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Total synthesis of 12-methoxydihydrochelerythrine and anti-tumour activity of its quaternary base: toward an efficient synthetic route for 12-alkoxybenzo[*c*]phenanthridine bases *via* naphthoquinone monooxime from 2-benzofuranyl-1-tetralone derivative

Toshiko Watanabe,*[a] Yoshiaki Ohashi,[a] Rie Yoshino,[a] Naoko Komano,[a] Miyuki Eguchi,[a] Sakiko Maruyama[b] and Tsutomu Ishikawa*[a]

[a] *Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan. E-mail: toshiw@p.chiba-u.ac.jp*

[b] *Drug Research Department, R&D Division, Nippon Kayaku Co., Ltd., 31-12 Shimo 3, Kita, Tokyo 115-8588, Japan*

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A concise total synthesis of 12-methoxydihydrochelerythrine (**6**), isolated from *Bocconia integrifolia*, is described. The synthesis features an efficient route to a 12-alkoxybenzo[*c*]phenanthridine skeleton *via* naphthoquinone monooxime **11** as a key compound. Starting from 7-methoxy-2-methylbenzo[*b*]furan (**9**), 3-aryl-1-tetralone **10** was synthesised, followed by aromatisation to 3-aryl-1-naphthol **17**. After oxidative cleavage of the furan ring, basic nitrosation of naphthol **22** gave the naphthoquinone **11**. The benzo[*c*]phenanthridine skeleton was formed by reductive cyclisation of **11**. Deoxygenation of the lactam moiety in **23** afforded nor-base **32** and methylation of **32** under reductive conditions gave the target dihydro base **6** (23 steps from benzofuran **9** in 10% overall yield). The corresponding quaternary base **7** showed moderate anti-tumour activity against cancer cell lines; on NCI-H460: IC_{50} 4.5 μM and on MDA-MB-231: IC_{50} 1.2 μM. Introduction of a methoxy group into the 12-position of the benzo[*c*]phenanthridine skeleton could cause enhanced activity against MDA-MB-231 by comparison of **7** with chelerythrine (**35**) (IC_{50} 5.3 μM).

Introduction

Benzo[*c*]phenanthridine alkaloids **1**, found in Papaveraceous and Rutaceous plants, have been synthetically approached by various methods[1] in view of their biologically important activities, such as anti-tumour and DNA-topoisomerase inhibitory activities.[2] We established a general synthetic method for benzo[*c*]phenanthridine alkaloids **1** (Z = H) using 2-aryl-1-tetralones **2** as key intermediates and examined the structure–activity relationship (SAR) of their antitumour activity.[3] An alternative route, in which an isomeric 3-aryl-1-tetralone **3** played an important role, has also been explored for 12-alkoxy type alkaloids **1** (Z = OMe) such as macarpine[4] (**4**) because of the difficult application of the general synthetic method. Recently, Duval and co-workers reported[5] the synthesis of a 12-ethoxybenzo[*c*]phenanthridine base **1** (Z = OEt) *via* the isoquinolone derivative **5** (Scheme 1).

12-Methoxydihydrochelerythrine (**6**) was isolated from a South American plant, *Bocconia integrifolia* (Papaveraceae) by Sticher and co-workers[6] in 1991 and its structure was elucidated by NMR spectral data (^1H, ^{13}C and NOESY). We tried to synthesise **6** by a combination of our routes[3b,4] for benzo[*c*]phenanthridine alkaloids. In this paper we present the synthesis of 12-methoxydihydrochelerythrine (**6**) and the antitumour activity of its quaternary salt **7** in a line of SAR of benzo[*c*]phenanthridine bases. It is noted that Harayama *et al.*[7] reported the first synthesis of **6** by the palladium-catalysed cyclisation of naphthylamide **8** during the course of our synthetic approach.

Results and discussion

For elaboration of the 7,8,12-trimethoxy groups in **6** (and **7**), we planned the synthetic strategy outlined in Scheme 2 starting from 7-methoxy-2-methylbenzo[*b*]furan[8] (**9**) *via* 3-aryl-1-tetralone **10** and naphthoquinone monooxime **11**, followed by reductive cyclisation to a benzo[*c*]phenanthridine skeleton.

Friedel–Crafts acylation of **9** with homopiperonyloyl chloride (**12**) in the presence of $SnCl_4$ afforded a deoxybenzoin derivative **13**. Reformatsky reaction of **13** with ethyl bromoacetate and zinc gave the hydroxyester **14**. Deoxygenation of **14** with Et_3SiH–CF_3COOH followed by alkaline hydrolysis quantitatively gave an acid **16**. Cyclisation of **16** under basic conditions (K_2CO_3 in CH_3CN)[9] afforded the desired 3-aryl-1-tetralone **10**. The tetralone **10** was aromatised to 1-naphthol **17** by an acetal exchange reaction with isopropenyl acetate followed by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and basic hydrolysis. The phenolic function in **17** was protected with a benzyl group. (Scheme 3)

Successive treatment of the benzyl ether **18** with a stoichiometric amount of OsO_4 in pyridine and then aqueous Na_2SO_3 afforded the ketoalcohol **19** through an air-oxidation step under basic conditions.[10] The ketoalcohol **19** was treated with HIO_4 in aqueous dioxane followed by alkaline hydrolysis to give a salicylic acid **20**. Methylation of **20** with Me_2SO_4 in the presence of a phase transfer catalyst (PTC) afforded a methyl ester **21**.

We[11] have found that basic nitrosation of phenolic compounds with alkyl nitrites, such as isoamyl nitrite (*i*-AmONO), resulted in regioselective introduction of a nitrogen function into their *para* positions. After reductive deprotection of the benzyl group in **21**, treatment of naphthol **22** with *i*-AmONO in DMF in the presence of K_2CO_3 at room temperature followed by methylation with dimethyl sulfate in a one-pot operation afforded the desired quinone monooxime **11** (Scheme 4). The geometry of the *O*-methyloxime group in **11** was deduced to be *Z*-configuration by nuclear Overhauser effect (NOE) enhancement between the methoxy group and the proton assignable to

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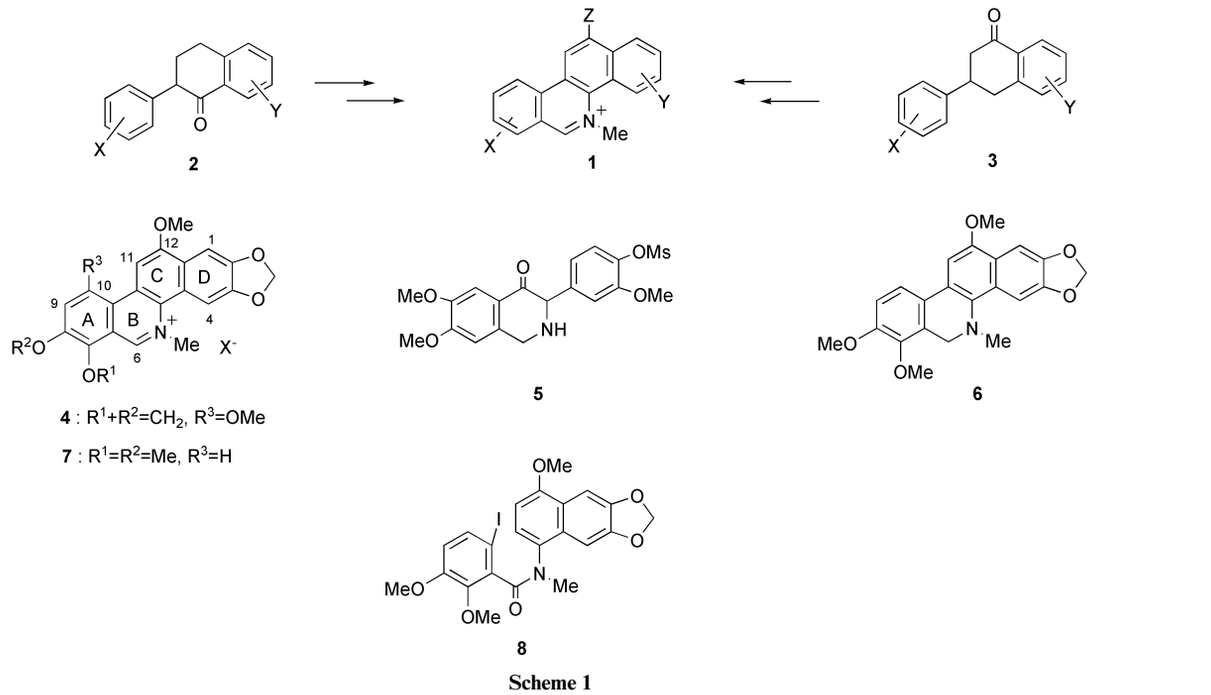
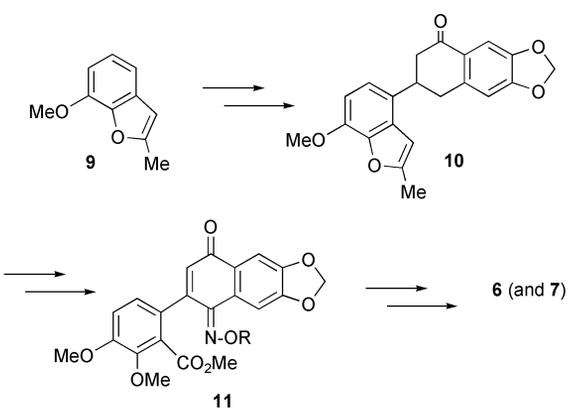


Scheme 1



Scheme 2

8-H (δ 8.32) (Fig. 1). We have reported that the same configuration was observed in this type of quinone monooxime toward the synthesis of macarpine[4] (**4**).

