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Efficient entry to 1-benzoxepine ring skeleton via tandem S_N2/Wittig reaction. Total synthesis of NADH: ubiquinone oxidoreductase (complex I) antagonist pterulinic acid

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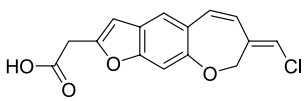
Abstract—Concise synthesis of NADH: ubiquinone oxidoreductase (complex I) antagonist pterulinic acid (**1a**) is reported. The key architectural framework in the natural product, 1-benzoxepine ring skeleton, was smoothly prepared from known salicylaldehyde **2g** and phosphorane **3** via tandem S_N2/Wittig reaction. Pterulinic acid was prepared in 5 steps from **2g** with overall yield of 25%. The versatility of tandem S_N2/Wittig reaction was investigated. This tandem reaction tolerated various alkyl, ether, tertiaryamine and nitro substituted salicylaldehyde, and it gave the corresponding 1-benzoxepine ring skeleton in moderated yield (21–72%).

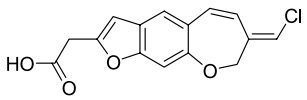
1. Introduction

NADH: ubiquinone oxidoreductase comprises the first phosphorylation site of mitochondria and is the energy-conserving enzyme complex that is commonly known as 'complex I'.[1] There are a wide variety of natural and synthetic inhibitors of complex I which have found multiple applications.[2] Complex I inhibitors have been used to elucidate the role of this enzyme in normal cell physiology and also have been used to mimic complex I deficiencies in order to study mitochondrial diseases.[3] Inhibitors of complex I have also been a preferred targeted for the development of commercial insecticides and acaricides for years.[4] Recently, it has been shown that inhibition of complex I causes concomitant reduction in the activity of orthine decarboxylase (ODC).[5] ODC is responsible for the biosynthesis of polyamine growth factors required for cellular prolification.[6] Since the overexpression of ODC in tumor cell contributes to aberrant proliferation, the ability of complex I inhibitors to reduce ODC activity makes them promising candidates as next generation antitumor agents.[7]

The fungal metabolite pterulinic acid (**1a** and **b**) were isolated from fermentations of a *Pterula sp* 82168 species.[8] The basic architectural framework in pterulinic acid (**1a** and **1b**) is a monochlorinated 2,3-dihydro-1-benzoxepine ring skeleton containing furan. The structures of **1** was assigned based on their physical and spectral characteristics.[8,9] The difference between **1a** and **1b** is the geometric configuration of the vinyl chloride. The vinyl chloride in pterulinic acid (**1a**) takes the *Z*-configuration. On the other hand, compound **1b** bears a vinyl chloride with the *E*-configuration. Pterulinic acid (**1a** and **b**) was isolated as 1:5 inseparable mixture of the two isomers (*Z*)-**1a** and (*E*)-**1b**, respectively. Pterulinic acid (**1a** and **b**) exhibited significant antifungal and weak or no cytotoxic activity, and it is effective inhibitors of eukaryotic respiration. The target of the antibiotics resides within the mitochondrial complex I with an IC_{50} value of 450 μM.[8]



(*Z*)-Pterulinic acid (1a)



(*E*)-Pterulinic acid (1b)

Synthesis of pterulinic acid is compelling due to their complex I antagonist activity, the synthetic challenges posed by their structure, and their status as potential new leads in drug discovery efforts. Since only a few 1-benzoxepin natural products have been previously reported,[10–12] an extensive survey of the literature did not reveal any efficient methods for the preparation of the 2,3-dihydro-1-benzoxepine ring skeleton, the architectural framework resident in **1**. As part of a going studies directed toward the synthetic approach for the preparation of 2,3-dihydro-1-benzoxepine ring skeleton,[13] disclosed herein is the detail investigation on the versatility of tandem S_N2/Wittig reaction sequence for preparation of 2,3-dihydro-1-benzoxepine ring skeleton. This approach also applied on

Keywords: pterulinic acid; NADH: ubiquinone oxidoreductase (complex I) antagonist; tandem S_N2/Wittig reaction.

