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Total synthesis, structure revision and cytotoxic activity of Sch 53825 and its derivatives†

 Leichuan Xu,  Haoyun Ma, Xinkun An, Yihao Li, Qian Zhang, Xinlei Liu and Mangan Wang*

The first total synthesis of Sch 53825 (**14**) was achieved in 12 steps from 5-hydroxy-1-tetralone in 16% overall yield through *N*-benzyl cinchoninium chloride-catalyzed asymmetric epoxidation and a Mitsunobu reaction as the key steps. On this basis, the synthesis of palmarumycin B₆ was improved using the same raw material with 6 steps and 32% overall yield. Also, three new analogues with two chlorine atoms were synthesized. Their structures were characterized by ¹H, ¹³C NMR, HR-ESI-MS and X-ray diffraction data. The structure of natural Sch 53825 was revised as an epimer of compound **1** with the anti-hydroxy epoxide at C-4. Their cytotoxic activities against several tumor cell lines (HCT116, U251, BGC823, Huh-7 and PC9) showed that compound **11** exhibited excellent cytotoxicity against above mentioned cancer cell lines with IC₅₀ < 0.5 μM.

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Introduction

Spirobisnaphthalenes (spirodioxynaphthalenes) belong to a novel family of natural products isolated from fungi and plants. Generally, they are divided into four subtypes, types A, B, C and D, according to the different linkages of the two naphthalene rings.^{1,2} Spirobisnaphthalenes have attracted much attention because of their unique structures and broad spectrum of biological activities including antibacterial, antifungal, herbicidal, insecticidal, cytotoxic and antitumor activities.^{1,2} In the past thirty years, many reports related to the total synthesis and bioactivity evaluation of the spirobisnaphthalene natural products have appeared, such as palmarumycin CP₁, CP₂, CP₁₇, preussomerin G, I, K and L.^{3,4} Recently, the biomimetic synthesis of rhytidenone A and elucidation of mode of action of the cytotoxic rhytidenone F were reported, the result showed that rhytidenone F had potent antitumor activity against several cancer cell lines with IC₅₀ values of 0.01–0.82 μM.⁵ Spiroxins A–E were isolated from a marine-derived fungus, and are a type of DNA cleaving antitumor antibiotics.⁶ Spiroxins A, C and D have also been synthesized in three groups.⁷ The derivatives of spiroamakone A, isolated in 2006, showed excellent cytotoxicity against cervical carcinoma HeLa cells.⁸ Spiromamakone A was totally synthesized by Doi and co-workers in 2018 and revised the structure of spiro-preussione A, which was isolated in 2009.⁹ Spiroaxillarone A, an unique spirobisnaphthalene natural product, which was isolated from *Cyanotis axillar* in

2019, has been synthesized *via* 5 steps in overall yield of 10%.¹⁰ Besides, it was reported that plecmillin A has excellent growth inhibition effect against human colorectal HCT116 cell line with IC₅₀ 2.08 μM and could induce both cell cycle arrest at G₂/M phase and cell death through the P53–P21 pathway.¹¹ Rhytidenone F also exhibited excellent growth inhibition effect against several cancer cell lines with IC₅₀ 0.01–0.82 μM, and the pulldown assay coupled with mass spectrometry analysis revealed the target protein PA28γ is covalently attached to rhytidenone F at the Cys92 residue. The interactions of rhytidenone F with PA28γ lead to the accumulation of P53. Consequently, the Fas-dependent signaling pathway is activated to initiate cellular apoptosis.⁵ These results indicated that these types of compounds are promising natural product leads for the discovery and development of antitumor drugs.

In our previous work, the total synthesis of several spirobisnaphthalenes such as palmarumycin B₆ (**2**, Fig. 1a) and C₁ (**3**, Fig. 1b) have been finished, and also revised the structure of palmarumycin B₆.^{12a,b} The bioassay results showed that palmarumycin B₆ had the larvicidal activity with an LC₅₀ value of 32.7 μM,^{12b} and also palmarumycin C₁ and guignardin E exhibited significant cytotoxicity against several tumor cell lines with an IC₅₀ in the range of 2.45–15.39 μM towards HCT116, U87-MG, HepG2, BGC823 and PC9.^{12c}

In 1996, Chu and co-workers identified two novel spirobisnaphthalene compounds Sch 53823 and Sch 53825 (**1**, Fig. 1c) from the fermentation broth of an unidentified fungus collected from the dead leaves of *Ruercus virginiana* Miller growing in Tamalupas, Mexico.¹³ Sch 53823 was easily obtained from reduction of palmarumycin C₂. Interestingly, Sch 53825, which has a chlorine atom on the *ortho* position of hydroxyl group, exhibited *in vitro* inhibitory activity in the

Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, People's Republic of China. E-mail: wangma@cau.edu.cn

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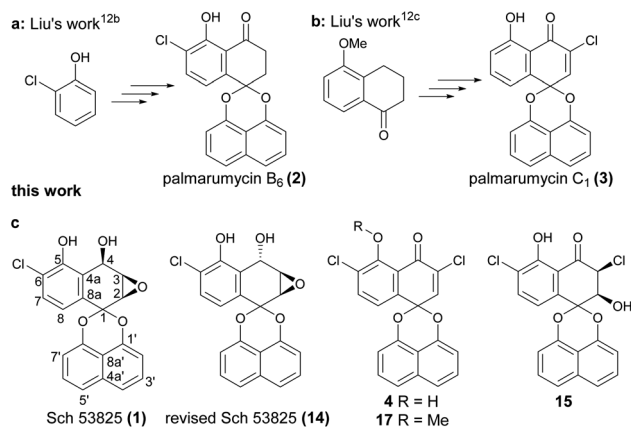


Fig. 1 The structures of Sch 53825, palmarumycin B₆ (a), C₁ (b), and three new derivatives (c).

formylmethionyl leucyl phenylalanine (fMLP)-stimulated phospholipase (PLD) assay with an IC₅₀ value of 19 μM.