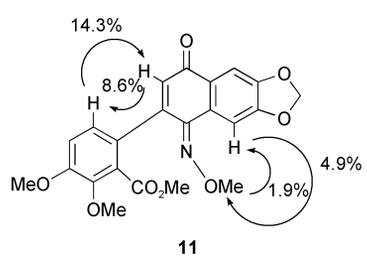
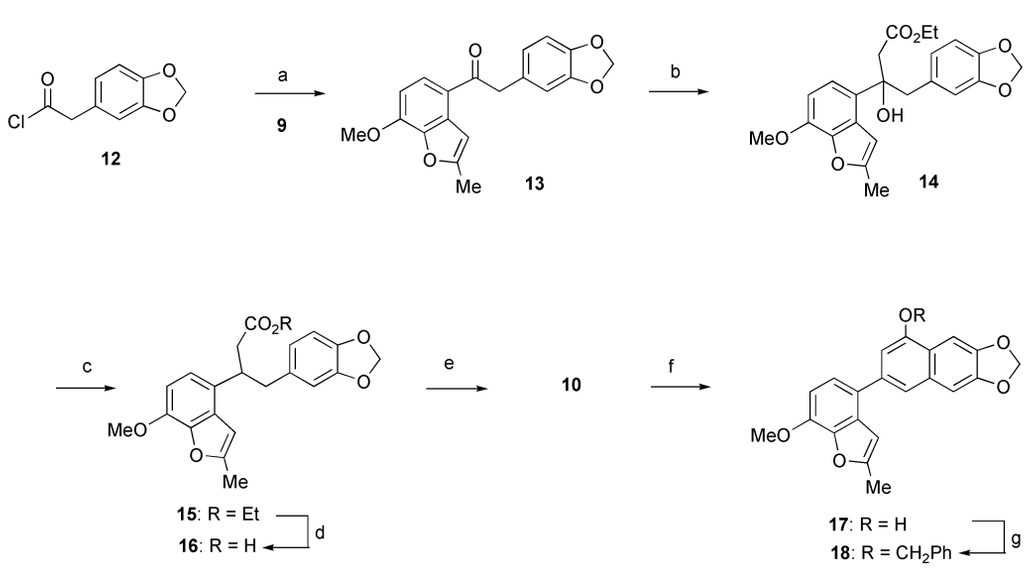
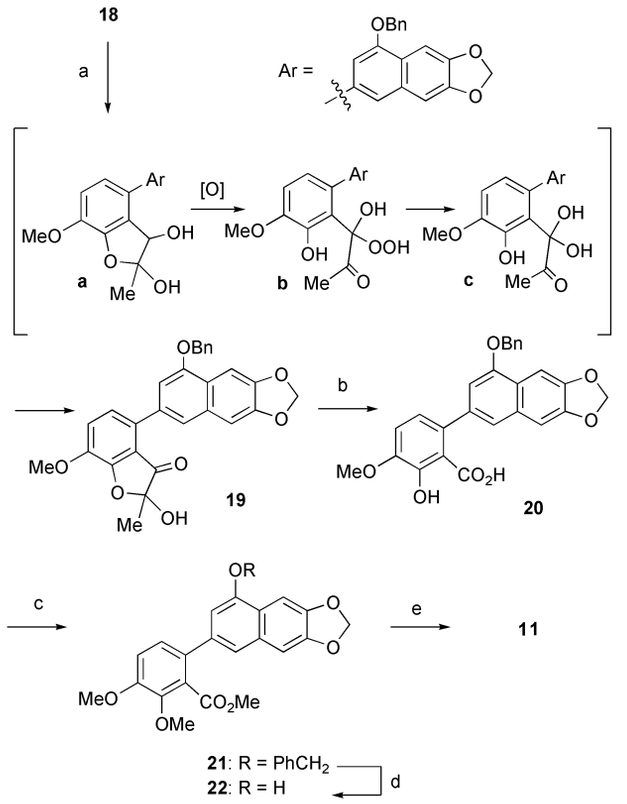


Fig. 1 Selected NOE enhancements in **11**.

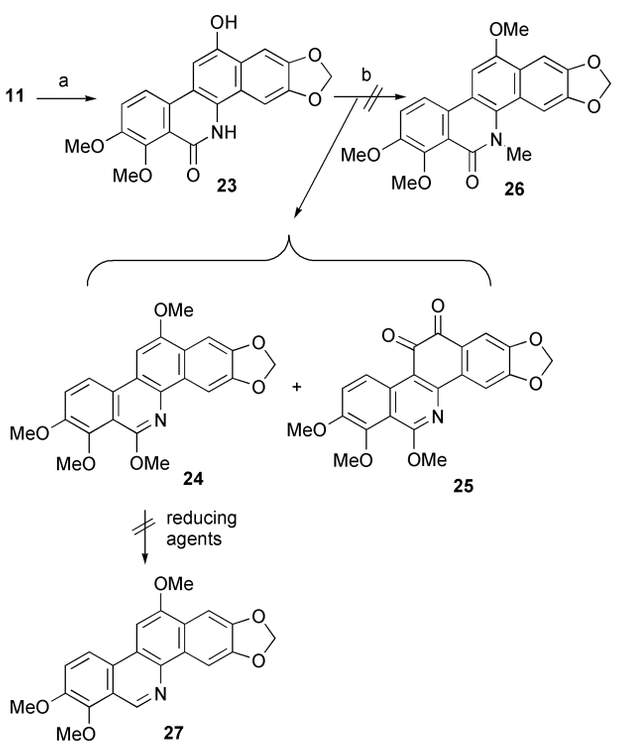
Construction of a benzo[*c*]phenanthridine ring system was examined under reductive cyclisation of **11**. Treatment of **11** with 10% Pd/C–H_2 in acetic acid smoothly provided a tetracyclic lactam **23** in quantitative yield, whereas unsuccessful results were obtained on reduction with $NaBH_4$ or $Na_2S_2O_4$. Methylation of **23** with dimethyl sulfate in the presence of PTC afforded two products (**24** and **25**) in nearly equal amounts (Scheme 5). The less polar compound **24** had molecular formula $C_{22}H_{19}NO_6$ and in the NMR spectra showed four methyl signals



Scheme 3 *Reagents and conditions:* a, $SnCl_4$, CH_2Cl_2, −15 °C, 2.5 h, 64%; b, $BrCH_2CO_2Et$, Zn, I_2, THF, reflux, 0.5 h, 93%; c, Et_3SiH, TFA, CH_2Cl_2, 0 °C, 1.5 h, 91%; d, KOH aq., EtOH reflux, 1 h, 100%; e, $POCl_3$, K_2CO_3, CH_3CN, 55 °C, 3 h, 81%; f, (i), $TsOH{\cdot}H_2O$, isopropenyl accetate, 95 °C, 13 h, (ii), DDQ, rt, 1 h, (iii) NaOHaq, EtOH, 85 °C, 1 h, 89%; g, $PhCH_2Br$, K_2CO_3, DMF, 50 °C, 2 h, 91%.



Scheme 4 *Reagents and conditions:* a, (i) OsO_4, pyridine, 30 °C, 3 h, (ii) Na_2SO_3, EtOH, 75 °C, 7 h, 92%; b, (i) HIO_4, H_2O-dioxane, rt, 24 h, (ii), NaOHaq., rt, 4 h, 100%; c, Me_2SO_4, $BnN^+Bu_3{\cdot}Cl^-$, NaOHaq., benzene, rt, 3 h, 87%; d, H_2, Pd/C, AcOH, rt, 3.5 h, 82%; e, (i) *i*-$C_5H_{11}ONO$, K_2CO_3, DMF, rt, 3.5 h, (ii) Me_2SO_4, rt, 1.5 h, 86%.

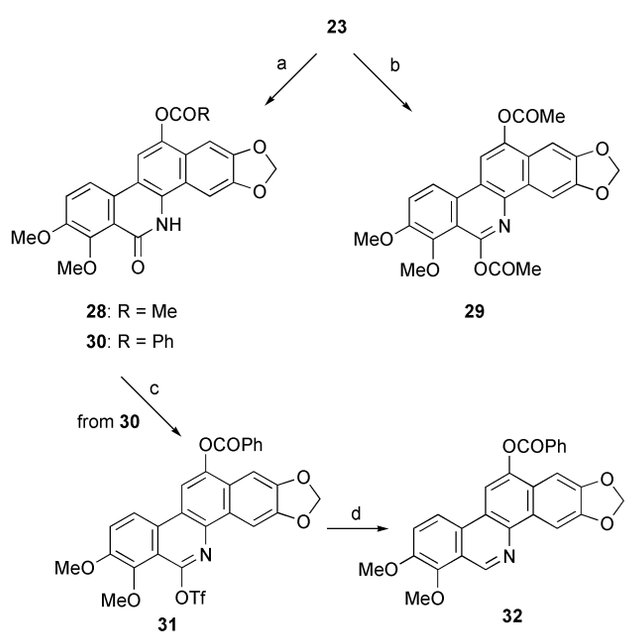


Scheme 5 *Reagents and conditions:* a, H_2, Pd/C, AcOH, rt, 1.5 h, 95%; b, Me_2SO_4, $BnN^+Bu_3{\cdot}Cl^-$, NaOHaq., CH_2Cl_2, rt, 1.5 h, **24** (45%), **25** (39%).

assignable to methoxy groups (δ_H 3.99, 4.03, 4.14 and 4.33; δ_C 53.7, 55.6, 57.0 and 61.9). Among them, two methoxy signals were derived from the starting lactam **23**, and one of the remaining signals should be a 12-methoxy group. One more methoxy group observed could be formed by *O*-alkylation on the lactam carbonyl group in **23**. Therefore, compound **24** was not the desired *N*-methylated lactam **26**, but an imino ether. Trials for reductive cleavage of the 6-methoxy group in **24** with various reagents ($LiAlH_4$, $LiBEt_3H$, Et_3SiH–CF_3COOH, *etc.*) to nor-base **27** resulted in the recovery of the starting material.

