Efficient Microwave-Assisted Synthesis of Ellipticine through *N*-(1,4-Dimethyl-9*H*-carbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde Diethyl Acetal

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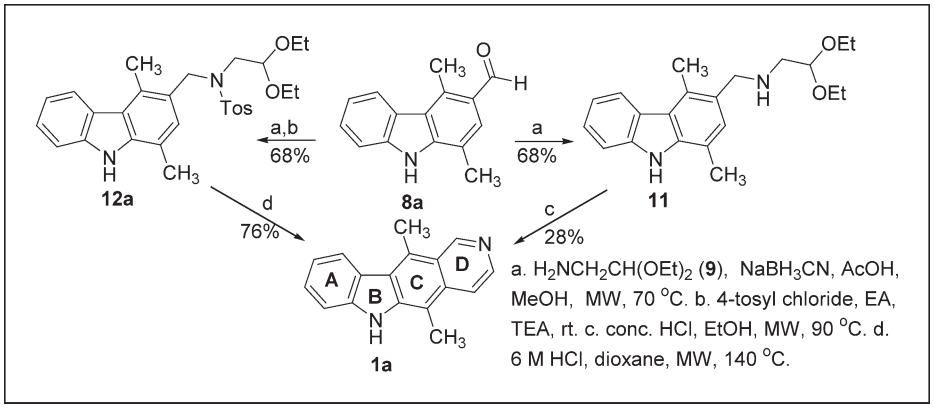

The long-lasting problematic low yield in the D-ring cyclization of ellipticine (**1a**) was dramatically improved through *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetal with microwave irradiation. The overall yield of **1a** starting from indole was significantly increased by 25-fold. This new approach is superior to reported methods in yields and, reaction time, and it provides efficient access to a broad spectrum of ellipticine derivatives.

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INTRODUCTION

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, **1a**), a tetracyclic natural alkaloid, was isolated from *Ochrosia elliptica* Labill. in 1959 [1] and found to be a potent anticancer agent [2]. Analogs bearing substituents on N-1 and C-9 of ellipticine such as 9-hydroxyellipticine (**2**) [3] and 9-hydroxy-2-methylellipticium (**3**) [4] possess potent antitumor activities as well. The structures of ellipticine and its analogs are shown in Figure 1.

In view of the interesting biological activity, it has attracted great attention to functionalize ellipticine. As shown in Scheme 1, a five-step synthetic pathway of ellipticine was first reported by Cranwell and Saxton [5]: starting from indole (**6a**) to give 1,4-dimethylcarbazole (C-ring formation), then through Vilsmeier-Haack formylation and Schiff base formation followed by reduction and isoquinoline cyclization (D-ring formation) to afford ellipticine. However, the final step of isoquinoline cyclization suffered a 9% low yield, and the total yield of **1a** starting from indole was as low as 0.8%.

The low yield of the D-ring closure leading to ellipticine has been improved to 30% *via* treating azomethine with orthophosphoric acid by Dalton et al. [6]. A perusal of literature revealed the general synthetic strategy to build up the tatracycline skeleton involving a connection of substituted indoles and various pyridines through Diels-Alder annulation, Friedel-Crafts acylation, and radical reactions. These methods could be simplified as [2 + 1] concept. For examples, Diels-Alder annulation from 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*] indole and 3,4-pyridyne gave a mixture of **1a** and isoellipticine (**4**) in Gribble's investigation [7]. In addition, synthesis of ellipticine quinone (**5**), which could be converted into ellipticine [8], demonstrated an alternative pathway of [2 + 1] annulation. Intramolecular reaction between 2-indolylacyl radicals derived from phenyl selenoester with pyridines [9] furnished polycyclic indolylpyridyl ketones including ellipticine quinone.