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the first total synthesis of pterulinic acid **1a** in 5 steps from known salicylaldehyde **2g**. The tandem S_N2/Wittig reaction sequence demonstrated to be an efficient approach for preparation of 2,3-dihydro-1-benzoxepine ring skeleton, and we believe this approach holds promise for providing future analogues of **1**, if desired.

2. Results and discussion

The synthesis of pterulinic acid (**1**) began with the development of an efficient entry to basic architectural framework, 2,3-dihydro-1-benzoxepine ring skeletons. We envisioned the synthesis of 2,3-dihydro-1-benzoxepine ring skeleton through a tandem reaction sequence that began with a S_N2 ether formation followed by the Wittig olefination; as resulting from this design, we deduced two basic starting units, salicylaldehyde **2** and triphenylchloroacetonylphosphorane (**3**)[14] (Scheme 1). Treatment of salicylaldehyde **2** with 1.2 equiv. of sodium ethoxide generated the corresponding sodium salt of salicylaldehyde; its subsequent O-alkylation with α-chloroketone **3** produced **4**. Intramolecular ring formation via Wittig olefination between the tethered triphenylacetophosphorane and the formyl group in **4** gave highly functionalized **5** in 53% overall yield based on **2**.

Upon the success of this tandem reaction for preparation of **5**, the versatility of this reaction was investigated. The results of various salicylaldehyde derivatives reacted with phosphorane **3** under the same reaction condition to give the corresponding 2,3-dihydro-1-benzoxepine ring skeleton were listed in Table 1. This one pot synthesis tolerated alkyl, ether, tertiaryamine and nitro substituted salicylaldehydes, and it smoothly gave the corresponding 2,3-dihydro-1-benzoxepine ring skeleton in moderated yield (21–72%) base from the starting salicylaldehyde. The reaction condition was optimized, and sodium ethoxide in polar aprotic solvents, DMF or THF, gave the best yield for this reaction, and the presences of KI with reaction temperature at 70°C were essential conditions for this reaction.

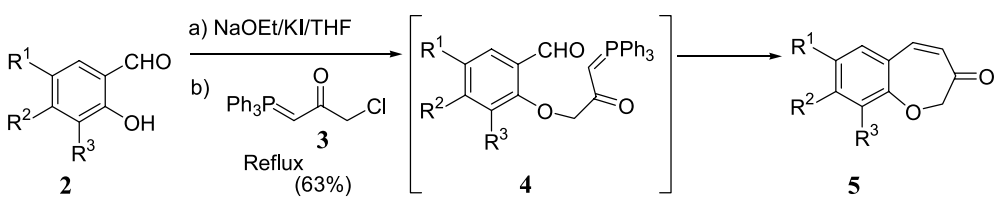
The difference in yield of this tandem reaction sequence with various salicylaldehyde derivatives was influenced by either electronic or steric factors. The salicylaldehydes substituted with moderated and weak electron donating group (entry 4, 6, and 7) gave the best yield for this reaction. The strong electron donating group substituted on salicylaldehyde (entry 5) gave the lowest yield for this reaction. The strong electron donating effect by the diethylamine group induced the corresponding formyl group on **4** to become more electron rich which resulting less electrophilic toward the Wittig olefination; therefore, the electron rich salicylaldehyde gave low yield for this reaction. On the other hand, the strong electron withdrawing group substituted on salicylaldehyde (entry 3) also gave low yield for this reaction. This result could be explained by the electronic effect on nucleophile in the S_N2 reaction. The strong electron withdrawing group substituted on salicylaldehyde polarized the corresponding nucleophile, phenoxide, to become more electronegative atom which binds its electrons more tightly. Since the S_N2 process requires donating of electron density to an antibonding orbital of the reactant, the high electronegativity is unfavorable;[16] as result, the strong electron withdrawing group substituted on salicylaldehyde gave the poor yield of this reaction. The steric hinder effect by the position of the substituents would also influence this tandem reaction, and this effect was shown on the *ortho* substituted salicylaldehyde (entry 8) which did not give any desired product **12** with only recovering of starting material.

