 2). Compound (−)-**4** also readily underwent a Negishi coupling reaction with $ZnMe_2$ to provide (−)-myrtuspirone A (**1**, 90% ee, after recrystallization: >99% ee). The ^1H and ^{13}C NMR spectra of synthetic **1** were identical to those of the natural product (see the Supporting Information).

The antibacterial activities of (+)-**1**, (−)-**1**, and (±)-**1** were evaluated against six Gram-positive and five Gram-negative bacteria (see the Supporting Information). All compounds exhibited moderate antibacterial activities against Gram-positive bacteria, including three multidrug-resistant strains (MRSA, VISA, and VRE) with MIC values in the range of 16 to 32 μg/mL. The results also showed that there is no obvious

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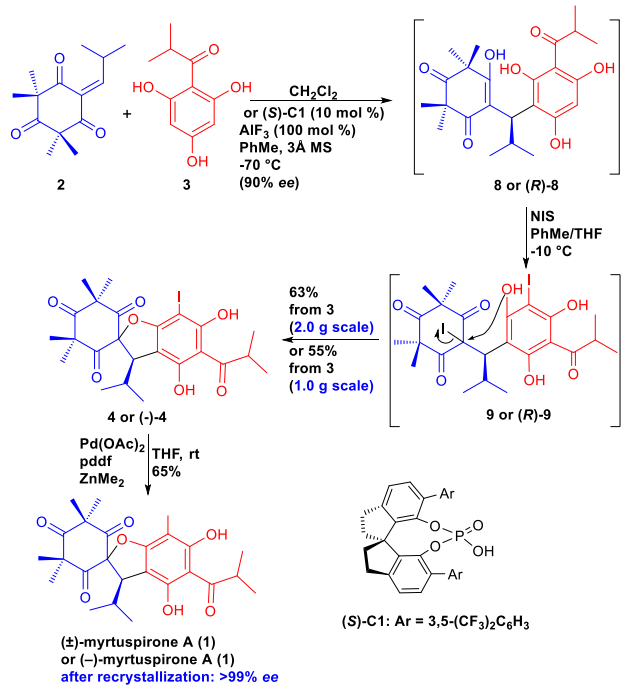
Scheme 2. Total Syntheses of (±)-1 and (−)-(1)



difference in the antibacterial activity of each enantiomer of myrtuspirone A (**1**).

In conclusion, a pair of enantiomeric triketone−phloroglucinol hybrids, (+)- and (−)-myrtuspirone A (**1**), with an unprecedented skeleton were isolated from the leaves of *M. communis*. Furthermore, the bioinspired total syntheses of (±)-**1** and (−)-**1** were achieved in only four steps in 33.5 and 29.3% overall yield, respectively. This synthetic strategy was enabled by a unique Michael−NIS-mediated (3 + 2)-annulation approach, which shows excellent redox and step economy and avoids the need for protecting groups. Moreover, myrtuspirone A (**1**) exhibited moderate antibacterial activity against Gram-positive bacteria including some multidrug-resistant strains. This work presents an unusual natural product with a new skeleton and a new approach to the synthesis of the spirodihydrobenzofuran backbone. Further studies on the syntheses and antibacterial activities of analogues of myrtuspirone A are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00108.

Detailed descriptions of the experimental procedure; UV, IR, MS, and NMR spectra for compound **1**; ECD calculations for **1** (PDF)

Accession Codes

CCDC 1875660 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chywc@aliyun.com.
*E-mail: cpuwanglei@126.com.
*E-mail: ccli@sustc.edu.cn.

ORCID

Ying Wang: 0000-0003-4524-1812
Chuang-Chuang Li: 0000-0003-4344-0498
Lei Wang: 0000-0001-9242-1109
Wen-Cai Ye: 0000-0002-2810-1001

Author Contributions

‖M.-J.C. and X.-Y.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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