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# Naphthospironone A: An Unprecedented and Highly Functionalized Polycyclic Metabolite from an Alkaline Mine Waste Extremophile

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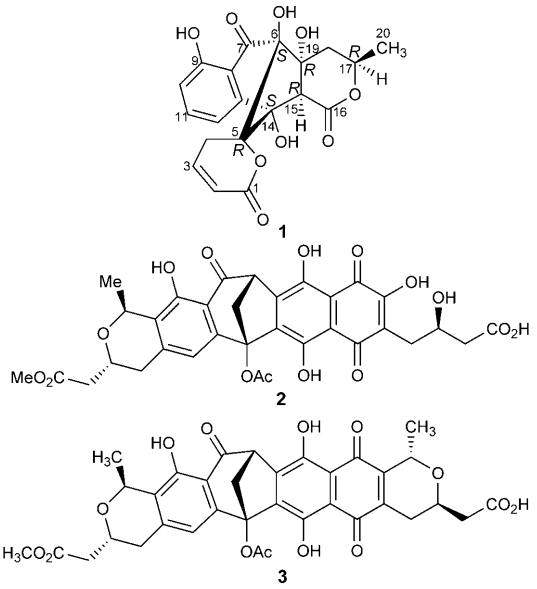
*Dedicated to Professor Han-Dong Sun on the occasion of his 70th birthday*

Extremophiles, microorganisms surviving in various extreme environments, have developed unique defenses that either tolerate or favor extremes of pH, temperature, salinity, pressure and radiation. These special characteristics frequently lead to synthesis of novel molecules encompassing a variety of unusual structural classes with significant biological activities.[1] In comparison with extremophiles from natural environments, microorganisms isolated from man-made extreme environments are emerging as a valuable resource for bioactive natural products. For example, Stierle and coworkers have recently isolated several novel molecules, including berkelic acid, which inhibits protein-cleaving enzymes caspase-1 and matrix metalloproteinase-3, from acidophilic fungi found in Berkeley Pit Lake (an abandoned copper mine filled with acidic water at pH 2.7).[2] This implies that there are miniature natural product libraries to be found in the most unexpected places. Extremophiles surviving in man-made extreme environments around the world could be an untapped mine for drug discovery.

Inspired by Stierle's work, we profiled the metabolite patterns of alkalophilic actinomycetes, which were isolated from an alkaline soil sample (pH 10) collected from the Datun tin mine tailings area (Yunnan province, Southwest China; 103°18′36″ E, 23°22′12″ N; formed by the materials remaining after extraction and beneficiation of tin ores over 50 years). The TLC and HPLC-DAD analysis of the acetone extract of *Nocardiopsis* sp. (YIM DT266) revealed the presence of a new metabolite, naphthospironone A (**1**, Scheme 1). The compound was obtained as a colorless solid (3 mg $L^{-1}$) by standard chromatographic procedures from solid fermentation (30 L) of the strain. Even though some structural elements resemble those of actinomycetes metabolites, such as α-naphthocyclinone (**2**) and β-naphthocycli-




Scheme 1. Absolute configuration of naphthospironone A (**1**) and related metabolites (**2**, **3**) from *Streptomyces arenae*.

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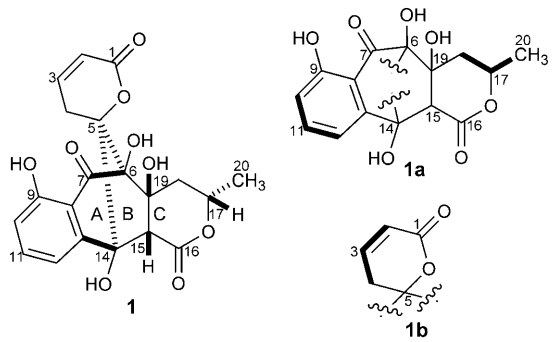
none (**3**) from *Streptomyces arenae* (Scheme 1)[3] the presence of an unusual spiro[bicyclo[3.2.1]octene-pyran]dione ring system in **1** makes it chemically unique. Here, we report the complete structural assignment with the absolute stereochemistry and biological activity of the novel compound naphthospironone A from tin mine tailings derived actinomycetes of the genus *Nocardiopsis*.