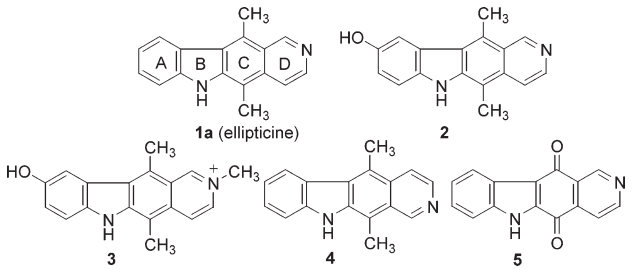
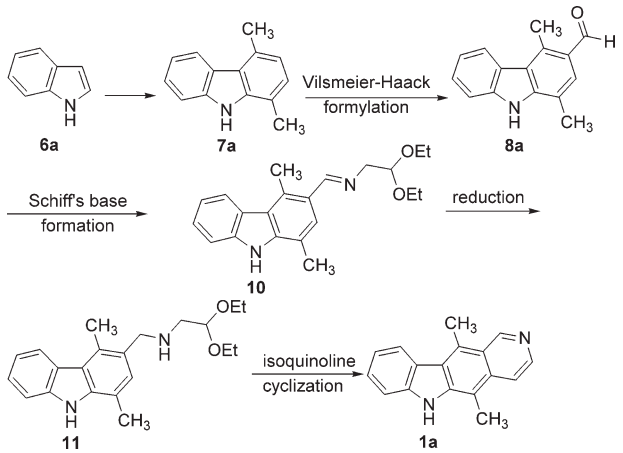


Figure 1. Ellipticine and its derivatives.

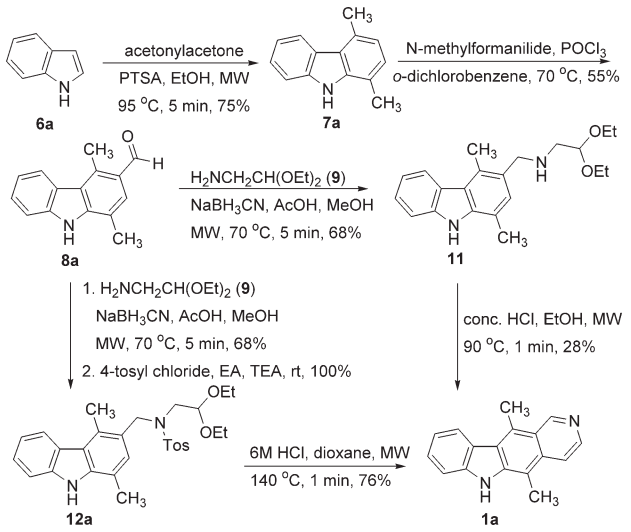
Friedel-Crafts acylation of *N*-protected indole with 3-chlorocarbonylisonicotinic acid methyl ester [8a] was followed by regioselective C-2 lithiation to yield ellipticine quinine (**5**). Recently, a radical cascade protocol has been used for the synthesis of ellipticine in higher yield [10]. Although these approaches provided better reaction yields and could be comprehensively applied in the development of ellipticine analogs, it underwent an intensively synthetic works to prepare intermediates for the last annulation steps in comparison to the Saxton's approach. Nevertheless, the reported methods were still unsatisfactory in preparing a number of derivatives for the development of ellipticine derivatives as potential anticancer drugs. Microwave (MW) irradiation has been illustrated to give superior results and to shorten reaction times in various aspects [11]. Further, MW irradiation has been widely applied to the organic synthesis including the total synthesis of natural products such as quinazolinobenzodiazepine alkaloids by a one-pot reaction [12] and biphenomycin B by the intramolecular Suzuki-Miyaura reaction [13] Herein, we report an efficient approach for the preparation of ellipticine by a modified Saxton's method with the assistance of MW irradiation.

A treatment of indole (**6a**) with acetonylacetone in the presence of *p*-toluenesulfonic acid (PTSA) in ethanol

Scheme 1. Saxton approach for the synthesis of ellipticine (**1a**).