The second product **25**, obtained as purple prisms, had molecular formula $C_{21}H_{15}NO_7$. The ^1H NMR spectrum showed three methyl signals at δ 3.95, 4.00 and 4.34 ppm assignable to methoxy groups. In addition, two carbonyl signals (δ 178.6 and 181.0 ppm) were observed in the ^{13}C NMR, indicating the presence of an imino ether moiety similar to **24** and an *o*-quinone function in **25**. The formation of **25** could be explained by air-oxidation at the α-naphthol function of lactam **23** under basic conditions followed by methylation, even in an argon atmosphere. Structural confirmation of these imino ethers (**24** and **25**) was done by 2D-NMR experiments [heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond connectivity (HMBC)].

Selective methylation of the phenolic group in lactam **23** was attempted using Me_2SO_4–K_2CO_3 or CH_2N_2; however, the reaction mixtures were complex on thin-layer chromatography (TLC). This situation caused us to adopt an alternative route for removal of the oxygen function at the 6-position in **23** giving **32** (Scheme 6). Mono-acetylation with Ac_2O under solvent-free conditions proceeded smoothly to yield 12-acetoxylactam **28** in high yield. The acetylated position was confirmed by 2D-NMR and NOE experiments with comparison to diacetoxylactam **29**, prepared from **23** with the Ac_2O-4-(dimethylamino)pyridine (DMAP)–Et_3N system (Fig. 2 and Table 1). However, **28** was labile under the conditions of trifluoromethanesulfonylation (triflation) in the next step.

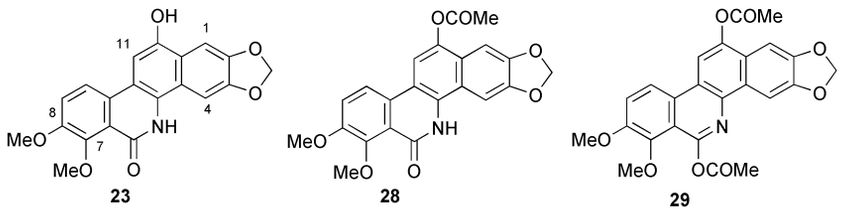


Scheme 6 *Reagents and conditions:* a, **28**: Ac_2O, 80 °C, 1 d (91%); **30**: $(PhCO)_2O$, 60 °C, 14 d, (96%); b, Ac_2O, DMAP, 80 °C, 11 h then Et_3N, rt, 15 h, (74%); c, Tf_2O, *i*Pr_2EtN, 0 °C, 5 h, 83%; d, $Pd(OAc)_2$, dppp, Et_3SiH, DMF, 60 °C, 5 h, 89%.

Thus, mono-benzoylation of **23** was similarly carried out with benzoic anhydride, leading to the benzoyl lactam **30** in excellent yield, although a longer reaction time was required (14 days).[12] The benzoylated position in **30** was also confirmed by 2D-NMR and comparison with the acetate **28**. Triflation of **30** followed by reduction with a palladium catalyst [$Pd(OAc)_2$–1,3-bis(diphenylphosphino)propane (dppp)–Et_3SiH] afforded 6-deoxygenated base **32** in high yield.

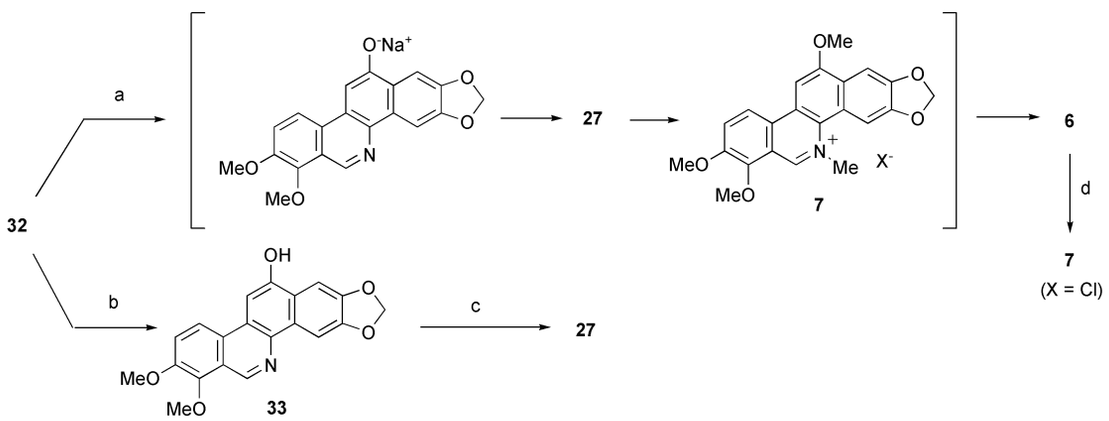
Alkaline hydrolysis of **32** followed by methylation gave the desired nor-base **27** in 64% yield. However, difficult isolation of phenolic imine **33** was observed due to its amphoteric character.

Table 1 Selected chemical shifts on ^{1}H NMR of **23**, **28** and **29** (400 MHz, $CDCl_3$, δ ppm)



Protons	**23**	**28** ($\Delta\delta$)[a]	**29** ($\Delta\delta$)[a]
C_1–H	7.47	7.30 (−0.17)	7.24 (−0.20)
C_{11}–H	7.46	8.04 (+0.58)	8.08 (+0.62)
C_7–OMe	3.83	3.82 (−0.01)	4.01 (+0.18)

[a] The difference was calculated using **23** as a standard.



Scheme 7 *Reagents and conditions:* a, (i) NaOMe, MeOH, 45 °C, 18 h, (ii) Me_2SO_4, $NaBH_4$, HMPA, 60 °C, 11 h, 64%; b, KOH, MeOH, 50 °C, 29 h, 67%; c, Me_2SO_4, K_2CO_3, DMF, 0 °C, 1.5 h, 100%; d, (i) DDQ, NaOHaq., benzene, rt, 20 min, (ii) HClaq., $CHCl_3$, 78%.

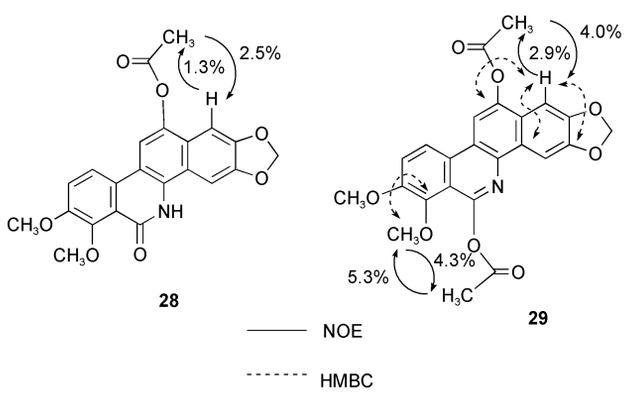


Fig. 2 Selected NOE enhancements and HMBC correlations in **28** and **29**.

(Scheme 7) Thus, we tried direct conversion of **32** to the target *N*-methyldihydrobase **6** in a one-pot operation by application of our preparation method[14] for dihydrobenzo[*c*]phenanthridines from the corresponding nor-bases without isolation of **33**. After methanolysis of **32** with NaOMe followed by evaporation of the solvent, the residual sodium naphthoxide was treated with $NaBH_4$ in hexamethylphosphoryltriamide (HMPA) in the presence of Me_2SO_4. Double methylation at the *N*- and *O*-functions under reductive conditions as expected, afforded a dihydrobase **6** in 67% yield. Synthetic 12-methoxydihydrochelerythrine (**6**) was identical to a sample prepared by Professor Harayama's group.[7,15] The base **6** was further oxidised to the corresponding quaternary base **7** with DDQ under basic conditions[14] for the testing of anti-tumour activities.