Table 1. Tandem S_N2/Wittig reaction of salicylaldehyde **2** and phosphorane **3**

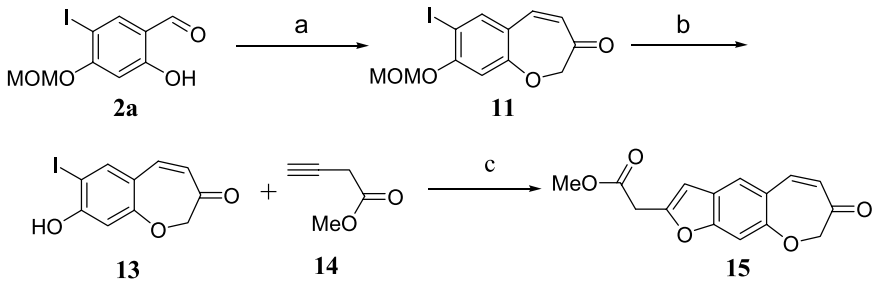
Entry	Aldehyde	R^1	R^2	R^3	Product	Yield (%)
1	**2a**	H	H	H	**5**	53
2	**2b**	Br	H	H	**6**	63
3	**2c**	O_2N	H	H	**7**	34
4	**2d**	MeO	H	H	**8**	65
5	**2e**	H	Et_2N	H	**9**	21
6	**2f**	Me	H	H	**10**	72
7	**2g**[15]	I	MOMO	H	**11**	68
8	**2h**	H	H	Me	**12**	NR

This tandem S_N2/Wittig reaction was applied toward the total synthesis of pterulinic acid. The synthesis of pterulinic acid (**1a**) is outlined in Schemes 2 and 3. The synthesis started with the preparation of benzoxepine-3-one (**11**) from known salicylaldehyde **2a**.[15] The salicylaldehyde **2a** underwent tandem S_N2/Wittig reaction with phosphorane **3** to give **11** in 68% overall yield based on **2a**. Removing the MOM group on **11** with 2N HCl gave *o*-iodophenol **13** in 99% yield. The *o*-iodophenol **13** underwent palladium-catalyzed heteroannulation with methyl 3-butynoate (**14**)[17] to give the tricyclic **15** in 53% yield.[18] The synthesis sequence, tandem S_N2/Wittig reaction followed by palladium-catalyzed heteroannulation efficiently constructed the tricyclic **15** which composed the core structure of the pterulinic acid and the essential functional handle for the completion of the synthesis.

Next, the vinyl chloride moiety was installed (Scheme 3). Benzoxepin-3-one **15** was treated with chloromethylphosphonium ylide to provide isomer **16** in 86% yield with >20:1 *Z*/*E* selectivity, and the final assignment of the configuration for purified (*Z*)-**16** was determined by NOE and 2D-heteronuclear correlation experiments. Finally, hydrolysis of the methyl ester **16** under basic condition



Scheme 1.



Scheme 2. *Conditions*: (a) EtONa, KI, THF, **3** reflux, 68%; (b) 2N HCl, THF, rt, 99%; (c) 10 mol% $(Ph_3P)_2PdCl_2$, 1.9 equiv. CuI, 1.6 equiv. Et_3N, DMF, 60°C, 53%.

followed by acidic work up gave pterulinic acid (**1a**) in 83% yield. The spectral and physical characteristics (IR, ^1H NMR, ^{13}C NMR, and MS) of synthetic **1a** were identical to the published data.[8]

3. Conclusion

The aim of the present study provides the first insight in the manner in which different types of substituted salicylaldehyde undergoes tandem S_N2/Wittig reaction with phosphorane **3**. In addition, this one-pot, tandem S_N2/Wittig reaction of salicylaldehyde and phosphorane **3** allows for the easy introduction of 2,3-dihydro-1-benzoxepine ring skeleton. The total synthesis reported herein provides pterulinic acid **1a** in 5 steps with overall yield of 25% base on the salicylaldehyde **2g**. This new synthetic application had demonstrated to be an efficient approach toward the total synthesis of natural product, pterulinic acid. A synthesis of this type, if reduced to practice, promised to provide ready access to **1a** and analogue thereof.