Scheme 2. Synthesis of ellipticine (**1a**).



at 100°C for 5 min under MW irradiation afforded 1,4-dimethylcarbazole (**7a**) in 75% yield (Scheme 2). MW irradiation shortened the reaction time and improved the yield as compared with those in the conventional heating method (45 min, 36%) [5]. Subsequently, Vilsmeier-Haack formylation of **7a** by *N*-methylformanilide and $POCl_3$ in *o*-dichlorobenzene afforded aldehyde **8a** in 55% yield. The reaction was proceeded by Bobbitt-modified Pomeranz-Fritsch reaction [14] in which a Schiff base would be reduced to an amino-acetal and followed by a cyclization to isoquinoline. First, a one-pot reaction of **8a**, aminoacetaldehyde diethyl acetal (**9**), and $NaBH_3CN$ in the presence of catalytic amount of acetic acid at 70°C for 3 h furnished the desired hydrogenated *N*-(1,4-dimethylcarbazol-3-ylmethyl)-aminoacetaldehyde diethyl acetal (**11**) in 31% yield. Then, the use of MW irradiation in this one-pot reaction resulted in a twofold increase in the yield (68%). This modified MW-assisted one-pot reaction dramatically shortened the reaction time and increased the yield for the synthesis of secondary amine **11** in comparison to the Saxtons's method (2 h, 61%) [5]. Accordingly, **11** was subjected to cyclization reaction with concentrated HCl in ethanol at reflux by conventional heating. Unsurprisingly, ellipticine (**1a**) was obtained in a low yield of 9.0% as reported [5]. Then again, MW irradiation was used for the cyclization under the same condition to furnish **1a** in 28% yield. MW irradiation improved the long-lasting problematic low yield in the D-ring cyclization.

Nevertheless, a yield of 28% for the D-ring cyclization is still unsatisfactory in preparing a number of ellipticine derivatives. Birch et al. [15] illustrated that *N*-tosylated *N*-benzylaminoacetaldehyde dimethyl acetals were cyclized under mild acidic conditions and in good

Table 1

Comparison of reaction time and yields by microwave irradiation and conventional heating.

	MW irradiation		Heating[a]	
Reaction	Time (min)	Yield (%)	Time (min)	Yield (%)
6a → **7a**	5	75	45	36
8a → **11**	5	68	120[b]	61[b]
8a → **12a**	5	68		
11 → **1a**	1	28	60	9
12a → **1a**	1	76		

Overall yield from **6a** to **1a**

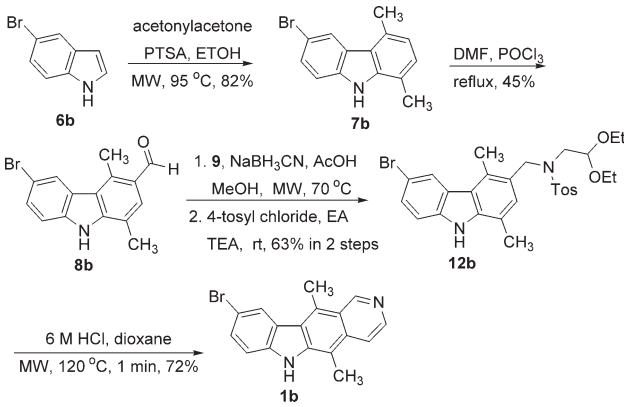
Path	Method	Yield (%)[a]
6a → **7a** → **8a** → **10** → **11** → **1a**	Heating	0.8
6a → **7a** → **8a** → **11** → **1a**	MW	7.8
6a → **7a** → **8a** → **12a** → **1a**	MW	21.3

[a] Data taken from ref. 5.
[b] Total yield in 2 steps of **8a** → **10** → **11**.

yields to isoquinolines in a one-pot reaction when the benzyl groups were substituted with sufficiently activating groups. The carbazole moiety is a well known strong electron donor [16]. We expected that the 1,4-dimethylcarbazol-3-ylmethyl group could act as an activated group, and an *N*-tosylated derivative of **11** might lead to ellipticine in an improved yield. Thus, *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetal (**12a**) was obtained by a treatment of **11** with tosyl chloride in quantitative yield. Subsequently, *N*-tosylated diethyl acetal **12a** was subjected to cyclization to afford **1a** in 76% yield in a reaction time of 1 min under the same condition as for the cyclization of **11** to **1a**. As a result, a 51% yield of ellipticine from aldehyde **8a** was obtained through an *N*-tosylated acetal **12a** together with the assistance of MW irradiation. This approach improves the yield by nine folds in comparison to the Saxton's method (5.5%). Importantly, the overall yield of ellipticine starting from indole (**6a**) was significantly increased by 25-fold (21%) as compared to that (0.8%) reported by Saxton (Table 1).