From the structure point, Sch 53825 and palmarumycin B₆ should have the same biosynthetic pathway, and to the best of our knowledge, total synthesis of Sch 53825 or its structure modification has not been reported to date. Also, the absolute configuration of Sch 53825 has not been verified. Based on these and the excellent phospholipase D inhibitory activity of Sch 53825, it attracted our attention after we completed the synthesis of palmarumycin B₆.^{12b} So we launched a project to investigate the synthesis and druggability of the target compound. Chlorinated spirobisenaphthalenes generally have better biological activity in this kind of natural products. For example, Spiroxin A exhibited a mean cytotoxicity (IC₅₀ = 0.09 μg mL⁻¹), which was stronger than spiroxin C and D.^{6a} Moreover, due to the excellent larvicidal and antitumor activity of palmarumycin B₆ and C₁ respectively, the three new Sch 53825 derivatives with two chlorine atoms (4, 15, 17, Fig. 1c) were designed based on the character of the two structures and synthesized to further improve their larvicidal or antitumor activities. In this context, a feasible route for the total synthesis of Sch 53825 and its derivatives were designed, and their cytotoxic activities were also evaluated.

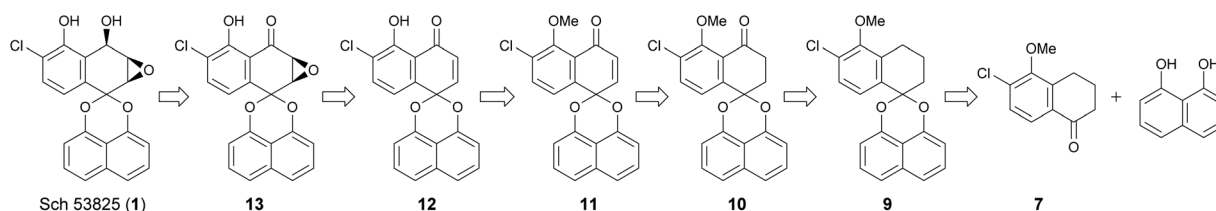
Results and discussion

The retro-synthetic analysis of Sch 53825 was shown in Scheme 1. Sch 53825 can be obtained through asymmetric reduction of 13, which can be synthesized by stereoselectivity

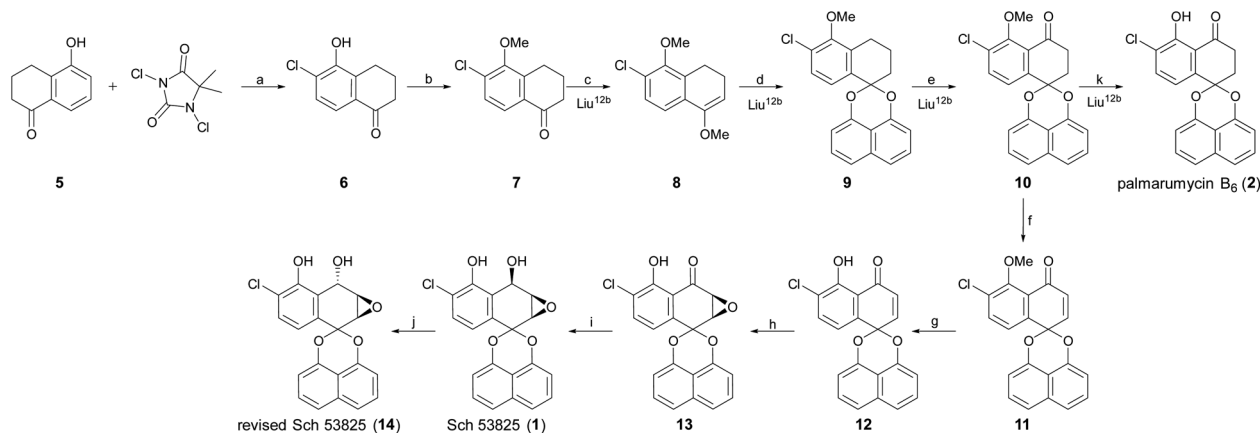
epoxidation of 12. Compound 12 can be prepared from a ketalization of 5-methoxy-6-chlorotetralone (7) and 1,8-dihydroxynaphthalene (DHN) in a similar process used in the synthesis of palmarumycin B₆.^{12b} Following the same procedure, we could obtain enough amount of compound 10 easily, the final assembly of Sch 53825 was carried out as summarized in Scheme 2.

First, starting with the intermediate ketone 10 of palmarumycin B₆, we attempted direct α,β-dehydrogenative oxidations by utilizing DDQ,^{12c} IBX, or iodic acid.¹⁴ However, both DDQ and IBX failed to introduce double bonds at the α,β-position in 10. Although the use of iodic acid successfully introduced the double bonds, one of the hydrogen atom on naphthalene ring of the target molecule will be substituted by iodine in the meantime since the oxidation reactions tend to produce varying amounts of detrimental iodine as a by-product.¹⁴ After extensive experiments, a ketone–enone conversion was conducted using Saegusa conditions in 82% yield.¹⁵ Then, compound 11 was demethylated with B-bromocatecholborane to afford compound 12 as the literature described.^{12c} Next, the stereoselective epoxidation of 12 with *t*-BuOOH catalyzed with *N*-benzyl cinchoninium chloride at 0 °C yielded epoxide 13 in 97.4% ee value.^{4c,12b} Two methods were tried to reduce the carbonyl of compound 13. First, palmarumycin CP₂ could be efficiently converted into its corresponding dihydro derivative (93% ee) by asymmetric reduction using (+)-B-chlorodiisopinocampheylborane.^{3a} But it was inactive with our substrate. In the synthesis of palmarumycin C₁₁, *syn*-hydroxy epoxide was achieved in one step using sodium borohydride.^{3d} Thus, Sch 53825 (1) was obtained using this method, and confirmed the *syn*-hydroxy epoxide structure with X-ray crystallographic data. It could also be found that the proton on C-4 is spatially correlated with the protons on C-2 and C-3 positions from NOESY spectra of compound 1 (Fig. S17†).