12-Methoxychelerythrine (**7**) and the related quaternary bases were examined in human lung cancer cell line NCI-H460 and human breast cancer cell line MDA-MB-231 (Table 2). Synthetic base **7** showed moderate activities (on NCI-H460: IC_{50} 4.5 μM and on MDA-MB-231: IC_{50} 1.2 μM), which were slightly stronger than natural nitidine (**34**) (IC_{50}: 8.7 and 1.6 μM respectively) and chelerythrine (**35**) (IC_{50}: 4.1 and 5.3 μM respectively), but lower than NK109 (**36**) (IC_{50}: 0.072 and 0.25 μM respectively), which is a candidate for anti-tumour drug inhibiting DNA topoisomerase II activity.[16] Introduction of a methoxy group into the 12-position of the benzo[*c*]phenanthridine skeleton could cause enhanced activity against MDA-MB-231 by comparison of **7** with **35** as in the case of macarpine (**4**).[4]

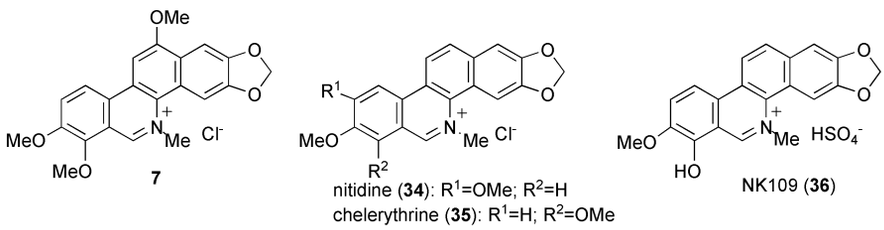
In summary, we have achieved the total synthesis of 12-methoxydihydrochelerythrine (**6**) *via* naphthoquinone monooxime **11** as a key compound by 23 steps from a benzofuran **9** in 10% overall yield. Though the number of steps is more than that of Harayama's synthesis (15 steps, 7% from commercial tetralone derivative),[7] our method may have the potential for preparing a wide variety of 12-alkoxy derivatives, because the *O*-alkylation step for 12-hydroxy group is in the final stage. This synthetic method could provide an efficient route for 12-alkoxybenzo[*c*]phenanthridine alkaloids to examine the SAR of their anti-tumour activity.

Experimental

General

All melting points were measured on a micro melting-point hot stage, MP-3S (Yanaco) and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-300E spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) unless otherwise stated, on JEOL JNM GSX-400A, GSX-500A, and ECP-400 spectrometers with tetramethylsilane as internal reference. Low-resolution mass spectra were recorded

Table 2 Anti-tumour activities of quaternary benzo[*c*]phenanthridines against human cancer cells (NCI-H460 and MDA-MB-231)[a]



Compound	IC_{50}/μM	
	NCI-H460	MDA-MB-231
7	4.5	1.2
34	8.7	1.6
35	4.1	5.3
36	0.072	0.25

[a] The anti-tumour activity tests of **7** and NK109 (**36**) were carried out at the same time, while those of nitidine (**34**) and chelerythrine (**35**) were separately examined.

on a JEOL JMS-AM20 with electron impact (EI) ionisation, and JEOL JMS-AX500 and JMS-HX 10A with fast atom bombardment (FAB) ionisation. High-resolution mass spectra were recorded on JEOL JMS-HX 10A (FAB) and Hitachi M-60 (EI) spectrometers. For column chromatography, silica gel (particle size: 100 μm) (Fuji Silysia) was used unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon prior to use.

4-(7-Methoxy-2-methylbenzo[*b*]furanyl) 3,4-methylenedioxybenzyl ketone 13. Oxalyl chloride (19.2 mL, 22 mmol) was added to 3,4-methylenedioxyphenylacetic acid (13.78 g, 77 mmol) under ice-cooling and the mixture was stirred at room temperature for 3 h. After removal of excess oxalyl chloride under reduced pressure, the residual acid chloride was dissolved in dry CH_2Cl_2 (32 mL). To a solution of acid chloride was added a solution of benzofuran[8] **9** (12.41 g, 76 mmol) in dry CH_2Cl_2 (100 mL) followed by $SnCl_4$ (36 mL, 0.31 mol) at −15 °C (ice–sodium chloride bath) and the mixture was stirred at the same temperature for 2.5 h. The reaction mixture was poured into water (1 L) and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried (K_2CO_3), and evaporated *in vacuo*. The crude yellow prisms (25.60 g) were washed with Et_2O to afford **13** (15.84 g, 64%) as colourless fine needles (mp 120–121.5 °C, Et_2O–hexane) (Found: C, 70.4; H, 4.8. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%); ν_{max} (Nujol)/cm^{-1} 1676 (C=O); δ_H (400 MHz) 2.50 (3 H, s, 2′-Me), 4.07 (3 H, s, OMe), 4.21 (2 H, s, CH_2), 5.93 (2 H, s, OCH_2O), 6.72–6.78 (4 H, m, ArH), 7.20 (1 H, s, 3′-H) and 7.84 (1 H, d, *J* 8.2, 5′-H); δ_C (125 MHz) 14.1, 45.2, 56.2, 100.9, 104.5, 105.0, 108.3, 109.9, 122.1, 122.4, 127.1, 128.8, 131.2, 143.9, 146.4, 147.7, 148.5, 158.3 and 196.7.

Ethyl 3-hydroxy-3-[4-(7-methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)butyrate 14. To a stirred suspension of **13** (5.00 g, 15.4 mmol) and zinc powder (4.94 g, 75.5 mmol) in THF (100 mL) was added iodine (2.40 g, 9.46 mmol) and ethyl bromoacetate (5.18 g, 30.9 mmol) under reflux, and the mixture was refluxed for 30 min under an argon atmosphere. The reaction mixture was poured into water (180 mL) and filtered through a Celite pad. The filtrate was extracted with $CHCl_3$. The organic layer was washed with 1% aqueous KI solution, water and brine, dried (K_2CO_3), and evaporated *in vacuo*. The residual yellow oil was crystallised and washed with hexane–Et_2O to yield **14** (5.93 g, 93%) as colourless fine needles (mp 88.5–90 °C, EtOH) (Found: C, 67.0; H, 5.6. $C_{23}H_{24}O_7$ requires C, 67.0; H, 5.9%); ν_{max} (Nujol)/cm^{-1} 3489 (OH) and 1718 (C=O). δ_H (400 MHz) 1.09 (3 H, t, *J* 7.0, CH_2CH3), 2.49 (3 H, s, 2′-Me), 2.77 (1 H, d, *J* 16.2, 2-H), 3.04 (1 H, d, *J* 13.6, 4-H), 3.08 (1 H, d, *J* 16.2, 2-H), 3.11 (1 H, d, *J* 13.6, 4-H), 3.98 (3 H, s, OMe), 4.01 (2 H, q, *J* 7.0, OCH_2CH_3), 4.54 (1 H, s, OH), 5.88 (2 H, s, OCH_2O), 6.39 (1 H, d, *J* 7.8, 6″-H), 6.46 (1 H, s, 2″-H), 6.59 (1 H, d, *J* 8.2, 6′-H), 6.62 (1 H, d, *J* 7.8, 5″-H), 6.74 (1 H, s, 3′-H) and 6.84 (1 H, d, *J* 8.2, 5′-H); δ_C (125 MHz) 13.95, 14.00, 43.1, 47.9, 55.9, 60.7, 75.9, 100.7, 103.9, 104.3, 107.6, 111.0, 119.6, 123.6, 127.9, 129.7, 130.3, 144.1, 144.2, 146.1, 147.0, 155.0 and 173.0.

Ethyl 3-[4-(7-methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)butyrate 15. To a solution of **14** (1.00 g, 2.42 mmol) in CH_2Cl_2 (12 mL) was added triethylsilane (1.2 mL, 7.51 mmol) and trifluoroacetic acid (0.75 mL, 9.74 mmol) at 0 °C and the mixture was stirred at the same temperature for 1.5 h. After neutralisation by slow addition of K_2CO_3 (4.7 g), insoluble materials were filtered off and washed with CH_2Cl_2. The combined organic solution was evaporated *in vacuo*. The residual yellow oil was purified by column chromatography (gradient elution: 100 : 0⟶0 : 100 hexane–EtOAc) to yield **15** (873 mg, 91%) as a colourless oil; ν_{max} (neat)/cm^{-1}: 1735 (C=O); δ_H (400 MHz) 1.09 (3 H, t, *J* 7.0, OCH_2CH_3), 2.46 (3 H, d, *J* 1.0, 2′-Me), 2.67–2.70 (2 H, m, 2- or 4-H_2), 2.83–2.96 (2 H, m, 2- or 4-H_2), 3.57 (1 H, m, 3-H), 3.94–4.01 (2 H, m, OCH_2CH_3), 3.96 (3 H, s, OMe), 5.87 and 5.88 (each 1 H, d, *J* 1.2, OCH_2O), 6.42 (1 H, q, *J* 1.0, 3′-H), 6.48 (1 H, dd, *J* 8.0, 1.8, 6″-H), 6.53 (1 H, d, *J* 1.6, 2″-H), 6.63 (2 H, d, *J* 8.0, 6′- and 5″-H) and 6.84 (1 H, d, *J* 8.0, 5′-H); δ_C (125 MHz) 14.04, 14.05, 39.7, 41.2, 41.7, 55.9, 60.2, 100.7, 101.6, 105.2, 107.9, 109.5, 120.7, 122.1, 127.7, 129.4, 133.5, 143.4, 143.5, 145.8, 147.3, 155.2 and 172.4; *m*/*z*: (FAB) 397 (MH^+) and 261.

3-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)butyric acid 16. A mixture of **15** (9.76 g, 24.6 mmol) and 17% aqueous KOH (20 mL, 60.6 mmol) in EtOH (98 mL) was refluxed for 1 h. The reaction mixture was poured into water (300 mL) and extracted with Et_2O. The aqueous layer was acidified with concentrated hydrochloric acid to pH 1 and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield **16** as a yellow oil (9.4 g, quantitatively), which was used for the next step without purification. ν_{max} (neat)/cm^{-1} 3300–2500 (OH) and 1707 (C=O); δ_H (400 MHz) 2.46 (3 H, s, 2′-Me), 2.71–2.73 (2 H, m, 2- or 4-H_2), 2.82–2.96 (2 H, m, 2- or 4-H_2), 3.53–3.57 (1 H, m, 3-H), 3.96 (3 H, s, OMe), 5.87 and 5.88 (each 1 H, d, *J* 1.2, OCH_2O), 6.40 (1 H, d, *J* 1.2, 3′-H), 6.47 (1 H, dd, *J* 8.0, 1.5, 6″-H), 6.52 (1 H, d, *J* 1.5, 2″-H), 6.63 (2 H, d, *J* 8.0, 6′- and 5″-H) and 6.84 (1 H, d, *J* 8.0, 5′-H); δ_C (125 MHz) 14.0,

39.0, 40.9, 41.6, 55.9, 100.7, 101.5, 105.2, 107.9, 109.5, 120.7, 122.1, 127.3, 129.4, 133.3, 143.56 143.59, 145.9, 147.4, 155.3 and 177.9; *m*/*z*: (FAB) 369 (MH^+).