To explore the general application of this approach, condensation of 5-bromoindole (**6b**) with acetonylacetone was proceeded, and the resulting carbazole **7b** was formylated to the aldehyde **8b** by *N*,*N*-dimethylformamide (DMF) and $POCl_3$ (Scheme 3). Compound **8b** then reacted with aminoacetaldehyde diethyl acetal (**9**) under MW irradiation, and the resulting Schiff base was reduced *in situ*. Removal of solvent followed by tosylation afforded *N*-tosylated derivative **12b**, which was cyclized under acidic condition with MW irradiation to 9-bromoellipticine (**1b**) in 72%. As a result, the bromo substituent has little effect to the reactions in this

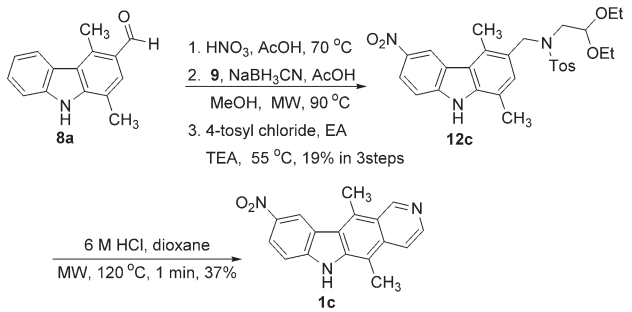
Scheme 3. Synthesis of 9-bromoellipticine (**1b**).



approach with MW irradiation. The slightly decrease in overall yield of **1b** with regard to ellipticine (**1a**) was due to the lower yield in the formylation reaction of 6-bromo-1,4-dimethylcarbazole (**7b**).

Birch et al. [15] reported that sufficiently activating substituents on the benzyl group were required for the cyclization of the *N*-benzyl-*N*-tosylaminoacetaldehyde dimethyl acetals to isoquinolines. Otherwise, cyclization failed and the *N*-benzyl-*N*-tosyl acetals would be first hydrolyzed to *N*-benzyl-*N*-tosylaminoacetaldehyde and then *N*-tosylbenzylamine. To investigate this substituent effect in the synthesis of ellipticine derivatives, a direct nitration of **8a** led to 1,4-dimethyl-6-nitrocarbazole-3-carbaldehyde (**8c**) which was condensed with aminoacetaldehyde diethyl acetal (**9**) to the Schiff base and reduced *in situ* under MW irradiation (Scheme 4). Without further isolation and purification, a subsequent treatment with tosyl chloride at 55°C yielded the *N*-tosylated compound **12c** in 19% (three steps). Then, compound **12c** was cyclized to 9-nitroellipticine (**1c**) in 37% yield under the same conditions as described above. The cyclization to isoquinoline was proposed as electrophilic substitution on the benzene ring [15], and lacking of sufficiently activated substituents on the aromatic ring failed in cyclization. Although a lower yield of 37% was obtained, the cyclization to 9-nitroellipticine was

Scheme 4. Synthesis of 9-nitroellipticine (**1c**).



still succeeded in this case. Apparently, the 1,4-dimethylcarbazole moiety could serve as an electron-efficient aromatic moiety even with a strong deactivated nitro group substituted at position 6.

In summary, we have developed a fast, efficient, and high-yield approach for the synthesis of ellipticine and its derivatives through *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetals by the use of MW irradiation. In this modified process, MW irradiation increased the overall yield by 10-fold as compared with the reported yield (0.8%) in considerably shortened reaction time. In an effort to synthesize the derivatives of ellipticine efficiently, the key step of D-ring construction is modified by converting the secondary amine to *N*-tosylated derivative based on Birch's investigation [15]. The long-lasting problematic low yield in the D-ring cyclization was dramatically improved in this study. Even a strong electron-withdrawing substituent on the 1,4-dimethylcarbazole moiety was endured in this method. This new approach is superior to previously reported methods in yields, reaction time, and versatility, and it will allow a broad evaluation of this highly promising class of potential antitumor drugs.