4. Experimental

4.1. General

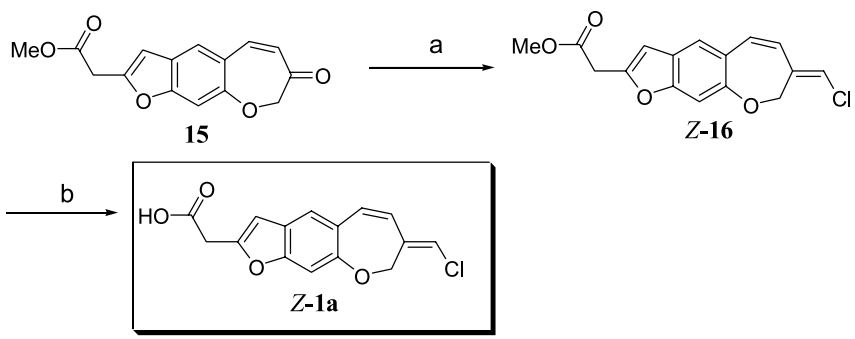
Proton and carbon NMR were obtained on a Bruker AMX-500 spectrometer. NMR spectra were recorded in $CDCl_3$ solution, expect as otherwise stated. Chemical shifts were reported in ppm relative to tetramethylsilane (δ units). Fast atom bombardment (FAB) mass spectra and elemental analyses were recorded on a Micromass ZAB spectrometer and Perkin–Elmer 2400 elemental analyzer repetitively at the Analytical Facility of The National Taiwan University. IR spectra were obtained on Perkin–Elmer Spectrum RXI FT-IR system. Silica gel TLC was performed on 60F-254 pre-coated sheets (E. Merck) and column chromatography was done on silica gel (60–120 mesh). All of chemicals were used directly as purchased from Acros, Aldrich, or TCI unless otherwise noted.

4.2. General procedure for the synthesis of 2,3-dihydro-1-benzoxepine ring skeleton

The freshly prepared sodium ethoxide (2.40 mmol) were added at 0°C to a well stirred solution of appropriated salicylaldehyde (2.00 mmol) and KI (3.00 mmol) in anhydrous THF (2 mL) under nitrogen atmosphere. After the resulting suspension was stirred at 0°C for 1 h, the α-chlorotriphenylacetophosphorane (**3**) (3.00 mmol) was added into suspension under nitrogen atmosphere. The corresponding reaction mixture was stirred at 70°C for 12 h; the solvent was removed under reduced pressure. Then, the mixture was diluted with ethyl acetate and washed with 1N HCl and water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixture gave analytically pure compounds. Spectroscopic and analytical data of benzoxepin-3-one follow.

4.2.1. Benzo[*b*]oxepin-3-one (5). From 200.0 mg of salicylaldehyde **2a**, 142.3 mg (53%) of compound **5** was obtained as yellow oil after purification by flash chromatography (hexanes/ethyl acetate 4:1). ^1H NMR: δ 4.54 (s, 2H), 6.35 (d, 1H, J=12.1 Hz), 7.14 (m, 2H), 7.18 (d, 1H, J=12.1 Hz), 7.34–7.37 (m, 2H). ^{13}C NMR: δ 77.8, 120.8, 124.3, 127.5, 129.2, 132.2, 133.4, 142.2, 160.0, 196.9. IR (oil, cm^{-1}): ν 2978, 1667. MS (EI) m/z: 160. Anal. calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.95; H, 5.08.

4.2.2. 7-Bromo-benzo[*b*]oxepin-3-one (6). From 200.2 mg



Scheme 3. *Conditions*: (a) *n*-BuLi, $Ph_3PCH_2Cl_2$, THF, rt, 86%; (b) 0.5 M NaOH, MeOH, then HCl, 83%.

of salicylaldehyde **2b**, 161.3 mg (66%) of compound **6** was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate 4:1). Mp 104–105°C (hexane/ethyl acetate). ^{1}H NMR: δ 4.52 (s, 2H), 6.37 (d, 1H, J=12.1 Hz), 7.02 (d, 1H, J=8.6 Hz), 7.07 (d, 1H, J=12.1 Hz), 7.44 (dd, 1H, J=8.6, 2.4 Hz), 7.50 (d, 1H, J=2.4 Hz). ^{13}C NMR: δ 79.7, 116.8, 122.6, 129.2, 130.3, 134.8, 135.4, 140.4, 158.0, 196.2. IR (KBr, cm^{-1}): ν 1664. MS (EI) *m*/*z*: 239. Anal. calcd for $C_{10}H_7O_2Br$: C, 50.24; H, 2.95. Found: C, 50.19; H, 2.99.