3,4-Dihydro-3-[4-(7-methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-1(2*H*)-naphthalenone 10. To a solution of **16** (1.71 g, 4.63 mmol) in CH_3CN (14 mL) was added K_2CO_3 (1.47 g, 10.6 mmol) and phosphorus oxychloride (2.2 mL, 23.6 mmol) at room temperature and the mixture was stirred at 55 °C for 3 h. The reaction mixture was poured into water (120 mL), basified with 10% aqueous NaOH solution to pH 10–11, and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residual yellow solid was washed with hexane–Et_2O to give **10** as pale yellow prisms (1.31 g, 81%), mp 177–181 °C. Recrystallisation of a portion from EtOAc gave colourless prisms (mp 182–184 °C) (Found: C, 71.7; H, 5.2. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.2%); ν_{max} (Nujol)/cm^{-1} 1663 (C=O); δ_H (400 MHz) 2.48 (3 H, s, 2′-Me), 2.81–2.98 (2 H, m, 2- or 4-H), 3.09–3.23 (2 H, m, 2- or 4-H), 3.59–3.65 (1 H, m, 3-H), 4.00 (3 H, s, OMe), 6.02 and 6.03 (each 1 H, d, *J* 1.0, OCH_2O), 6.43 (1 H, s, 3′-H), 6.69 (1 H, s, 5-H), 6.71 (1 H, d, *J* 8.2, 6′-H), 6.98 (1 H, d, *J* 8.2, 5′-H) and 7.53 (1 H, s, 8-H); δ_C (125 MHz) 14.1, 37.1, 38.5, 44.9, 56.0, 101.3, 101.7, 105.4, 106.3, 108.0, 119.5, 127.0, 127.6, 129.1, 140.5, 143.7, 143.9, 147.2, 152.3, 155.7 and 196.2.

3-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-1-naphthol 17. A solution of **10** (1.17 g, 3.35 mmol) and *p*-toluenesulfonic acid monohydrate (99 mg, 0.52 mmol) in isopropenyl acetate (18 mL) was stirred at 95 °C for 13 h under an argon atmosphere. Then, DDQ (914 mg, 4.03 mmol) was added to the reaction mixture and stirred at room temperature for 1 h. After addition of CH_2Cl_2 (50 mL) to the reaction mixture, the organic solution was washed with 1% aqueous NaOH solution and evaporated *in vacuo*. The residue was dissolved in EtOH (55 mL) and 5% aqueous NaOH solution (55 mL, 68.8 mmol). The mixture was stirred at 85 °C for 1 h, poured into water (200 ml), acidified with 10% hydrochloric acid and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residual brown solid (1.28 g) was recrystallised from $CHCl_3$–MeOH to afford **17** (1.04 g, 89%) as pale pink prisms (mp 259–262 °C); ν_{max} (Nujol)/cm^{-1} 3347 (OH); δ_H (400 MHz) 2.50 (3 H, s, 2′-Me), 4.05 (3 H, s, OMe), 5.18 (1 H, s, OH), 6.07 (2 H, s, OCH_2O), 6.62 (1 H, d like, *J* 0.5, 3′-H), 6.83 (1 H, d, *J* 8.2, 6′-H), 6.94 (1 H, d, *J* 1.3, 4-H), 7.14 (1 H, s, 5-H), 7.24 (1 H, d, *J* 8.2, 5′-H), 7.44 (1 H, d, *J* 1.3, 2-H) and 7.50 (1 H, s, 8-H). Found (EI): 348.0998 (M^+), $C_{21}H_{16}O_5$ requires 348.0996.

1-Benzyloxy-3-[4-(7-methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxynaphthalene 18. To a mixture of **17** (695 mg, 2.00 mmol), K_2CO_3 (554 mg, 4.01 mmol) and DMF (5.6 mL) was added benzyl bromide (0.29 mL, 2.44 mmol) and the mixture was stirred at 50 °C for 2 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc. The organic layer was washed with 2% aqueous NaOH solution, water and brine, dried (K_2CO_3), and evaporated *in vacuo*. The residual red solid (0.924 g) was washed with hexane–Et_2O to give benzyl ether **18** (793 mg, 91%) as colourless plates (mp 149–152 °C, EtOAc–hexane) (Found: C, 76.6; H, 5.05. $C_{28}H_{22}O_5$ requires C, 76.7; H, 5.1%); ν_{max} (Nujol)/cm^{-1} no characteristic absorption; δ_H (400 MHz) 2.46 (3 H, s, 2′-Me), 4.05 (3 H, s, OMe), 5.31 (2 H, s, OC*H*$_2$Ph), 6.06 (2 H, s, OCH_2O), 6.29 (1 H, d like, *J* 0.8, 3′-H), 6.82 (1 H, d, *J* 8.2, 6′-H), 6.99 (1 H, d, *J* 1.1, 4-H), 7.14 (1 H, s, 5-H), 7.26 (1 H, d, *J* 8.2, 5′-H), 7.26 (1 H, s, 2-H), 7.35–7.53 (5 H, m, –CH_2*Ph*) and 7.66 (1 H, s, 8-H); δ_C (125 MHz) 14.1, 56.1, 70.1, 99.1, 101.0, 102.5, 103.9, 105.7, 106.0, 118.8, 121.0, 122.5, 127.16, 127.24, 127.8, 128.6, 129.0, 131.9, 136.5, 137.3, 143.8, 144.2, 147.2, 148.2, 153.9 and 155.9.

1-Benzyloxy-3-[4-(2-hydroxy-7-methoxy-2-methyl-3-oxo-2,3-dihydrobenzo[*b*]furanyl)]-6,7-methylenedioxynaphthalene 19. To a solution of **18** (2.55 g, 5.82 mmol) in pyridine (25 mL) was added OsO_4 (1.78 g, 6.98 mmol) and stirred at 30 °C for 3 h. Then a solution of sodium sulfite (8.27 g, 58.2 mmol) in water (77 mL) and EtOH (38 mL) was added to the reaction mixture and the mixture was stirred at 75 °C for 7 h. The precipitates were filtered off using Celite and the filtrate was extracted with EtOAc. The organic layer was washed with saturated cupric sulfate, water and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residual yellow amorphous solid was purified by column chromatography (elution gradient 1 : 5⟶1 : 3 EtOAc–hexane, then MeOH) to afford **19** as yellow prisms (2.51 g, 92%). Recrystallisation of a portion from Et_2O–hexane gave **19** as yellow prisms (mp 171–174 °C) (Found: C, 71.4; H, 4.7. $C_{28}H_{22}O_7$ requires C, 71.5; H, 4.7%); ν_{max} (Nujol)/cm^{-1} 3483 (OH) and 1725 (C=O); δ_H (400 MHz) 1.72 (3 H, s, 2′-Me), 3.30 (1 H, s, 2′-OH), 4.00 (3 H, s, OMe), 5.26 (2 H, d, *J* 1.8, OC*H*$_2$Ph), 6.05 (2 H, s, OCH_2O), 7.02 (1 H, d, *J* 1.3, 4-H), 7.11 (1 H, d, *J* 8.2, 6′-H), 7.13 (1 H, s, 5-H), 7.20 (1 H, d, *J* 8.2, 5′-H), 7.26 (1 H, s, 2-H), 7.33–7.54 (5 H, m, CH_2*Ph*) and 7.62 (1 H, s, 8-H); δ_C (125 MHz) 22.3, 56.3, 70.4, 99.1, 101.0, 103.2, 104.1, 106.4, 115.6, 119.2, 120.1, 122.0, 123.6, 127.5, 127.8, 128.5, 131.3, 132.7, 134.4, 137.3, 145.2, 147.6, 148.1, 153.6, 160.7 and 197.8.

6-[3-(1-Benzyloxy-6,7-methylenedioxynaphthyl)]-2-hydroxy-3-methoxybenzoic acid 20. To a solution of **19** (305 mg, 0.65 mmol) in dioxane (12 mL) was added a solution of periodic acid dihydrate (222 mg, 0.97 mmol) in water (1.3 mL) and dioxane (3.3 mL) and the mixture was stirred at room temperature for 24 h under an argon atmosphere. Then 1% aqueous NaOH solution (16 mL) was added to the reaction mixture and the mixture was stirred at room temperature for 4 h. To the reaction mixture water (30 mL) was added and acidified with 5% hydrochloric acid followed by extraction with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give **21** (287 mg, 100%) as a brown oil, which was used for the next step without further purification. ν_{max} (neat)/cm^{-1} 3016 (OH) and 1719 (C=O); δ_H (400 MHz) 3.95 (3 H, s, OMe), 5.20 (2 H, s, OC*H*$_2$Ph), 6.05 (2 H, s, OCH_2O), 6.72 (1 H, s, 4-H), 6.82 (1 H, d, *J* 8.3, 4′-H), 7.04 (1 H, d, *J* 8.3, 5′-H), 7.08 (1 H, s, 5-H), 7.22 (1 H, s, 2-H), 7.35–7.49 (5 H, m, CH_2*Ph*), 7.63 (1 H, s, 8-H) and 10.83 (1 H, br s, OH).