EXPERIMENTAL

The reactions assisted by microwave were achieved on Biotage Emrys™ Optimizer and Biotage Initiator™. Reaction temperatures were observed using built-in IR-sensor. Melting points were taken on Laboratory Devices, INC. (Box 6402) melting point apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained on Bruker AMX-400 and DPX-200 spectrometers. Mass spectra were obtained on Finnigan TSQ 7000 mass spectrometer. Elemental analysis for C, H, S, and N was carried out on Heraeus VarioEL III-CHNS apparatus. Thin layer chromatography (TLC) was carried out on precoated plates (silical gel, Kieselgel 60F_{254}, Merck). Column chromatography was performed with Kieselgel Si 60 (40–63 μm, Merck). All starting materials were obtained from commercial suppliers (Acros, Lancaster and Riedel-de Haën) and used without purification.

General procedure for the synthesis of *N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-9*H*-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12). A mixture of 3-formyl-1,4-dimethylcarbazole (8a, 1.0 g, 4.48 mmol), sodium cyanoborohydride (0.35 g, 5.57 mmol), 9 (0.7 mL, 5.25 mmol) and acetic acid (0.1 mL) in methanol (4 mL) was placed in a sealed tube. Reaction was heated by microwave (75 W) at 70°C for 5 min. Methanol was removed *in vacuo*, and then ethyl acetate (EA, 100 mL) was added. The solution was purified through column chromatography to afford viscous residue. To the residue, 4-tolueneulfonyl chloride (0.9 g, 4.72 mmol), triethylamine (0.5 mL, 4.94 mmol), and EA (30 mL) were added and stirred at room temperature for 2 h. The mixture was subsequently purified with column chromatography.

***N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-9H-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12a).** White solid, mp 183–184°C (lit. [17] 184°C); MS (ESI):*m*/*z* = 493.3 (M-H$^+$); ^{1}H NMR (400 Hz, DMSO-d_6): δ = 0.88 (t, *J* = 7.0 Hz, 6H), 2.38 (s, 3H), 2.41 (s, 3H), 2.73 (s, 3H), 3.01 (d, J = 5.36 Hz, 2H, CH_2), 3.08 (m, 2H), 3.30 (m, 2H), 4.04 (t, *J* = 5.24 Hz, 1H), 6.94 (s, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.77 Hz, 1H), 7.41 (d, *J* = 7.97 Hz, 2H), 7.50 (d, *J* = 8.06 Hz, 1H), 7.75 (d, *J* = 8.05 Hz, 2H), 8.14 (d, *J* = 7.97 Hz, 1H),11.17 (s, 1H); ^{13}C NMR (100 Hz, DMSO-d_6): δ = 15.5, 16.0, 17.1, 21.5, 49.8, 51.2, 62.6, 101.1, 111.5, 117.5, 119.2, 121.6, 122.8, 123.9, 123.7, 125.3, 127.6, 129.0, 130.1, 130.3, 136.9, 139.2, 140.7, 143.7.

***N*-(6-Bromo-1,4-dimethyl-9H-carbazol-3-ylmethyl)-*N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide (12b).** White solid, mp 196–197°C; MS (ESI): *m*/*z* = 571.2 (M-H$^+$); ^{1}H NMR (200 Hz, DMSO-d_6): δ = 0.88 (t, *J* = 7.0 Hz, 6H), 2.39 (s, 3H), 2.41 (s, 3H), 2.70 (s, 3H), 3.0–3.2 (m, 4H), 3.3–4.1 (m, 2H), 4.49 (s, 2H), 7.00 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 11.40 (s, 1H); ^{13}C NMR (50 Hz, DMSO-d_6): δ = 15.0, 15.5, 16.6, 21.0, 49.3, 50.5, 62.0, 100.6, 110.7, 112.9, 117.3, 120.2, 123.7, 124.4, 125.1, 127.1, 127.2, 129.2, 129.8, 129.9, 136.4, 138.9, 139.2, 143.2. Anal. Calcd for $C_{28}H_{33}BrN_2O_4S$): C, 58.64; H, 5.80; N, 4.88; S, 5.59. Found, C, 58.27; H, 6.08; N, 4.76; S, 5.38.