4.2.3. 7-Nitro-benzo[*b*]oxepin-3-one (7). From 200.0 mg of salicylaldehyde **2c**, 84.3 mg (34%) of compound **7** was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate 3:1). Mp 128–129°C (hexane/ethyl acetate). ^{1}H NMR: δ 4.62 (s, 2H), 6.50 (d, 1H, J=12.1 Hz), 7.22 (d, 1H, J=12.1 Hz), 7.28 (d, 1H, J=8.9 Hz), 8.21 (dd, 1H, J=8.9, 2.7 Hz), 8.31 (d, 1H, J=2.7 Hz). ^{13}C NMR: δ 77.6, 122.0, 126.9, 127.4, 128.8, 131.3, 139.8, 144.0, 163.3, 194.5. IR (KBr, cm^{-1}): ν 1667. MS (EI) *m*/*z*: 205. Anal. calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.51; H, 3.46; N, 6.80.

4.2.4. 7-Methoxy-benzo[*b*]oxepin-3-one (8). From 100.0 mg of salicylaldehyde **2d**, 81.4 mg (65%) of compound **8** was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate 5:1). Mp 35–37°C (hexane/ethyl acetate). ^{1}H NMR: δ 3.79 (s, 3H), 4.50 (s, 2H), 6.34 (d, 1H, J=12.1 Hz), 6.84 (d, 1H, J=2.9 Hz), 6.89 (dd, 1H, J=8.8, 2.9 Hz), 7.06 (d, 1H, J=8.8 Hz), 7.11 (d, 1H, J=12.1 Hz). ^{13}C NMR: δ 55.8, 78.2, 116.8, 117.9, 121.6, 128.1, 129.6, 141.8, 152.9, 155.9, 197.4. IR (KBr, cm^{-1}): ν 2917, 1667. MS (EI) *m*/*z*: 190. Anal. calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.55; H, 5.20.

4.2.5. 8-Diethylamino-benzo[*b*]oxepin-3-one (9). From 200.0 mg of salicylaldehyde **2e**, 49.3 mg (21%) of compound **9** was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate 3:1). Mp 72–74°C (hexane/ethyl acetate). ^{1}H NMR: δ 1.14 (t, 3H, J=6.6 Hz), 3.38 (q, 2H, J=6.6 Hz), 4.50 (s, 2H), 6.34 (d, 1H, J=12.1 Hz), 6.84 (d, 1H, J=2.9 Hz), 6.89 (dd, 1H, J=8.8, 2.9 Hz), 7.06 (d, 1H, J=8.8 Hz), 7.11 (d, 1H, J=12.1 Hz). ^{13}C NMR: δ 55.8, 78.2, 116.8, 117.9, 121.6, 128.1, 129.6, 141.8, 152.9, 155.9, 197.4. IR (KBr, cm^{-1}): ν 2917, 1667. MS (EI) *m*/*z*: 231 (M). Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.33; N, 5.99.

4.2.6. 7-Methyl-benzo[*b*]oxepin-3-one (10). From 200.0 mg of salicylaldehyde **2f**, 185.2 mg (72%) of compound **9** was obtained as yellow oil after purification by flash chromatography(hexanes/ethyl acetate 3:1). ^{1}H NMR: δ 2.32 (s, J=3 Hz), 4.50 (s, 2H), 6.32 (d, 1H, J=12.1 Hz), 7.02 (d, 1H, J=12.1 Hz), 7.11-7.15 (m, 3H). ^{13}C NMR: δ 20.5, 77.9, 120.4, 127.1, 129.1, 132.9, 133.5, 133.8, 142.3, 156.9, 197.1. IR (KBr, cm^{-1}): ν 2917, 1667. MS (EI) *m*/*z*: 174. Anal. calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.77; H, 5.66.