Methyl 6-[3-(1-benzyloxy-6,7-methylenedioxynaphthyl)]-2,3-dimethoxybenzoate 21. To a solution of **20** (2.23 g, 5.02 mmol) in benzene (200 mL) was added benzyltributylammonium chloride (1.41 g, 4.52 mmol) and 2% aqueous NaOH solution (94 mL) followed by dropwise addition of Me_2SO_4 (2.4 mL, 25.4 mmol), the reaction mixture was stirred at room temperature for 3 h, and poured into 5% aqueous ammonia (35 mL). The mixture was stirred for 1 h and extracted with EtOAc. The organic layer was washed with 5% aqueous ammonia, water and brine, dried (K_2CO_3), and evaporated *in vacuo*. The residue was crystallised and washed with hexane–EtOAc to yield **21** (2.06 g, 87%) as colourless prisms (mp 154–156 °C), which were recrystallised from Et_2O (Found: C, 70.9; H, 5.2. $C_{28}H_{24}O_7$ requires C, 71.2; H, 5.1%); ν_{max} (Nujol)/cm^{-1} 1739 (C=O); δ_H (400 MHz) 3.63 (3 H, s, CO-OMe), 3.93 (3 H, s, ArOMe), 3.94 (3 H, s, ArOMe), 5.20 (2 H, s, OC*H*$_2$Ph), 6.04 (2 H, s, OCH_2O), 6.87 (1 H, d *J* 1.4, 4-H), 7.03 (1 H, d, *J* 8.5, 4′-H), 7.09 (1 H, s, 5-H), 7.17 (1 H, d, *J* 8.5, 5′-H), 7.27 (1 H, br s, 2-H), 7.35–7.53 (5 H, m, CH_2*Ph*) and 7.61 (1 H, s, 8-H); δ_C (125 MHz) 52.3, 56.1, 61.7, 70.1, 99.0, 101.1, 103.9, 105.4, 113.6, 119.2, 121.2, 125.5, 127.5, 128.0, 128.6, 129.0, 131.6, 132.9, 136.0, 137.0, 146.1, 147.4, 148.3, 151.9, 154.0 and 168.2; *m*/*z*: (EI) 472 (M^+, 33%) and 147 (100).

Methyl 6-[3-(1-hydroxy-6,7-methylenedioxynaphthyl)]-2,3-dimethoxybenzoate 22. To a solution of **21** (2.03 g, 4.29 mmol) in AcOH (130 mL) was added a solution of 1% palladium–hydrochloric acid[17] (9.5 mL, 0.89 mmol) and activated carbon (876 mg, 73.0 mmol), and the mixture was hydrogenated at 20 °C for 3.5 h. The catalyst was filtered off using Celite. The filtrate was evaporated *in vacuo.* The residual orange solid was washed with Et_2O–hexane to afford **22** (1.35 g, 82%) as colourless prisms (mp 200–201 °C, EtOAc–hexane) (Found: C, 65.7; H, 4.7. $C_{21}H_{18}O_7$ requires C, 66.0; H, 4.7%); ν_{max} (Nujol)/cm^{-1} 3340 (OH) and 1686 (C=O); δ_H (400 MHz) 3.65 (3 H, s, CO-OMe), 3.92 (3 H, s, ArOMe), 3.93 (3 H, s, ArOMe), 5.49 (1 H, s, OH), 6.04 (2 H, s, OCH_2O), 6.73 (1 H, d, *J* 1.5, 4-H), 7.01 (1 H, d, *J* 8.4, 4′-H), 7.07 (1 H, s, 5-H), 7.15 (1 H, d, *J* 8.4, 5′-H), 7.24 (1 H, s, 2-H) and 7.47 (1 H, s, 8-H).

(*Z*)-Methyl 2,3-dimethoxy-6-[2-(1-methoxyimino-6,7-methylenedioxy-4-oxo-1,4-dihydronaphthyl)]benzoate 11. A mixture of **22** (350 mg, 0.92 mmol) and pulverised K_2CO_3 (1.27 g, 9.16 mmol) in DMF (3.5 mL) was stirred at room temperature for 20 min under an argon atmosphere. After addition of *i*-AmONO (0.21 mL, 1.56 mmol) under ice-cooling, the mixture was stirred at room temperature for 3.5 h and cooled. After addition of Me_2SO_4 (0.11 mL, 1.16 mmol) under ice-cooling, the reaction mixture was stirred at room temperature for 1.5 h, poured into 5% aqueous ammonia (0.7 mL) and stirred for 1 h. After addition of water (16 mL) the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried (K_2CO_3), and evaporated *in vacuo.* The residual yellow solid was purified by column chromatography (benzene–EtOAc = 12 : 1) to give **11** (336 mg, 86%) as yellow prisms (mp 171–173 °C, EtOAc–hexane) (Found: C, 62.1; H, 4.4; N, 3.2. $C_{22}H_{19}NO_8$ requires C, 62.1; H, 4.5; N, 3.3%); ν_{max} (Nujol)/cm^{-1} 1742 (C=O, ester) and 1638 (4-C=O); δ_H (400 MHz) 3.66 (3 H, s, COOMe), 3.93 (6 H, s, OMe × 2), 4.08 (3 H, s, NOMe), 6.12 (2 H, s, OCH_2O), 6.57 (1 H, s, 3-H), 7.01 (1 H, d, *J* 8.5, 4′-H), 7.11 (1 H, d, *J* 8.5, 5′-H), 7.69 (1 H, s, 5-H) and 8.32 (1 H, s, 8-H); δ_C (125 MHz) 52.1, 56.0, 61.7, 64.4, 102.2, 106.2, 109.8, 113.3, 124.2, 125.4, 128.3, 128.8, 129.1, 129.3, 145.3, 146.8, 149.4, 151.4, 151.6, 153.5, 166.9 and 183.4.

7,8-Dimethoxy-12-hydroxy-2,3-methylenedioxybenzo[*c*]-phenanthridin-6(5*H*)-one 23. To a solution of **11** (252 mg, 0.59 mmol) in AcOH (90 mL) was added 10% palladium–carbon (50 mg, 0.047 mmol) and the mixture was hydrogenated at room temperature for 1.5 h under atmospheric pressure. After addition of $CHCl_3$ (500 mL) the catalyst was filtered off using Celite and the filtrate was evaporated *in vacuo*. The yellow residue was crystallised and washed with Et_2O to yield **23** (207 mg, 95%) as yellow prisms (mp > 300 °C). ν_{max} (Nujol)/cm^{-1} 1654 (C=O); δ_H (400 MHz, DMSO-d_6) 3.83 (3 H, s, 7-OMe), 3.92 (3 H, s, 8-OMe), 6.17 (2 H, s, OCH_2O), 7.46 (1 H, s, 11-H), 7.47 (1 H, s, 1-H), 7.64 (1 H, d, *J* 9.0, 9-H), 7.96 (1 H, d, *J* 9.0, 10-H), 8.27 (1 H, s, 4-H), 9.84 (1 H, s, NH) and 11.0 (1 H, s, OH); δ_C (125 MHz, DMSO-d_6) 56.2, 60.9, 99.2, 99.3, 100.2, 101.5, 112.5, 118.4, 119.3, 119.9, 122.0, 124.6, 128.2, 129.2, 147.2, 147.8, 148.2, 149.2, 151.9 and 159.3; Found (FAB) 366.0979 (MH^+), $C_{20}H_{16}NO_6$ requires 366.0978.

Methylation of phenolic lactam 23. To a solution of **23** (50 mg, 0.14 mmol) in CH_2Cl_2 (12 mL) was added 2% aqueous NaOH solution (4.5 mL), benzyltributylammonium chloride (86 mg, 0.27 mmol) and Me_2SO_4 (0.135 mL, 1.42 mmol). The mixture was stirred at room temperature for 1.5 h, poured into 5% aqueous ammonia (2.85 mL) and stirred at room temperature for 1 h. After addition of water (6 mL) the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried (K_2CO_3), and evaporated *in vacuo.* The purple residue (83 mg) was purified by column chromatography using $CHCl_3$ as eluent to give two compounds.

(i) 6,7,8,12-Tetramethoxy-2,3-methylenedioxybenzo[*c*]-phenanthridine 24. 24 (24 mg, 45%) was obtained as less polar yellow prisms (mp 237–240 °C) (Found: C, 67.2; H, 4.8; N, 3.3. $C_{22}H_{19}NO_6$ requires C, 67.2; H, 4.9; N, 3.6%); ν_{max} (Nujol)/cm^{-1} no characteristic absorption; δ_H (400 MHz) 3.99 (3 H, s, 7-OMe), 4.03 (3 H, s, 8-OMe), 4.14 (3 H, s, 12-OMe), 4.33 (3 H, s, 6-OMe), 6.11 (2 H, s, OCH_2O), 7.49 (1 H, s, 11-H), 7.52 (1 H, d, *J* 9.2, 9-H), 7.65 (1 H, s, 1-H), 8.24 (1 H, d, *J* 9.2, 10-H) and 8.50 (1 H, s, 4-H); δ_C (125 MHz) 53.7 (6-OMe), 55.6 (12-OMe), 57.0 (8-OMe), 61.9 (7-OMe), 95.6 (11-C), 99.4 (1-C), 101.2 (OCH_2O), 102.1 (4-C), 115.4 (6a-C), 117.5 (10b-C), 117.8 (9-C), 118.6 (10-C), 122.9 (12a-C), 128.9 (4a-C), 131.1 (10a-C), 133.2 (4b-C), 146.5 (7-C), 147.9 (3-C), 148.2 (2-C), 151.6 (8-C), 152.4 (12-C) and 156.4 (6-C); *m*/*z*: (EI) 393 (M^+, 100%) and 378 (M^+–Me, 30).