The molecular formula of naphthospironone A, $C_{20}H_{18}O_9$, was derived from the HR-ESIMS of the protonated molecular ion $[M+H]^+$ ($m/z$ found: 403.1021, calcd: 403.1023) and was in accord with $^1$H and $^{13}$C NMR spectroscopic data. While the UV spectrum in MeOH showed maximum absorption at 227 nm, the IR spectrum in KBr clearly suggested the presence of ester or keto groups based on two intense sharp bands at 1741 and 1665 cm$^{-1}$, as well as characteristic bands of hydroxyl groups at 3332 cm$^{-1}$.

Further insight into the structure of naphthospironone A was provided by its NMR spectra recorded in [D$_6$]DMSO. The $^{13}$C NMR spectra of **1** contained signals for all 20 carbon atoms and revealed the presence of one ketone group ($\delta_C$=200.6 ppm), two ester or lactone groups ($\delta_C$= 174.4 and 161.5 ppm), three olefinic quaternary carbon atoms, five olefinic methine carbon atoms, four oxygenated quaternary carbon atoms ($\delta_C$=79.2, 80.9, 90.3, and 93.1 ppm), one oxymethine group ($\delta_C$=72.3 ppm), one methine group, two methylene groups, and one methyl group (Table 1). Three carbonyl signals and eight olefinic signals in the $^{13}$C NMR spectrum accounted in total for seven double bond equivalents, with the rest having to be edited into five rings in the molecule. Fourteen protons of the elemental composition $C_{20}H_{18}O_9$ of **1** could be assigned unambiguously to their corresponding carbons in the HSQC spectrum. The remaining four protons were identified as hydrogen atoms of hydroxyl groups because the $^1$H NMR signals at $\delta$=11.07 (1H), 7.42 (1H), 6.15 (1H) and 5.50 ppm (1H) immediately disappeared after addition of $D_2O$ (20 μL) to the sample in [D$_6$]DMSO. The exchangeable protons at $\delta$=11.07, 7.42, 6.15 and 5.50 ppm were assigned as hydroxyl groups at positions C-9, C-14, C-6 and C-19 based on HMBC correlations, respectively.

Analysis of the COSY and HMQC-TOCSY spectra of **1** revealed the presence of three discrete $^1$H,$^1$H spin systems: H-2/H-3/H$_2$-4, H-10/H-11/H-12, and H$_3$-20/H-17/H$_2$-18, while H-15 was isolated. Comprehensive analysis of HMBC spectrum of **1** resulted in the elucidation of two main structural fragments **1a** and **1b** (Scheme 2). In fragment **1a**, a 3,4-di-




Scheme 2. Relative configuration of **1** (solid and broken bars indicate the relative stereochemistry) and partial structures **1a**, **1b** (bold bonds indicate connectivities as deduced by COSY data).

substituted 4-hydroxy-6-methyltetrahydro-2*H*-pyran-2-one moiety was deduced from the HMBC correlations of H-15, H-17 and H-18β with oxygenated quaternary carbon C-19, as well as H-15, H$_2$-18 and H-20 with the tetrahydropyranone carbonyl C-16. Additionally, the HMBC correlations of 6-OH with the carbonyl C-7 and C-19, 14-OH with C-13 and C-15, H-15 with oxygenated quaternary carbons C-6 and C-14, enabled the connections of C-19/C-6/C-7 and C-15/C-14/C-13 to be assigned. Furthermore, the 1,2,3-trisubstituted phenyl group fused into fragment **1a** at positions C-8/C-13 was deduced by the $^3J_{C,H}$ couplings (H-10, H-12 and 9-OH/C-8; H-11/C-13; H-12/C-14) and $^4J_{C,H}$ couplings (H-11/C-8; H-10 and H-12/C-7; H-10/C-13; H-11/C-14) observed in the HMBC spectrum. Thus, a fused six/seven/six-membered cyclic skeleton was deduced for fragment **1a**. Similarly, fragment **1b** was established as a 6,6-disubstituted 5,6-dihydro-2*H*-pyran-2-one moiety by the HMBC correla-