After completion the reported structure of Sch 53825, it was found that its ¹H, ¹³C NMR and optical rotation data were not consistent with those of the reported natural product (Fig. 2).¹³ The chemical shifts of protons on C-2, C-3 and C-4 lie in a higher-field region than those of the natural product, the chemical shifts of carbon on C-2, C-3 and C-4 lie in a lower-field region than those of the natural product (Table 1). These differences in the chemical shifts may be related to the relative configuration of hydroxy at C-4. Thus, it was hypothesized that the correct structure of Sch 53825 possibly was the epimer of compound 1 at C-4 with an anti-hydroxy epoxide. To verify the real structure of natural Sch 53825, Mitsunobu reaction was



Scheme 1 Retrosynthetic analysis of Sch 53825.



Scheme 2 Total synthesis of Sch 53825 and palmarumycin B₆ (2). Reagents and conditions: (a) diisopropylamine hydrochloride, toluene, $-10\text{ }^{\circ}\text{C}$, 93%; (b) CH_3I , K_2CO_3 , acetone, reflux, 97%; (c) $(\text{CH}_3\text{O})_3\text{CH}$, PPTS, MeOH, reflux; (d) 1,8-dihydroxynaphthalene, TsOH, toluene, reflux, 69% for two steps; (e) PDC, Celite, $t\text{-BuOOH}$, benzene, rt, 77%; (f) (I) TMSOTf, Et_3N , $0\text{ }^{\circ}\text{C}$, (II) $\text{Pd}(\text{OAc})_2$, CH_3CN , rt, 82% for two steps; (g) B-bromocatecholborane, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 77%; (h) *N*-benzylcinchoninium chloride, $t\text{-BuOOH}$, NaOH (0.1 M), toluene/ H_2O , $0\text{ }^{\circ}\text{C}$, 77%; (i) NaBH_4 , THF/MeOH, rt, 71%; (j) (I) *p*-nitrobenzoic acid, PPh_3 , DEAD, THF, $0\text{ }^{\circ}\text{C}$, (II) LiOH, THF/ H_2O , rt, 95% for two steps; (k) TMSI, CHCl_3 , $0\text{ }^{\circ}\text{C}$, 68%.

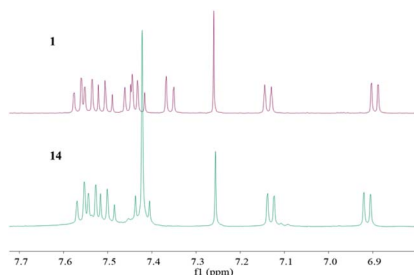


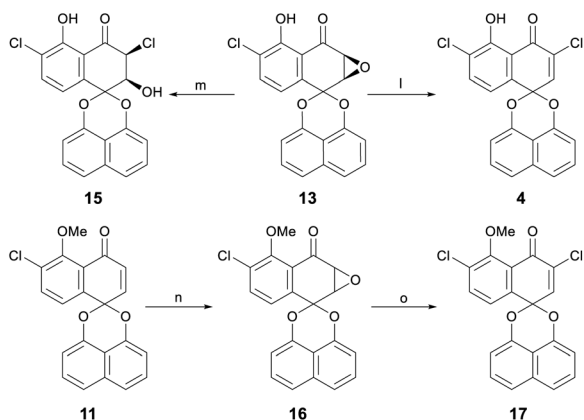
Fig. 2 Comparison of ^1H NMR spectra of compounds **1** and **14** in the low-field region.

employed to transfer **1** to its *p*-nitrobenzoate, then hydrolyzed with LiOH to afford the epimer **14**, the spectroscopic and optical rotation data of **14** is in accordance with that reported by Chu and co-workers.¹³ So, the total synthesis of Sch 53825 was first furnished in 12 steps and 16% overall yield from commercially available 5-hydroxy-1-tetralone (**5**), and the structure of Sch 53825 was revised to be the anti-hydroxy epoxide of **1**.

With the successful total synthesis of Sch 53825, its three analogues were explored. Compound **4** could be afforded conveniently by the usage of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ at reflux temperature from epoxide **13** using the same method

Table 1 The ^1H , ^{13}C NMR chemical shifts of Sch 53825, compounds **1** and **14**

Position	Sch 53825 (CDCl_3)		Compound 1 (CDCl_3)		Compound 14 (CDCl_3)	
	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}
1	—	97.5	—	96.53	—	97.65
2	3.81 (d, 4.0)	50.5	3.74–3.76 (m)	52.59	3.81 (d, 3.9)	50.73
3	3.72 (dd, 2.3, 4.0)	52.9	3.42–3.45 (m)	54.09	3.72 (dd, 2.4, 3.9)	52.75
4	5.66 (brd, 2.3)	61.5	5.47 (dd, 2.5, 10)	66.44	5.66 (brs)	62.03
4a	—	122.3	—	121.22	—	121.94
5	—	150.2	—	151.70	—	149.72
6	—	123.4	—	123.60	—	123.02
7	7.44–7.48 (m)	130.0	7.42–7.46 (m)	130.76	7.45–7.49 (m)	129.76
8	7.44–7.48 (m)	120.1	7.42–7.46 (m)	120.00	7.45–7.49 (m)	120.24
8a	—	131.3	—	130.90	—	131.64
1'	—	147.3	—	147.12	—	147.21
2'	7.42–7.63 (m)	121.2	7.51 (d, 7.5)	121.14	7.45–7.49 (m)	121.29
3'	7.42–7.63 (m)	127.6	7.57 (d, 7.8)	127.48	7.53–7.62 (m)	127.62
4'	6.97 (d, 7.3)	109.2	6.90 (d, 8.0)	109.11	6.97 (d, 7.4)	109.31
4a'	—	134.3	—	134.17	—	134.31
5'	7.18 (d, 7.3)	110.0	7.14 (d, 7.4)	110.07	7.18 (d, 7.4)	110.12
6'	7.42–7.63 (m)	127.9	7.55 (d, 8.2)	127.79	7.53–7.62 (m)	127.88
7'	7.42–7.63 (m)	121.2	7.37 (d, 8.4)	120.41	7.53–7.62 (m)	121.25
8'	—	147.4	—	147.16	—	147.24
8a'	—	112.9	—	112.80	—	112.94



Scheme 3 Synthesis of three derivatives of Sch 53825. Reagents and conditions: (l) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{MeOH}/\text{H}_2\text{O}$, reflux, 92%; (m) CeCl_3 , MeCN , rt, 47%; (n) $t\text{-BuOOH}$, TBD, toluene, rt, 87%; (o) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{MeOH}/\text{H}_2\text{O}$, reflux, 78%.

described in our previous work,^{12c} while compound **15** with hydroxy at β -position was obtained when CeCl_3 was used in CH_3CN at room temperature. In addition, compound **17** was synthesized from **11** through the same method to investigate the differences of hydroxy and methoxy at C-5 position of these compounds on cytotoxicity (Scheme 3).