4.2.7. 7-Iodo-8-methoxymethoxy-benzo[*b*]oxepin-3-one (11). From 2.76 g of salicylaldehyde **2g**, 2.16 g (68%) of compound **11** was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate 10:1). Mp 109–110°C (hexane/ethyl acetate). ^{1}H NMR: δ 3.50 (s, J=3 Hz), 4.52 (s, 2H), 5.25 (s, 2H), 6.25 (d, 1H, J=12.1 Hz), 6.86 (s, 1H), 7.03 (d, 1H, J=12.1 Hz), 7.77 (s, 1H). ^{13}C NMR: δ 56.7, 77.7, 80.2, 94.9, 106.6, 123.3, 127.9, 140.7, 143.3, 158.5, 160.6, 195.8. IR (KBr, cm^{-1}): ν 2918, 1651. MS (EI) *m*/*z*: 346. Anal. calcd for $C_{12}H_{11}IO_4$: C, 41.64; H, 3.20. Found: C, 41.55; H, 3.09.

4.2.8. 8-Hydroxy-7-iodo-benzo[*b*]oxepin-3-one (13). A solution of the benzo[*b*]oxepin-3-one **11** (1.73 g, 5 mmol) and 0.1 mL of conc. HCl in 5 mL of EtOH was stirred at reflux temperature for 2 h. The mixture was diluted with ethyl acetate and washed with water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixture gave 1.47 g (99%) of a yellow solid. Mp 154–155°C (hexane/ethyl acetate). ^{1}H NMR: δ 4.54 (s, 1H), 5.58 (s, 1H), 6.27 (d, J=12.0 Hz), 6.80 (s, 1H), 7.05 (d, J=12.0 Hz), 7.69 (s, 1H). ^{13}C NMR: δ 77.7, 79.4, 107.1, 123.0, 127.7, 140.6, 142.4, 157.7, 161.1, 195.9. IR (KBr, cm^{-1}): ν 2918, 1651. MS (EI) *m*/*z*: 302. Anal. calcd for $C_{10}H_7IO_3$: C, 39.76; H, 2.34. Found: C, 39.59; H, 2.50.

4.2.9. (7-Oxo-7,8-dihydro-1,9-dioxa-cyclohepta[*f*]inden-2-yl)-acetic acid methyl ester (15). To a well-stirred mixture of *o*-iodophenol **13** (151.0 mg, 0.5 mmol), $Pd(Ph_3P)_2Cl_2$ (35.1 mg, 0.05 mol), CuI (183.1 mg, 0.95 mmol) and triethylamine (0.11 mL, 0.8 mmol) in anhydrous DMF (2 mL), methyl 3-butynoate (**14**) (130.1 mg, 1.25 mmol) was added under a N_2 atmosphere. The mixture was stirred at 60°C for 16 h. The mixture was cooled, diluted with ethyl acetate and washed with 1N NaOH and water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes 1:4 mixture gave 72.1 mg (53%) of **15** as off yellow solid. Mp 110–111°C (hexane/ethyl acetate). ^{1}H NMR: δ 3.77 (s, 3H), 3.83 (s, 2H), 4.58 (s, 2H), 6.32 (d, 1H, J=12.1 Hz), 6.83 (s, 1H), 7.24 (s, 1H), 7.27 (d, 1H, J=12.1 Hz), 7.53 (s, 1H). ^{13}C NMR: δ 34.2, 52.5, 78.3, 103.6, 104.9, 124.2, 125.0, 125.5, 127.6, 142.7, 152.4, 156.2, 156.7, 168.9, 197.4. MS (EI) *m*/*z*: 272. Anal. calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.10; H, 4.54.

4.2.10. 7-Chloromethylene-7,8-dihydro-1,9-dioxa-cyclohepta[*f*]inden-2-yl)-acetic acid methyl ester (16). The *n*-BuLi (0.25 mmol) were added at 0°C to a well stirred solution of (chloromethyl)triphenylphosphonium chloride (90.27 mg, 0.26 mmol) in anhydrous THF (1 mL) under nitrogen atmosphere. After the resulting suspension was stirred at 0°C for 30 min, the enone **15** (23.93 mg, 0.088 mmol) in anhydrous THF (1 mL) was added dropwise into mixture under nitrogen atmosphere at 0°C. The corresponding reaction mixture was stirred at 0°C for 1 h. Then, the mixture was quenched with 1N HCl at 0°C and extracted with ethyl acetate. The combine organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:5) mixture gave 23.1 mg (86%) of off yellow solid. Mp 65–67°C (hexane/ethyl acetate). ^{1}H NMR: δ 3.75 (s, 3H), 3.81 (s, 2H), 4.91 (s, 2H), 6.28 (s, 1H),