(ii) 6,7,8-Trimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-11,12-dione 25. 25 (21 mg, 39%) was obtained as more polar purple prisms (mp > 300 °C). ν_{max} (KBr)/cm^{-1} 1681 (C=O) and 1648 (C=O); δ_H (400 MHz) 3.95 (3 H, s, 7-OMe), 4.00 (3 H, s, 8-OMe), 4.34 (3 H, s, 6-OMe), 6.14 (2 H, s, OCH_2O), 7.53 (1 H, s, 1-H), 7.55 (1 H, d, *J* 9.6, 9-H), 8.06 (1 H, s, 4-H) and 9.24 (1 H, d, *J* 9.6, 10-H); δ_C (125 MHz) 55.1 (6-OMe), 56.7 (8-OMe), 61.8 (7-OMe), 102.6 (OCH_2O), 107.0 (4-C), 108.4 (1-C), 114.6 (10b-C), 115.6 (6a-C), 121.0 (9-C), 123.3 (10-C), 126.5 (12a-C), 132.1 (10a-C), 135.4 (4a-C), 145.2 (7-C), 149.9 (4b-C), 150.0 (2-C), 152.2 (8-C), 154.4 (3-C), 163.9 (6-C), 178.6 (12-C) and 181.0 (11-C); *m*/*z*: (FAB) 394 (MH^+) and 416 (MNa^+).

12-Acetoxy-7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]-phenanthridin-6(5*H*)-one 28. A mixture of **23** (51 mg, 0.14 mmol) and acetic anhydride (1 mL) was stirred at room temperature for 2 h, at 50 °C for 21 h and then at 80 °C for 27 h under an argon atmosphere. The reaction mixture was washed with Et_2O–hexane to give **28** (51 mg, 91%) as a colorless powder (mp > 300 °C). ν_{max} (Nujol)/cm^{-1} 1752 (C=O) and 1653 (C=O); δ_H (400 MHz, DMSO-d_6) 2.45 (3 H, s, OCOMe), 3.82 (3 H, s, 7-OMe), 3.92 (3 H, s, 8-OMe), 6.20 (2 H, s, OCH_2O), 7.30 (1 H, s, 1-H), 7.62 (1 H, d, *J* 9.2, 9-H), 8.04 (1 H, s, 11-H), 8.20 (1 H, d, *J* 9.2, 10-H), 8.35 (1 H, s, 4-H) and 11.2 (1 H, s, NH); δ_C (125 MHz, DMSO-d_6) 20.8 ($COCH_3$), 56.2 (8-OMe), 60.9 (7-OMe), 98.6, 99.5, 101.9 (OCH_2O), 111.8, 112.2, 118.5, 119.0, 119.2, 119.7, 123.8, 128.9, 129.1, 141.3, 148.4, 148.5, 149.1, 152.3, 159.7 (6-C) and 169.8 ($COCH_3$); *m*/*z*: (EI) 407 (M^+, 85%), 365 (M^+–COMe, 81) and 347 (100).

6,12-Diacetoxy-7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]-phenanthridine 29. A mixture of **25** (20 mg, 0.055 mmol) and DMAP (12 mg, 0.098 mmol) in AcOH (0.5 mL, 5.3 mmol) was stirred at room temperature for 5.5 h, at 50 °C for 3.5 h and at 80 °C for 1.5 h under argon atmosphere. Triethylamine (0.1 mL, 0.72 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 15 h. After addition of MeOH (1 mL) the solvent was evaporated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and the organic layer was washed with 1 M hydrochloric acid, water, saturated aqueous $NaHCO_3$ solution, water and brine, dried ($MgSO_4$), and evaporated *in vacuo.* The residual yellow solid (30 mg) was purified by column chromatography using $CHCl_3$ as an eluent to give **29** (18 mg, 74%) as colourless needles, which were recrystallised from $CHCl_3$–hexane (mp 230 °C, dec.) (Found: C, 64.0; H, 4.35; N, 3.15. $C_{24}H_{19}NO_8$ requires C, 64.1; H, 4.3; N, 3.1%); ν_{max} (Nujol)/cm^{-1} 1751 (C=O); δ_H (400 MHz) 2.51 (3 H, s, 6-OAc), 2.53 (3 H, s, 12-OAc), 4.01 (3H, s, 7-OMe), 4.04 (3 H, s, 8-OMe), 6.14 (2 H, s, OCH_2O), 7.24 (1 H, s, 1-H), 7.60 (1 H, d, *J* 9.3, 9-H), 8.08 (1 H, s, 11-H), 8.30 (1 H, d, *J* 9.3, 10-H) and 8.55 (1 H, s, 4-H); δ_C (125 MHz) 21.1 (OAc × 2), 56.6 (8-OMe), 62.0 (7-OMe), 98.4 (1-C), 101.6 (OCH_2O), 102.8 (4-C), 110.2 (11-C), 115.9 (6a-C), 118.4 (9-C), 119.4 (10-C), 120.4 (10b-C),

123.7 (12a-C), 129.8 (4a-C), 131.2 (10a-C), 136.0 (4b-C), 144.4 (7-C), 145.6 (12-C), 148.9 (2-C), 149.0 (3-C), 151.2 (6-C), 151.4 (8-C), 169.4 (C=O) and 169.7 (C=O); *m*/*z*: (EI) 449 (M^+, 48%), 407 (M^+–COMe, 63) and 365 (M^+-2 × COMe, 100).

12-Benzoyloxy-7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]-phenanthridin-6(5*H*)-one 30. A suspension of **23** (46 mg, 0.13 mmol) and benzoic anhydride (57 mg, 0.25 mmol) in dry CH_2Cl_2 (0.3 mL) was stirred at 60 °C for 14 days under argon atmosphere. During the course of reaction, dry CH_2Cl_2 (0.3 mL) and benzoic anhydride (22 mg, 0.098 mmol) were added once a day and after 2 days, respectively. The reaction mixture was diluted with $CHCl_3$ (100 mL). The organic solution was washed with water, saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residual solid was washed with Et_2O–EtOAc and then CH_2Cl_2–hexane to give **30** (57 mg, 96%) as colourless prisms, which were recrystallised from CH_2Cl_2 (mp > 300 °C). ν_{max} (Nujol)/cm^{-1} 1734 (C=O) and 1647 (NHC=O); δ_H (400 MHz, DMSO-d_6) 3.86 (3 H, s, 7-OMe), 3.95 (3 H, s, 8-OMe), 6.22 (2 H, s, OCH_2O), 7.20 (1 H, s, 1-H), 7.62 (1 H, d, *J* 9.0, 9-H), 7.70 (2 H, dd, *J* 7.2, 7.9, 3′- and 5′-H), 7.83 (1 H, t, *J* 7.2, 4′-H), 8.26 (1 H, s, 11-H), 8.29 (1 H, d, *J* 9.0, 10-H), 8.30 (2 H, d, *J* 7.9, 2′- and 6′-H), 8.43 (1 H, s, 4-H) and 11.29 (1 H, s, NH); δ_C (125 MHz, DMSO-d_6) 56.2, 60.9, 98.1, 99.7, 102.0, 112.1, 112.3, 118.5, 119.0, 119.4, 119.7, 123.6, 128.8, 128.9, 129.0, 129.3, 130.0, 134.2, 141.3, 148.5, 149.1, 152.3, 159.7 and 165.1; Found (FAB) 470.1231 (MH^+), $C_{27}H_{20}NO_7$ requires 470.1240; *m*/*z*: (EI) 469 (M^+, 100%) and 364 (M^+–COPh, 83).

12-Benzoyloxy-7,8-dimethoxy-2,3-methylenedioxy-6-trifluoromethanesulfonyloxybenzo[*c*]phenanthridine 31. A mixture of **30** (30 mg, 0.064 mmol), diisopropylethylamine (18 μL, 0.10 mmol) and trifluoromethanesulfonic anhydride (14 μL, 0.083 mmol) in dry CH_2Cl_2 (13 mL) was stirred at 0 °C for 5 h under argon atmosphere and poured into water (4 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated *in vacuo.* The brown residue was purified by column chromatography using toluene as an eluant to afford **31** (32 mg, 83%) as colourless prisms, which were recrystallised from EtOAc (mp 239–241 °C) (Found: C, 55.6; H, 3.0; N, 2.25. $C_{28}H_{18}F_3NO_9S$ requires C, 55.9; H, 3.0; N, 2.3%); ν_{max} (Nujol)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 4.05 (3 H, s, 7-OMe), 4.10 (3 H, s, 8-OMe), 6.14 (2 H, s, OCH_2O), 7.31 (1 H, s, 1-H), 7.61 (1 H, d, *J* 9.3, 9-H), 7.61 (2 H, m, 3′- and 5′-H), 7.74 (1 H, dt, *J* 7.5, 1.3, 4′-H), 8.17 (1 H, s, 11-H), 8.27 (1 H, d, *J* 9.3, 10-H), 8.36 (2 H, dd, *J* 7.1, 1.3, 2′- and 6′-H) and 8.40 (1 H, s, 4-H); δ_C (125 MHz) 55.6, 61.7, 99.7, 101.8, 102.4, 110.3, 114.5, 118.9, 119.1, 119.3, 121.2, 124.2, 128.9, 129.0, 129.7, 130.4, 131.6, 134.1, 134.7, 144.3, 146.7, 148.4, 149.3, 149.4, 151.9 and 165.1; *m*/*z*: (EI) 601 (M^+, 100%).