After finishing the synthesis of the desired compounds, all structures were characterized with the ^1H , ^{13}C NMR, HR-ESI-MS data. In order to determine the absolute configuration of Sch 53825, the X-ray diffraction analysis of compound **1** was performed using $\text{Cu K}\alpha$ radiation and its structure was depicted in Fig. 3, which unambiguously showed that the absolute configuration of C-2, C-3 and C-4 were 2*R*, 3*R* and 4*R* in Flack parameter 0.002(15) (CCDC ID 2169161,† Fig. 3). Based on this result, the actual absolute configuration of C-2, C-3 and C-4 of Sch 53825 (**14**) should be 2*R*, 3*R* and 4*S*. The C-2 and C-3 absolute configuration of compound **15** were 2*S* and 3*S*.

In addition, it should be noted that in our previous synthetic route of palmarumycin B₆,^{12b} compound **7** was prepared from 2-chlorophenol through **9** steps with a total yield of 10%. This was very inefficient in preparing compound **7**, so regioselective chlorination and then methylation of commercially available 5-hydroxy-1-tetralone (**5**) were attempted. The improved synthetic

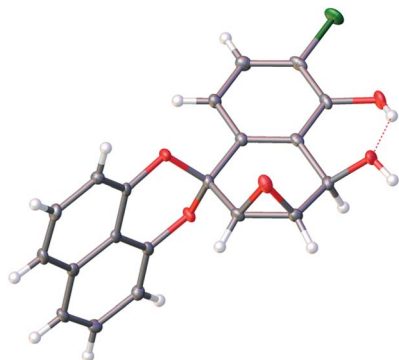


Fig. 3 ORTEP drawing of compound **1**.

Table 2 Cytotoxic activities of compounds **1**, **2**, **4**, **9–15**, **17** (IC_{50} , μM)

Compounds	HCT116	U251	BGC823	Huh-7	PC9
1	>50.0	>50.0	>50.0	>50.0	>50.0
2	47.11	>50.0	32.12	>50.0	>50.0
4	19.71	14.11	11.03	13.64	19.65
9	31.10	>50.0	4.02	>50.0	>50.0
10	24.56	>50.0	49.33	>50.0	24.16
11	<0.5	0.38	<0.5	<0.5	<0.5
12	23.65	16.69	9.82	12.79	17.34
13	18.60	5.39	13.05	1.42	7.14
14	>50.0	>50.0	>50.0	>50.0	>50.0
15	4.07	13.27	3.22	12.91	3.21
17	>50.0	21.46	4.69	13.86	16.97
Taxol	0.000037	1.667	0.000605	0.007930	0.000044

route of palmarumycin B₆ was delineated in Scheme 2. First, there are many novel reports about the aromatic chlorination,¹⁶ but only 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, 1.2 eq.) was convenient to this substrate.^{16b} The key intermediate 5-methoxy-6-chlorotetralone (**7**) was afforded successfully through two steps on this base. It is worth mentioning that there would appear an 6,8-dichlorinated by-product when the temperature was risen to room temperature. The latter experimental procedures were followed our previous reported methods.^{12b} Here, a convenient synthetic route of palmarumycin B₆ from 5-hydroxy-1-tetralone was finished in 32% total yield within 6 steps.

The cytotoxic activities of these compounds against the tumor cell lines (HCT116, U251, BGC823, Huh-7 and PC9) were evaluated using a MTT assay^{11,12a} and the results are shown in Table 2. These results indicated that compound **11** exhibited excellent cytotoxicity against above mentioned cancer cells ($\text{IC}_{50} < 0.5 \mu\text{M}$), while its demethylation product **12** had a reduced activity against these five cancer cells. In addition, compound **10** exhibited weaker cytotoxic activity than compound **11** having a α,β -unsaturated double bond. Comparison with the IC_{50} data of compounds **1**, **13** and **14**, we found that the reduction products of carbonyl group at C-4 (**1** and **14**) were inactive against these cancer cells ($\text{IC}_{50} > 50 \mu\text{M}$). The new target (**4**), bearing two chlorine atoms at the C-3 and C-6 positions, respectively, didn't have an increased cytotoxicity compared with palmarumycin C₁₁ (ref. 2c) as we expected, while its synthetic precursor (**15**) which is not dehydrated exhibited significant cytotoxicity with an IC_{50} in the range of 3.21–13.57. Furthermore, compound **17** with a methoxy exhibited stronger cytotoxic activity ($\text{IC}_{50} = 4.69 \mu\text{M}$) against BGC823 than compound **4** ($\text{IC}_{50} = 11.03 \mu\text{M}$) with a hydroxyl at C-5 position. These results indicated that the carbonyl at C-4, methoxy at C-5 and the α,β -unsaturated double bond play a critical role for cytotoxicity. This may provide some inspiration for further research on this kind of nature products.

Conclusions

In summary, Sch 53825 was first totally synthesized with a 16% overall yield for 12 steps and the structure was revised, also the

absolute configuration of Sch 53825 was confirmed. On the base, the synthesis of palmarumycin B₆ was improved greatly with a 32% total yield for 6 steps. Further, three new analogues (4, 15, 17) with two chlorine atoms in the molecule were synthesized. These compounds were characterized by ¹H, ¹³C NMR, HR-ESI-MS data and X-ray diffraction. Compound 11 displayed excellent cytotoxic activity against HCT116, U251, BGC823, Huh-7 and PC9 cell lines. Further biological studies and action mechanism of compound 11 are currently in progress in our lab.