***N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-6-nitro-9H-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12c).** Yellow solid. mp 190–192°C; MS (ESI): *m*/*z* = 538.3 (M-H$^+$); ^{1}H NMR (400 Hz, acetonitrile-d_3): δ = 0.92 (t, *J* = 7.0 Hz, 6H), 2.35 (s, 3H), 2.37 (s, 3H), 2.62 (s, 3H), 3.06 (d, *J* = 5.33 Hz, 2H), 3.13 (m, 2H), 3.35 (m, 2H), 4.14 (t, *J* = 5.31 Hz, 1H), 4.41 (s, 2H), 6.99 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 8.49 Hz, 1H), 7.71 (d, *J* = 8.07 Hz, 2H), 8.17 (d, *J* = 8.70 Hz, 1H), 8.80 (s, 1H), 9.99 (s, 1H); ^{13}C NMR (50 Hz, DMSO-d_6): δ = 15.0, 15.4, 16.6, 21.0, 62.8, 100.7, 118.2, 120.8, 121.1, 122.7, 125.5, 127.2, 129.8, 130.0, 130.2, 136.4, 139.7, 140.0, 142.4, 143.3, 143.8. Anal. Calcd for $C_{28}H_{33}N_3O_6S{\cdot}0.33H_20$: C, 61.63; H, 6.22; N, 7.70. Found, C, 61.77; H, 6.00; N, 8.08.

General procedure for the synthesis of Ellipticine (1). A mixture of **12a** (1.0 g, 2.02 mmol), dioxane (3 mL), and 6*M* HCl (1.0 mL) was placed in a sealed microwave tube. The mixture was irradiated by microwave (180 W) at 140°C for 1 min and then purified with column chromatography to afford **1a**.

Ellipticine (1a). Mp 309–310°C (dec.; lit. [5] 309–313°C, dec.); MS (ESI): m/z = 245.0 (M-H$^+$) ^{1}H NMR (400 Hz, DMSO-d_6): δ = 2.78 (s, 3H), 3.24 (s, 3H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.95 Hz, 1H), 7.91 (d, *J* = 6.03 Hz, 1H), 8.36 (d, *J* = 7.90 Hz, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 9.68 (s, 1H), 11.59 (s, 1H); ^{13}C NMR (100 Hz, DMSO-d_6): δ = 12.0, 14.4, 108.1, 110.8, 116.0, 119.2, 121.9, 123.1, 123.5, 123.8, 127.1, 128.1, 132.5, 140.2, 140.7, 142.7, 149.5.

9-Bromoellipticine (1b). Mp 330–332°C (lit. [6] 318–319°C); MS (ESI): 323.0 (M-H$^+$); ^{1}H NMR (200 Hz, DMSO-d_6): δ = 2.74 (s, 3H), 3.19 (s, 3H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 6.0 Hz, 1H), 8.41 (s, 2H), 9.68 (s, 1H), 11.53 (s, 1H); ^{13}C NMR (50 Hz, DMSO-d_6): δ = 12.0, 14.3, 108.6, 111.0, 112.5, 116.0, 122.0, 122.9, 125.0, 125.9, 128.9, 129.6, 132.7, 140.6, 140.8, 141.4, 149.9.

9-Nitroellipticine (1c). Mp (dec.) 352°C (dec., lit. [6] 350°C, dec.); MS (ESI): 290.1 (M-H$^+$); ^{1}H NMR (400 Hz, DMSO-d_6): δ = 2.75 (s, 3H), 3.08 (s, 3H), 7.61 (d, *J* = 8.6

Hz, 1H), 7.91 (d, $J = 6.1$ Hz, 1H), 8.38 (d, $J = 9.0$ Hz, 1H), 9.47 (d, $J = 5.9$ Hz, 1H), 9.02 (s, 1H), 9.71 (s, 1H), 12.13 (s, 1H); ^{13}C NMR (100 Hz, DMSO-d_6): $\delta = 11.9$, 14.3, 108.5, 110.9, 112.4, 115.9, 121.9, 122.3, 125.0, 125.8, 128.9, 129.5, 132.7, 140.6, 140.7, 141.4, 149.8.

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