Table 1. NMR spectral data for **1** in [D$_6$]DMSO.[a]

| Position | $\delta_C$ (ppm) | $\delta_H$ (ppm) | Position | $\delta_C$ (ppm) | $\delta_H$ (ppm) |
|---|---|---|---|---|---|
| 1 | 161.5 (s) | – | 13 | 146.6 (s) | – |
| 2 | 118.4 (d) | 5.57 (d, $J$=9.8 Hz, 1H) | 14 | 80.9 (s) | – |
| 3 | 144.1 (d) | 6.4 (m, 1H) | 15 | 52.6 (d) | 2.50 (s, 1H)[b] |
| 4α | 23.4 (t) | 2.07 (dt, $J$=19.8, 3.0 Hz, 1H) | 16 | 174.4 (s) | – |
| 4β | – | 1.80 (dd, $J$=19.8, 3.0 Hz, 1H) | 17 | 72.3 (d) | 4.35 (m, 1H) |
| 5 | 90.3 (s) | – | 18α | 41.2 (t) | 1.92 (dd, $J$=14.7, 11.6 Hz, 1H) |
| 6 | 93.1 (s) | – | 18β | – | 1.67 (d, $J$=14.7 Hz, 1H) |
| 7 | 200.6 (s) | – | 19 | 79.2 (s) | – |
| 8 | 114.9 (s) | – | 20 | 20.5 (q) | 1.04 (d, $J$=6.1 Hz, 3H) |
| 9 | 159.8 (s) | – | 6-OH | – | 6.15 (s, 1H) |
| 10 | 116.9 (d) | 6.72 (d, $J$=8.6 Hz, 1H) | 9-OH | – | 11.07 (s, 1H) |
| 11 | 137.1 (d) | 7.39 (dd, $J$=7.3, 8.6 Hz, 1H) | 14-OH | – | 7.42 (s, 1H) |
| 12 | 116.1 (d) | 7.12 (d, $J$=7.3 Hz, 1H) | 19-OH | – | 5.50 (s, 1H) |

[a] The $^1$H NMR spectrum was recorded at 500 MHz, the $^{13}$C NMR spectrum at 125 MHz. [b] The signal is overlapped by a signal due to [D$_6$]DMSO; in $CDCl_3$, $\delta$=2.63 (s).

tions of H-2 and H-4β with the dihydropyranone carbonyl C-1, as well as $H_2$-4 with the oxygenated quaternary carbon C-5. Fragments **1a** and **1b** were linked through three oxygenated quaternary carbons C-6/C-5/C-14 as evidenced by HMBC correlations of H-15, 6-OH and 19-OH with C-5, as well as $H_2$-4 with C-6 and C-14. Combination of fragments **1a** and **1b** through the linkage of C-6/C-5/C-14 led to formation of a unique spiro[bicyclo[3.2.1]octene-pyran]dione ring system in the molecule (Scheme 2).

As for the relative stereochemistry, NOE correlations (ROESY) between H-18α and $H_3$-20 revealed C-20 to be α oriented. The NOEs between H-18β and H-17, H-17 and H-15, H-15 and 19-OH, H-15 and 14-OH, and H-4β and 6-OH indicated a β orientation for H-15, H-17, 6-OH, 14-OH and 19-OH. The β orientations between 6-OH and 14-OH, H-15 and 19-OH, led to *cis*/*cis* configurations for the A/B/C ring (Figure 1). The dihydropyranone moiety was situated

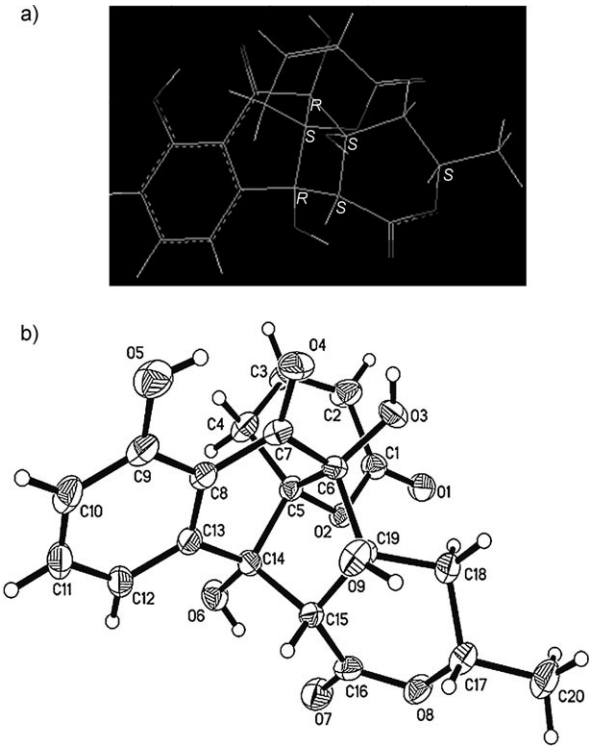



Figure 1. X-ray crystallographic structure of **1**. a) Chirality labeled X-ray structure; b) X-ray experimental structure.