Experimental

General experimental procedures

Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Flash column chromatography was performed using Qingdao Haiyang silica gel (200–300 mesh). Melting points (uncorrected) were measured on a WRX-4 microscopic melting point apparatus (Shanghai Yi Ce Instrument Factory). All ¹H and ¹³C NMR spectra were obtained on Bruker DPX 300, 400 and 500 MHz spectrometer with CDCl₃ as solvents and TMS as an internal standard. Chemical shifts are given in δ relative to residual solvent peak (usually chloroform: δ 7.26 for ¹H NMR or 77.16 for ¹³C NMR), and coupling constants (*J*) in Hz. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet). High-resolution mass spectrometry data were acquired using an Agilent 6520 Q-ToF analyzer. Optical rotation values were measured with a JASCO P-2000 Polarimeter. The crystal structure was analyzed with a Thermo Fisher ESCALAB 250 four-circle X-ray diffractometer (Xcalibur, Eos, Gemini). HPLC analyses were performed on an Agilent 1100 instruments, UV detection was monitored at 254 and 220 nm, an IB N-5 column (5 μ m, 4.6 \times 250 mm) was used as the chiral stationary phase, and hexane/*i*-PrOH (90 : 10) was used as the mobile phase at a flow rate of 1.0 mL min⁻¹.

5-Hydroxy-6-chlorotetralone (6). To a solution of 5-hydroxy-1-tetralone (5; 6.488 g, 40.0 mmol) and diisopropylamine hydrochloride (110 mg, 0.8 mmol) in anhydrous toluene (80 mL) were added 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (9.458 g, 48 mmol) in batches in an ice-salt bath. The resulting reaction mixture was stirred further for 3 h at -10 °C, then quenched with saturated Na₂SO₃ solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to give compound 6 (7.323 g, 93%) as a white powder. Mp 129–130 °C; (lit. 16 mp 133–135 °C); ¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 1H), 2.96 (t, *J* = 6.2 Hz, 2H), 2.64 (t, *J* = 8 Hz, 2H), 2.17–2.11 (m, 2H); ¹³C NMR (101 MHz, CDCl₃): δ = 197.82, 148.84, 132.70, 132.55, 126.64, 124.72, 119.77, 38.66, 23.51, 22.56. The data are consistent with that previous reported.¹⁷

5-Methoxy-6-chlorotetralone (7). To a solution of compound 6 (7.275 g, 37.0 mmol) and K₂CO₃ (6.129 g, 44.4 mmol) in

acetone (100 mL) were added CH₃I (7 mL, 111.0 mmol). The reaction mixture was heated to reflux for a further 4 h. The mixture was cooled to room temperature, and the solid was removed. The solvent was evaporated under vacuum, and the residue was diluted with EtOAc. The crude product was washed with saturated Na₂S₂O₃ solution and brine, and the combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 5 : 1) to give compound 7 (7.373 g, 97%) as a white solid. Mp 80–81 °C; (lit. 12b mp 82–84 °C); ¹H NMR (400 MHz, CDCl₃): δ = 7.77 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.2 Hz, 2H), 2.15–2.09 (m, 2H). The data are consistent with that previous reported.^{12b}

Synthesis of intermediates 9 and 10

The intermediates 9 and 10 were synthesized following the literature procedures, and their analytical data were consistent with the reported data.^{12b}

6-Chloro-5-methoxy-4H-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (11). To a stirred solution of compound 10 (110 mg, 0.3 mmol) in dry CH₂Cl₂ (5 mL) at 0 °C was added dry triethylamine (0.8 mL, 6 mmol) and TMSOTf (0.6 mL, 3 mmol) with syringe under a N₂ atmosphere. The mixture was stirred for another 1 h at 0 °C. Saturated NaHCO₃ solution was added to the mixture, which was then extracted with dichloromethane. The extract was combined, washed with brine, and dried over anhydrous Na₂SO₄, and concentrated to afford crude enol silyl ether. After the crude enol silyl ether was dissolved in dry acetonitrile, Pd(OAc)₂ (101 mg, 0.45 mmol) was added at 0 °C under a N₂ atmosphere. The vigorous stirring of the mixture was continued overnight at room temperature. Finally, the mixture was filtered, and the solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to give compound 11 (0.072 g, 82% for two steps) as a yellow solid. Mp 180–182 °C; ¹H NMR (300 MHz, CDCl₃): δ = 7.80 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 10.5 Hz, 1H), 6.31 (d, *J* = 10.5 Hz, 1H), 3.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 182.12, 156.07, 147.30, 139.27, 136.32, 135.30, 134.29, 132.60, 131.76, 127.74, 124.94, 124.87, 121.54, 113.16, 110.03, 93.10, 61.71; HRMS (ESI), *m/z* [M + H]⁺ calcd for C₂₁H₁₄ClO₄: 365.0575; found: 365.0570.

6-Chloro-5-hydroxy-4H-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (12). To a solution of 1,2-dihydroxybenzene (101 mg, 0.9 mmol) in dry CH₂Cl₂ (2 mL) at 0 °C was added BBr₃ (1 mol L⁻¹ in CH₂Cl₂) (1 mL, 0.99 mmol) with syringe under a N₂ atmosphere. The mixture was then stirred at 0 °C for another 3 h. Compound 11 (109 mg, 0.3 mmol) in 2 mL CH₂Cl₂ was added to the mixture with syringe. The mixture was stirred for another 30 min before quenched with methanol, and then extracted with EtOAc. The organic phase was combined and washed twice with brine, dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to give compound 12 (0.081 g,

77%) as a yellow solid. Mp 165–167 °C; ^1H NMR (400 MHz, CDCl_3): δ = 12.72 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.51–7.41 (m, 3H), 7.05 (d, J = 10.5 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.40 (d, J = 10.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 188.80, 157.57, 147.11, 140.44, 137.45, 136.58, 134.30, 129.56, 127.79, 124.42, 121.67, 119.78, 114.74, 113.05, 110.10, 92.74; HRMS (ESI), m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{12}\text{ClO}_4$: 351.0419; found: 351.0416.