6.27 (d, 1H, J=11.5 Hz), 6.43 (d, 1H, J=11.5 Hz), 6.56 (s, 1H), 7.13 (s, 1H), 7.34 (s, 1H). ^{13}C NMR: δ 29.7, 52.4, 69.2, 103.0, 104.8, 120.0, 123.3, 124.6, 124.8, 126.1, 128.5, 138.9, 151.3, 154.9, 157.1, 169.2. IR (KBr, cm^{-1}): ν 2920, 1744. MS (EI) m/z: 304. Anal. calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30. Found: C, 63.16; H, 4.51.

4.2.11. Pterulinic acid (1a). To a stirred solution of ester **16** (10.0 mg, 0.033 mmol) in MeOH (1 mL) in ice bath, 5 mL of 0.5 M NaOH was added. The mixture was stirred at 0°C for 1 h. The mixture was diluted with water and washed with ethyl acetate. The basic aqueous layer was neutralized with concentrated HCl at 0°C. The corresponding aqueous layer was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was recrystallized with chloroform/hexanes to give 8.3 mg (83%) of **1a** as yellow solid. Mp 165–167°C (chloroform/hexane). ^{1}H NMR ($CDCl_3$:CD_3OD 95:5): δ 3.74 (s, 2H), 4.86 (s, 2H), 6.24 (s, 1H), 6.23 (d, 1H, J=11.5 Hz), 6.38 (d, 1H, J=11.9 Hz), 6.52 (s, 1H), 7.08 (s, 1H), 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD 95:5): δ 34.3, 69.1, 102.9, 104.6, 118.9, 123.3, 124.6, 124.7, 125.9, 128.4, 138.8, 151.8, 154.7, 156.8, 171.0. IR (KBr, cm^{-1}): ν 3435, 2920, 1698. MS (EI) m/z: 290. Anal. calcd for $C_{15}H_{11}O_4Cl$: C, 61.98; H, 3.81. Found: C, 61.77; H, 3.92.

Acknowledgements

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References

1. Walker, J. E. *Q. Rev. Biophys.* **1992**, *25*, 253–324.
2. Degli Esposti, M. *Biochim. Biophys. Acta* **1995**, *1271*, 1–292.
3. Barrientos, A.; Moraes, C. T. *J. Biol. Chem.* **1999**, *274*, 16188–16197.
4. Lummen, P. *Biochim. Biophys. Acta* **1998**, *1363*, 287–296.
5. Fang, N.; Casida, J. E. *Proc. Natl Acad. Sci. USA* **1998**, *95*, 3380–3384.
6. Seiler, N.; Atanassov, C. L.; Raul, F. *Int. J. Oncol.* **1998**, *13*, 993–1006.
7. Udeani, G. O.; Gerhauser, C.; Thomas, C. F.; Moon, R. C.; Kosmeder, J. W.; Kinghorn, A. D.; Moriarty, R. M.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 3424–3428.
8. Engler, M.; Anke, T.; Sterner, O.; Brandt, U. *J. Antibiot.* **1997**, *50*, 325–329.
9. Engler, M.; Anke, T.; Sterner, O. *J. Antibiot.* **1997**, *50*, 330–333.
10. Dean, F. M.; Parton, B.; Somvichien, N.; Taylor, D. A. H. *Tetrahedron Lett.* **1967**, 3459–3464.
11. Mondon, A.; Callsen, H. *Chem. Ber.* **1957**, *108*, 2200–2205.
12. Baba, K.; Kawanishi, H.; Taniguchi, M.; Kozawa, M. *Phytochemistry* **1992**, *31*, 1367–1370.
13. Huang, S. T.; Kuo, H. S.; Chen, C. T. *Tetrahedron Lett.* **2001**, *42*, 7473–7475.
14. Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446–2447.
15. Kobertz, W. R.; Essigmann, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 7101–7107.
16. For general reviews of nucleophilicity, see Hudson, R. F. In *Chemical Reactivity and Reaction Paths*, Klopman, G., Ed.; Wiley: New York, 1974; Chapter 5.
17. Collin, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G.; Bauer, R. F. *J. Med. Chem.* **1987**, *30*, 193–197.
18. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820.