below the molecule at the spiro quaternary carbon C-5 because of α orientation between C-6/C-5 and C-14/C-5. In the $^1$H NMR spectrum the $\Delta^{2,3}$ *cis* configuration of the double bond was implied from the vicinal coupling constant of 9.8. Only the stereochemistry of the dihydropyranone attachment at position C-5 was still to be determined. The relative configuration of **1** was finally confirmed by single-crystal X-ray diffraction analysis (Scheme 2 and Figure 1).[4]

Absolute configuration of the six stereogenic centers in **1** was assigned by comparing computed optical rotation (OR) and experimental OR by using DFT methods that Stephens, Wipf, and other research groups have used.[5] These methods provided us with highly useful guidance in our recent absolute configurations studies.[6] Because of its very rigid ring system structure, only two stable conformations were found with the relative energy from 0–2.5 kcal mol$^{-1}$ at the B3LYP/6-31G(d) level. The two conformations were then used for OR calculations at the B3LYP/aug-cc-pVDZ level. The final OR computed for the suggested structure was +74.3 in the gas phase. It decreased to +66.2 in methanol when using single point energy (SPE) obtained at the B3LYP/aug-cc-pVDZ level with the PCM model. The OR increased a little to +72.2 in the gas phase when B3LYP/6-311+G(d,p)-optimized geometries were used in OR computations at the B3LYP/aug-cc-pVDZ level. It decreased to +71.9 by using SPE in methanol. Indeed, the recorded optical rotation was −57.4 cm$^3$ g$^{-1}$ dm$^{-1}$ ($c$ = 0.0055 g cm$^{-3}$ in MeOH). Its absolute value (57.4) is very close to the computed data (from 66.2 to 74.3) however, the OR signs are contrary. Due to the relative configuration of **1**, which was clear and confirmed by 2D NMR spectroscopy and X-ray experiments, the proposed structure must be the enantiomer of the real geometry (Scheme 2 and Figure 1). Accordingly, the absolute configurations of the six stereogenic centers in **1** are 5*R*, 6*S*, 14*S*, 15*R*, 17*R*, and 19*R* (Scheme 1).

Considering its low molecular mass, **1** contains an unusually large number of ring systems, quaternary carbons, and stereocenters. The bicyclo[3.2.1]octenone motif in **1** indicates a likely relationship to naphthocyclinone-type antibiotics,[3] for example, **2** and **3**, which have a very similar counterpart bicyclo[3.2.1]octadienone, and were originally isolated by Zeeck and co-workers from mycelium of *Streptomyces arenae* (Scheme 1). Although **1** shares the similar bicyclic ring system with **2** and **3**, it is uniquely functionalized. More specifically, the methylene bridge carbon of bicyclo[3.2.1]octadienone in **2** and **3** is oxidized to the spiro-bridge carbon in **1** by substitution of the methylene bridge protons in **2** and **3** with oxygen and methylene carbon of dihydropyranone in **1**. Thus, a unique spiro[bicyclo[3.2.1]octene-pyran]-dione ring system is formed in **1**, which is unprecedented among natural products. Further structural features characteristic of **1** are three hydroxyl groups at the C-6, C-14 and C-19 of ring juncture, and a tetrahydropyranone moiety fused with bicyclo[3.2.1]octenone ring system at C-15/C-19 positions.

In our general bioactivity profiling program, naphthospironone A (**1**) exhibited moderate cytotoxicity against HeLa, L929 and AGZY cells with $IC_{50}$ values in the range of 32–89 μg mL$^{-1}$. The MIC values of **1** for *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Aspergillus niger* were in the range of 11–25 μg mL$^{-1}$. From biogenesis and structural points of view, bioactivities of **1** were similar to that of kalafungin,[7] (+)-nanaomycin A,[8] griseusins,[9] and naphthocyclinones,[3] which were isolated from alkalophilic actinomycete *Nocardia dassonvillie*, *Nocardia* sp. (YS-02931K), *Nocardiopsis* sp. (YIM80133, DSM1664), and *Streptomyces arenae*, respectively.

We assume that **1** is formed by the polyketide biosynthesis pathway in analogy to naphthocyclinone-type antibiotics.[10] It can be reasoned that oxygenation of the polyketide backbone at C-5, C-6, and C-19 requires additional enzymatic oxygenation of the polyketide skeleton. Further investigations on biosynthetic precursors of **1** and the isolation of naphthospironone variants are currently in progress.