(1*a*'R,7*a*'S)-5'-Chloro-6'-hydroxy-1*a*',7*a*'-dihydro-7'*H*-spiro[naphtho[1,8-de][1,3]dioxine-2,2'-naphtho[2,3-b]oxiren]-7'-one (13). Compound **12** (350 mg, 1 mmol) was added into a toluene (20 mL) solution of *N*-benzylcinchoninium chloride (126 mg, 0.3 mmol) in a 100 mL round-bottom flask. NaOH solution (0.1 M; 15 mL, 1.5 mmol) was added dropwise in the mixture, followed by the addition of *t*-BuOOH (1.5 mL, 7.2 M, 10 mmol) at 0 °C (the ice-water bath) and stirred for 6 h. After completion of the reaction, the solution was diluted with EtOAc, washed with 0.2 M HCl solution (2 × 20 mL), brine, and the organic phase was dried over anhydrous Na_2SO_4 . The solvent was removed and the crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to afford compound **13** (0.282 g, 77%) as a yellow solid. Mp 238–240 °C; the ee value of compound **13** was analysed by HPLC to be 97.4%; $[\alpha]_{\text{D}}^{25} +325.0^\circ$ (c = 0.65, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 11.84 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 4.10 (d, J = 4.0 Hz, 1H), 3.72 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 196.64, 157.35, 146.72, 146.47, 137.43, 135.40, 134.17, 127.79, 127.66, 124.73, 121.58, 121.46, 119.36, 113.13, 112.68, 110.22, 109.38, 95.75, 53.27, 53.18; HRMS (ESI), m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{12}\text{ClO}_5$: 367.0368; found: 367.0371.

Putative Sch 53825 (1). NaBH_4 (22 mg, 0.54 mmol) was added into a mixture of compound **13** (66 mg, 0.18 mmol), THF (2 mL) and MeOH (1.5 mL) in a 25 mL round-bottom flask at 0 °C. The mixture was stirred at room temperature for 4 h. The solution was extracted with EtOAc. The organic phase was washed with brine, and dried over anhydrous Na_2SO_4 . The solvent was removed under the reduced pressure, the residue was subjected to flash column chromatography on silica gel and eluted with (petroleum ether–EtOAc, 5 : 1) to produce compound **1** (0.047 g, 71%) as a yellow solid. Mp 172–174 °C; $[\alpha]_{\text{D}}^{25} +120.0^\circ$ (c = 0.16, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ = 8.44 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.46–7.42 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.47 (dd, J = 10 Hz, 2.5 Hz, 1H), 3.85 (d, J = 4.4 Hz, 1H), 3.76–3.74 (m, 1H), 3.45–3.42 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 151.70, 147.16, 147.12, 134.17, 130.90, 130.76, 127.79, 127.48, 123.60, 121.22, 121.14, 120.41, 120.00, 112.80, 110.07, 109.11, 96.53, 66.44, 54.09, 52.59; HRMS (ESI), m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{14}\text{ClO}_5$: 369.0524; found: 369.0528.

Revised Sch 53825 (14). To a mixture of compound **1** (351 mg, 0.95 mmol), PPh_3 (748 mg, 2.85 mmol) and 4-nitrobenzoic acid in dry THF was added DEAD (0.6 mL, 3.8 mL) with syringe at 0 °C under a N_2 atmosphere. After 30 min, the solvent was quenched by water and extracted with EtOAc. The organic

phase was washed with saturated sodium bicarbonate aqueous solution, and then brine, dried over anhydrous Na_2SO_4 , and concentrated. The crude product was resolved in THF (3 mL), and then added to a solution of LiOH (50 mg) in water (5 mL). Stirred 2 h, the pH level of the solution was adjusted to pH 1 with 0.1 M HCl. The mixture was diluted with ethyl acetate, and after separation of the organic phase, the water phase was again extracted with ethyl acetate. The organic phase was combined and washed twice with brine, dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 3 : 1) to afford Sch 53825 (**14**, 0.336 g, 95% for two steps) as a white solid. Mp 126–127 °C; $[\alpha]_{\text{D}}^{25} +165.5^\circ$ (c = 0.15, CHCl_3); (lit. 13 mp 110–112 °C); $[\alpha]_{\text{D}}^{25} +167.0^\circ$ (c = 0.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ = 7.62–7.53 (m, 3H), 7.49–7.45 (m, 3H), 7.18 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.10 (s, 1H), 5.66 (s, 1H), 3.81 (d, J = 3.9 Hz, 1H), 3.72 (dd, J = 3.9 Hz, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 149.72, 147.24, 147.21, 134.31, 131.64, 129.76, 127.88, 127.62, 123.02, 121.94, 121.29, 121.25, 120.24, 112.94, 110.12, 109.31, 97.65, 62.03, 52.75, 50.73; HRMS (ESI), m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{13}\text{ClO}_5\text{Na}$: 391.0344; found: 391.0341. The data are consistent with that previous reported.¹³

6-Chloro-5-hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (2) (palmarumycin B₆, 2). To a solution of compound **10** (151 mg, 0.4 mmol) in CHCl_3 was added TMSI (0.6 mL, 4 mmol) in an ice-water bath. The mixture was stirred at 0 °C for a further 12 h, the solvent removed under vacuum, and the residue was subjected to flash column chromatography on silica gel and eluted with (petroleum ether–EtOAc, 15 : 1) to afford compound **2** (0.098 g, 68%) as a yellow solid. Mp 186–188 °C; (lit.12b mp 190–192 °C); ^1H NMR (300 MHz, CDCl_3) δ 13.02 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.56 (dd, J = 8.4, 1.0 Hz, 2H), 7.46 (t, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 6.99 (dd, J = 7.2, 1.0 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 2.49 (t, J = 6.6 Hz, 2H). The data are consistent with that previous reported.^{12b}

3,6-Dichloro-5-hydroxy-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (4). $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (90 mg, 0.24 mmol), compound **13** (73 mg, 0.20 mmol), MeOH (3 mL), and H_2O (1 mL) were added in a 25 mL round-bottom flask. The mixture was stirred at reflux temperature for 16 h, cooled to room temperature, and the mixture was diluted with EtOAc. The organic phase was washed with brine, and dried over anhydrous Na_2SO_4 . The solution was concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to give compound **4** (0.071 g, 92%) as a yellow solid. Mp 183–185 °C; ^1H NMR (500 MHz, CDCl_3): δ = 12.42 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.50 (t, J = 7.9 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.20 (s, 1H), 7.00 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ = 182.19, 157.81, 146.71, 137.22, 137.09, 136.41, 134.86, 134.31, 127.86, 124.98, 121.96, 120.02, 114.08, 112.84, 110.32, 93.32; HRMS (ESI), m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{11}\text{Cl}_2\text{O}_4$: 385.0029; found: 385.0024.

(2*S*,3*S*)-3,6-Dichloro-2,5-dihydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (15). CeCl_3

(90 mg, 0.36 mmol), compound **13** (110 mg, 0.30 mmol), CH₃CN (2 mL) were added in a 25 mL round-bottom flask. The mixture was stirred at room temperature for 10 h, and then diluted with EtOAc. The organic phase was washed with brine, and dried over anhydrous Na₂SO₄. The solution was concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 5 : 1) to produce compound **15** (0.056 g, 47%) as a yellow solid. Mp 121–122 °C; ¹H NMR (500 MHz, CDCl₃): δ = 12.36 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.53–7.43 (m, 4H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 5.32 (d, *J* = 1.7 Hz, 1H), 4.69 (s, 1H), 2.74 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 194.34, 157.58, 146.43, 145.74, 137.72, 135.90, 134.20, 127.84, 127.76, 124.98, 121.90, 121.73, 118.95, 114.97, 112.83, 110.08, 109.19, 98.21, 72.19, 62.36; HRMS (ESI); *m/z* [M + H]⁺ calcd for C₂₀H₁₄ClO₅: 403.0135; found: 403.0134.

5'-Chloro-6'-methoxy-1*a*',7*a*'-dihydro-7'*H*-spiro[naphtho[1,8-de][1,3]dioxine-2,2'-naphtho[2,3-*b*]oxiren]-7'-one (16).

Compound **11** (110 mg, 0.30 mmol) was added into a toluene (4 mL) solution of TBD (9 mg, 0.06 mmol) in a 25 mL round-bottom flask. NaOH solution (0.1 M; 4.5 mL, 0.45 mmol) was added dropwise in the mixture, followed by the addition of *t*-BuOOH (1.5 mL, 7.2 M, 10 mmol) at 0 °C (ice-water bath) and stirred for 11 h. After completion of the reaction, the solution was diluted with EtOAc, washed with 0.2 M HCl solution (2 × 20 mL), brine, and the organic phase was dried over anhydrous Na₂SO₄. The solvent was removed and the crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to afford compound **16** (0.133 g, 87%) as a yellow solid. Mp 164–165 °C; ¹H NMR (500 MHz, CDCl₃): δ = 7.69 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.56–7.51 (m, 2H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 4.08 (d, *J* = 4.4 Hz, 1H), 4.01 (s, 3H), 3.73 (d, *J* = 4.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 191.17, 155.50, 146.91, 146.69, 136.35, 135.27, 134.30, 132.26, 127.87, 127.82, 124.94, 123.50, 121.64, 121.51, 112.75, 110.22, 109.50, 96.67, 62.92, 54.17, 53.24; HRMS (ESI), *m/z* [M + H]⁺ calcd for C₂₁H₁₄ClO₅: 381.0524; found: 381.0529.

3,6-Dichloro-5-methoxy-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (17). CeCl₃·7H₂O (56 mg, 0.17 mmol), compound **16** (56 mg, 0.14 mmol), MeOH (9 mL), and H₂O (3 mL) were added in a 50 mL round-bottom flask. The mixture was stirred at reflux temperature for 16 h, cooled to room temperature and the mixture was diluted with EtOAc. The organic phase was washed with brine, and dried over anhydrous Na₂SO₄. The solution was concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20 : 1) to give compound **17** (0.046 g, 78%) as a yellow solid. Mp 189–191 °C; ¹H NMR (500 MHz, CDCl₃): δ = 7.82 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 4.02 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 175.19, 156.62, 146.88, 138.80, 136.89, 135.95, 134.30, 133.09, 132.85, 127.83, 124.85, 124.16, 121.85, 112.95, 110.26, 93.54, 61.82; HRMS (ESI), *m/z* [M + H]⁺ calcd for C₂₁H₁₃Cl₂O₄: 399.0185; found: 399.0186.

X-ray diffraction analysis of compound 1

Colourless plate-like crystals of compound **1** were obtained from a slowly evaporating mixed chloroform and methanol solution. A 0.22 × 0.19 × 0.17 mm³ crystal was selected for analysis. The parameters and structure information for compound **1** have been deposited at the Cambridge Crystallographic Data Centre. CCDC ID 2169161 contains the supplementary crystallographic data for this paper.†

Evaluation of cytotoxic activity of title compounds

The cytotoxicity of Sch 53825 and its derivatives was evaluated against five human carcinoma cell lines (HCT116, U251, BGC823, Huh-7 and PC9) by MTT assay described in the literature.^{11,12} Taxol was selected as the positive control. All of these cell lines (colon cancer cell HCT116, human glioma cell U251, gastric cancer cell BGC823, human hepatoma cells Huh-7 and lung carcinoma cell PC9), obtained from the American Type Culture Collection (ATCC) and purchased from the Cell Culture Center of Institute of Basic Medical Sciences, Peking Union Medical College, Chinese Academy of Medical Sciences, were cultured with 10% fetal bovine serum (FBS) and penicillin (100 U mL⁻¹)-streptomycin (100 μg mL⁻¹) in Dulbecco's minimum essential medium (DMEM). The cell culture medium, serum and antibiotics were purchased from Invitrogen. All the cells were maintained at 37 °C in 5% CO₂.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 K. Miyashita and T. Imanishi, *Chem. Rev.*, 2005, **105**, 4515.
- 2 (a) L. Zhou, J. Zhao, T. Shan, X. Cai and Y. Peng, *Mini-Rev. Med. Chem.*, 2010, **10**, 977; (b) Y. Cai, Y. Guo and K. Krohn, *Nat. Prod. Rep.*, 2010, **27**, 1840; (c) X. Liu, Y. Zhao, W. Wang, M. Wang and L. Zhou, *Chin. J. Org. Chem.*, 2017, **37**, 2883.
- 3 (a) A. G. M. Barrett, D. Hamprecht and T. Meyer, *Chem. Commun.*, 1998, **8**, 809; (b) J. P. Ragot, M.-L. Alcaraz and R. J. Taylor, *Tetrahedron Lett.*, 1998, **39**, 4921; (c) P. Wipf and J.-K. Jung, *J. Org. Chem.*, 1998, **63**, 3530; (d) J. Ragot, C. Steeneck, M. Alcaraz and R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1999, **8**, 1073; (e) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula and M. P. Doyle, *Org. Lett.*, 2005, **7**, 5167; (f) K. Krohn, S. Wang, I. Ahmed, S. Altun, A. Aslan, U. Flörke, I. Kock and S. Schlummer, *Eur. J. Org. Chem.*,