## Experimental Section

**Strain and cultivation**: Alkalophilic *Nocardiopsis* sp. (YIM DT266) was isolated from an alkaline soil sample (pH 10) collected from the Datun tin mine tailings area (103°18′36″ E, 23°22′12″ N), Yunnan province, Southwest China. It was classified according to 16S RNA analysis with 97.3 % identity. A voucher specimen is deposited at Yunnan Institute of Microbiology, Yunnan University with the code YIM DT266. The cultivation was performed in 1000 agar plates composed of glucose (1.0 %), peptone (0.5 %), yeast extract (0.5 %), $K_2HPO_4$ (0.1 %), $MgSO_4{\cdot}7H_2O$ (0.02 %), $Na_2CO_3$ (1.8 %) and agar (1.5 %) in distilled $H_2O$, pH 12. Sodium carbonate was sterilized separately and then added to the medium. The plates were incubated at 28 °C for 15 days.

**Extraction, isolation and purification**: The cultured plates were extracted with acetone. The extract was concentrated under reduced pressure and the aqueous residue was extracted with EtOAc. The EtOAc fraction was first chromatographed on a silica gel flash chromatography eluted with $CHCl_3$/MeOH (9:1) and then fractionated by using Sephadex LH-20 eluted with MeOH. Further purification was achieved by preparative reversed-phase HPLC by using an isocratic elution of MeOH/$H_2O$ (5:5) to obtain naphthospironone A (**1**, yield: 3 mg $L^{-1}$, $t_R$ 11.2 min). Finally, slow recrystallization of **1** from MeOH/$H_2O$ (99:1) furnished single crystals suitable for X-ray experiment.

**Computational methods**: Stable conformations were searched by different methods, such as by using HyperChem V8.0. Due to its very rigid ring system, only two stable conformations were found with the relative energy from 0–2.5 kcal $mol^{-1}$ at the B3LYP/6-31G(d) level. The two conformations were then used in optical rotation values by using the B3LYP method at the basis set of aug-cc-pVDZ. The final optical rotation was obtained by using the Bolzmann sum formula. The geometries were then optimized again at the B3LYP/6-311+G(d,p) level, and they were used in optical rotation computations again at the B3LYP/aug-cc-pVDZ level. Single point energy (SPE) computations were performed at the B3LYP/aug-cc-pVDZ in methanol by using the PCM model. The SPE magnitudes were then used in OR correction in methanol. The results are listed in Tables S2 and S3 in the Supporting Information. The 3D model with labeled relative configurations for X-ray structure is listed in Figure S11 in the Supporting Information for easy examination.

**Data for 1**: Colorless solid; m.p. 173 °C (decomp.); $[\alpha]_D^{25} = -57.4\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.0055\ g\,cm^{-3}$ in MeOH). 1D and 2D NMR data are summarized in Table S1 in the Supporting Information. IR (KBr) $\nu_{max} = 3332, 1741, 1665, 1617, 1457, 1242, 1081\ cm^{-1}$. UV (MeOH), $\lambda_{max}$ ($\log\varepsilon$) = 226.8 (4.2), 261.0 (3.9), 334.7 (3.7). HR-ESIMS: $C_{20}H_{18}O_9$. $[M+H]^+$ *m*/*z* calcd: 403.1023, found: 403.1021. $[M+NH_4]^+$ *m*/*z* calcd: 420. 1289, found: 420.1297. $[M+Na]^+$ *m*/*z* calcd: 425.0843, found: 425.0840.

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[4] X-ray measurements were made on a SMART CCD area detector with graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); **1** ($MF = C_{20}H_{18}O_9$, $M_r = 402.35$): crystal dimensions $0.28 \times 0.26 \times 0.15$ mm, orthorhombic, space group $P2_12_12_1$, $a = 11.4904(11)$ Å, $b = 11.7218(11)$ Å, $c = 13.5314(12)$ Å, $V = 1822.5(3)$ Å$^3$, $Z = 3$, $\rho_{calcd} = 1.466\ mg\,m^{-3}$, $\mu = 0.117\ mm^{-1}$, $T = 298(2)$ K, $2\theta_{max} = 56.6°$, 11790 measured reflections, 4279 independent reflections ($R_{int} = 0.0212$), 268 parameters refined, $R = 0.0365$ (for 4279 reflections with $I > 2.00\sigma(I)$), $R_w = 0.1187$, max/min residual peaks in the final difference map 0.195/−0.145 e Å$^{-3}$. CCDC-752596 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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