- 2010, **2010**, 4476; (g) R. Wang, G. Liu, M. Yang, M. Wang and L. Zhou, *Molecules*, 2016, **21**, 600.
- 4 (a) S. Chi and C. H. Heathcock, *Org. Lett.*, 1999, **1**, 3; (b) J. P. Ragot, M. E. Prime, S. J. Archibald and R. J. K. Taylor, *Org. Lett.*, 2000, **2**, 1613; (c) A. Barrett, F. Blaney, A. Campbell, D. Hamprecht, T. Meyer, A. White, D. Witty and D. Williams, *J. Org. Chem.*, 2002, **67**, 2735; (d) E. Quesada, M. Stockley and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 4877; (e) E. Quesada, M. Stockley, J. P. Ragot, M. E. Prime, A. C. Whitwood and R. J. Taylor, *Org. Biomol. Chem.*, 2004, **2**, 2483.
- 5 Z. Yue, H. C. Lam, K. Chen, I. Siridechakorn, Y. Liu, K. Pudhom and X. Lei, *Angew. Chem., Int. Ed.*, 2020, **59**, 4115.
- 6 (a) L. A. McDonald, D. R. Abbanat, L. R. Barbieri, V. S. Bernan, C. M. Discafani, M. Greenstein, K. Janota, J. D. Korshalla, P. Lassota, M. Tischler and G. T. Carter, *Tetrahedron Lett.*, 1999, **40**, 2489; (b) T. Wang, O. Shiota, K. Nakanishi, N. Berova, L. A. McDonald, L. R. Barbieri and G. T. Carter, *Can. J. Chem.*, 2001, **79**, 1786.
- 7 (a) K. Miyashita, T. Sakai and T. Imanishi, *Org. Lett.*, 2003, **5**, 2683; (b) Y. Ando, A. Hanaki, R. Sasaki, K. Ohmori and K. Suzuki, *Angew. Chem., Int. Ed.*, 2017, **56**, 11460; (c) Y. Ando, D. Tanaka, R. Sasaki, K. Ohmori and K. Suzuki, *Angew. Chem., Int. Ed.*, 2019, **58**, 12507; (d) X. Shu, C. Chen, T. Yu, J. Yang and X. Hu, *Angew. Chem., Int. Ed.*, 2021, **60**, 18514.
- 8 (a) S. A. v. d. San, J. W. Blunt and M. H. G. Munro, *Org. Lett.*, 2006, **8**, 2059; (b) S. Fuse, K. Inaba, M. Takagi, M. Tanaka, T. Hirokawa, K. Johmoto, H. Uekusa, K. Shin-Ya, T. Takahashi and T. Doi, *Eur. J. Med. Chem.*, 2013, **66**, 180; (c) H. Tsukamoto, S. Hanada, K. Kumasaka, N. Kagaya, M. Izumikawa, K. Shin-Ya and T. Doi, *Org. Lett.*, 2016, **18**, 4848.
- 9 (a) X. Chen, Q. Shi, G. Lin, S. Guo and J. Yang, *J. Nat. Prod.*, 2009, **72**, 1712; (b) H. Tsukamoto, S. Hanada, Y. Nomura and T. Doi, *J. Org. Chem.*, 2018, **83**, 9430.
- 10 (a) A. Wisetsai, R. Lekphrom, J. Boonmak, S. Youngme and F. T. Schevenels, *Org. Lett.*, 2019, **21**, 8344; (b) M. Liao, X. X. Li, Y. Zheng and Z. Xie, *J. Org. Chem.*, 2021, **86**, 4835.
- 11 J. Li, R. Ding, H. Gao, L. Guo, X. Yao, Y. Zhang and J. Tang, *RSC Adv.*, 2019, **9**, 39082.
- 12 (a) T. Shan, J. Tian, X. Wang, Y. Mou, Z. Mao, D. Lai, J. Dai, Y. Peng, L. Zhou and M. Wang, *J. Nat. Prod.*, 2014, **77**, 2151; (b) X. Liu, W. Wang, Y. Zhao, D. Lai, L. Zhou, Z. Liu and M. Wang, *J. Nat. Prod.*, 2018, **81**, 1803; (c) X. Liu, S. Li, X. Wei, Y. Zhao, D. Lai, L. Zhou and M. Wang, *RSC Adv.*, 2020, **10**, 1588; (d) X. Liu, L. Xu, X. An, J. Jiang and M. Wang, *Chin. J. Org. Chem.*, 2022, **42**, 519.
- 13 M. Chu, M. G. Patel, J.-K. Pai, P. R. Das and M. S. Puar, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 579.
- 14 K. C. Nicolaou, T. Montagnon and P. S. Baran, *Angew. Chem., Int. Ed.*, 2002, **41**, 1386.
- 15 Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011.
- 16 (a) S. Song, X. Li, J. Wei, X. Shi, Y. Zhang, X. Zhang, L. Ai, Y. Zhu, X. Shi, X. Zhang and N. Jiao, *Nat. Catal.*, 2020, **3**, 107; (b) X. Xiong and Y.-Y. Yeung, *ACS Catal.*, 2018, **8**, 4033; (c) R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 6908; (d) J. M. Gnaim and R. A. Sheldon, *Tetrahedron Lett.*, 2004, **45**, 8471; (e) J. M. Gnaim and R. A. Sheldon, *Tetrahedron Lett.*, 2004, **45**, 9397.
- 17 C. F. Schwender, R. E. Pike and J. Shavel, *J. Med. Chem.*, 1973, **16**, 254.