12-Benzoyloxy-7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]-phenanthridine 32. A mixture of **31** (40 mg, 0.066 mmol), palladium acetate (3 mg, 0.012 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (5 mg, 0.012 mmol) in DMF (1 mL) was heated at 60 °C for 10 min under argon atmosphere. To this mixture was added triethylsilane (29 μL, 0.18 mmol) and the mixture was heated at 60 °C for 5 h and diluted with $CHCl_3$ (20 mL). The organic solution was washed with water, saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4), and evaporated *in vacuo.* The yellow residue was purified by column chromatography (toluene, $CHCl_3$–EtOAc = 40 : 1, then $CHCl_3$–MeOH) to afford **32** (27 mg, 89%) as colourless prisms, which were recrystallised from $CHCl_3$–EtOAc (mp 249–250 °C). ν_{max} (Nujol)-cm^{-1} 1735 (C=O); δ_H (400 MHz) 4.06 (3 H, s, 7-OMe), 4.14 (3 H, s, 8-OMe), 6.14 (2 H, s, OCH_2O), 7.34 (1 H, s, 1-H), 7.59 (1 H, d, *J* 9.0, 9-H), 7.62 (2 H, dd, *J* 7.4, 7.4, 3′- and 5′-H), 7.74 (1 H, t, *J* 7.4, 4′-H), 8.26 (1 H, s, 11-H), 8.27 (1 H, d, *J* 9.0, 10-H), 8.39 (2 H, d, *J* 7.4, 2′- and 6′- H), 8.78 (1 H, s, 4-H) and 9.75 (1 H, s, 6-H); δ_C (125 MHz) 56.7, 61.9, 98.6, 101.6, 102.7, 110.5, 118.5, 118.7, 120.2, 121.9, 123.7, 127.7, 128.8, 129.2, 130.4, 130.7, 134.0, 138.2, 145.2, 145.8, 146.4, 148.9, 149.0, 149.6 and 165.3. Found (FAB) 454.1316 (MH^+), $C_{27}H_{20}NO_6$ requires 454.1291; *m*/*z*: (EI) 453 (M^+, 39%) and 105 (100).

12-Hydroxynorchelerythrine 33. A mixture of **32** (9 mg, 0.019 mmol) and 3% KOH in MeOH (0.5 mL) was stirred at room temperature for 6 h under argon atmosphere. Additional 3% KOH in MeOH was added twice (50 μL, 0.03 mmol and 0.1 mL, 0.05 mmol) and the whole mixture was stirred at 50 °C for 20 h. The reaction mixture was diluted with water (7 mL) and extracted with Et_2O. The aqueous layer was acidified (pH 4) with 1 M hydrochloric acid and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford **33** (4 mg, 64%) as yellow prisms, which were used for the next step without further purification. δ_H (400 MHz, $CDCl_3$–CD_3OD) 4.06 (3 H, s, 7-H), 4.12 (3 H, s, 8-H), 6.14 (2 H, s, OCH_2O), 7.57 (1 H, d, *J* 9.2, 9-H), 7.68 (1 H, s, 11-H), 7.69 (1 H, s, 1-H), 8.26 (1 H, d, *J* 9.2, 10-H), 8.62 (1 H, s, 4-H) and 9.54 (1 H, s, 6-H); *m*/*z*: (EI) 349 (M^+, 8.5%), 149 (100) and 105 (95.7).

12-Methoxynorchelerythrine 27. To a mixture of hydroxy compound **33** (4 mg, 0.011 mmol) and K_2CO_3 (21 mg, 0.15 mmol) in DMF (0.5 mL) was added Me_2SO_4 (10 μL, 0.11 mmol) and the whole mixture was stirred at 0 °C for 1.5 h under argon atmosphere. The reaction mixture was quenched with aqueous ammonia (0.1 mL), stirred for 1 h, diluted with water (5 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was washed with Et_2O to afford **27** (4 mg, quantitatively) as brown prisms. Purification by column chromatography ($CHCl_3$–EtOAc = 40 : 1) gave pale orange prisms (mp 209–210 °C). ν_{max} (Nujol)/cm^{-1} no characteristic absorption; δ_H (400 MHz) 4.07 (3 H, s, 7-OMe), 4.12 (3 H, s, 8-OMe), 4.18 (3 H, s, 12-OMe), 6.14 (2 H, s, OCH_2O), 7.58 (1 H, d, *J* 9.2, 9-H), 7.60 (1 H, s, 11-H), 7.70 (1 H, s, 1-H), 8.30 (1 H, d, *J* 9.2, 10-H), 8.69 (1H, s, 4-H) and 9.62 (1H, s, 6-H); *m*/*z*: (EI) 363 (M^+, 100%).

12-Methoxydihydrochelerythrine 6. To a solution of **32** (30 mg, 0.066 mmol) in anhydrous MeOH (0.4 mL) was added a solution of sodium methoxide in MeOH (0.8 mL, 0.15 mmol) and the whole mixture was stirred at 45 °C for 18 h under argon atmosphere. After evaporation of the solvent in *vacuo*, the residue was dissolved in HMPA (1 mL). To this solution Me_2SO_4 (0.1 mL, 1.1 mmol) and $NaBH_4$ (40 mg, 1.1 mmol) were added and the mixture was stirred at 60 °C for 1.5 h. Additional reagents were added as follows: Me_2SO_4 (0.1 mL, 1.1 mmol) then $NaBH_4$ (39 mg, 1.0 mmol) with stirring at 60 °C for 4.5 h; Me_2SO_4 (0.2 mL, 2.1 mmol) and $NaBH_4$ (100 mg, 2.7 mmol) with stirring at 60 °C for 3 h; HMPA (0.5 mL) with stirring at 60 °C for 1.5 h. The reaction mixture was quenched with ice–water and basified with 5% aqueous NaOH solution and extracted with EtOAc. The organic layer was washed with water and brine, dried (K_2CO_3), and evaporated *in vacuo.* The yellow residue was purified by column chromatography on aluminium oxide (Merck) (benzene, EtOAc, $CHCl_3$, then $CHCl_3$–MeOH) to afford **6** (17 mg, 67%) as pale yellow prisms, mp 182–183.5 °C (lit.[7] 173–174.5 °C),[18] which were recrystallised from benzene–MeOH. (Found: C, 69.4; H, 5.7; N, 3.6. $C_{22}H_{21}NO_5$ requires C, 69.6; H, 5.6; N, 3.7%); ν_{max} (KBr)/cm^{-1} no characteristic absorption; δ_H (400 MHz) 2.53 (3 H, s, NMe), 3.88 (3 H, s, 7-OMe), 3.94 (3 H, s, 8-OMe), 4.04 (3 H, s, 12-OMe), 4.27 (2 H, s, 6-H), 6.05 (2 H, s, OCH_2O), 6.95 (1 H, d, *J* 8.4, 9-H), 7.05 (1 H, s, 11-H), 7.48 (1 H, d, *J* 8.4, 10-H), 7.55 (1 H, s, 1-H) and 7.65 (1 H, s, 4-H); *m*/*z*: (EI) 379 (M^+, 100%) and 364 (M^+–Me, 61). This compound was completely identical to the authentic sample of **6**.[7]

12-Methoxychelerythrine chloride 7. To a solution of **6** (4 mg, 0.011 mmol) in benzene (0.5 mL) was added 5% aqueous NaOH solution (0.2 mL) and a solution of DDQ (6 mg, 0.025 mmol) in benzene (0.2 mL) and the whole mixture was stirred at room temperature for 0.5 h. After evaporation of the solvent in *vacuo*, the residue was dissolved in water (10 mL) and extracted with $CHCl_3$. The organic layer was washed with water, dried (K_2CO_3), and evaporated to reduce the volume of solvent (0.5 mL). To this solution 10% hydrochloric acid was added to yield a yellow precipitate. After co-evaporation with benzene and MeOH the residual orange solid was washed with Et_2O and hexane–benzene to give **7** (3 mg, 78%) as orange prisms, mp 181–187 °C (dec.). δ_H (500 MHz, CD_3OD) 4.14 (3 H, s, OMe), 4.27 (3 H, s, OMe), 4.29 (3 H, s, OMe), 4.97 (3 H, s, NMe), 6.27 (2 H, s, OCH_2O), 7.88 (1 H, s, ArH), 7.97 (1 H, s, ArH), 8.16 (1 H, s, ArH), 8.18 (1 H, d, *J* 9.3, 9- or 10-H), 8.73 (1 H, d, *J* 9.3, 10- or 9-H) and 9.81 (1 H, s, 6-H). Found (FAB) 378.1316 (M^+–Cl), $C_{22}H_{20}NO_5$ requires 378.1342; *m*/*z*: 378 (M^+–Cl).

In vitro cytotoxicity assay

The cytotoxicity of benzo[*c*]phenanthridines against human lung cancer cell line NCI-H460 and human breast cancer cell line MDA-MB-231 obtained from ATCC (American Type Culture Collection) was assessed by the methylene blue staining method. Briefly, 1.5×10^3 NCI-H460 cells/well and 4.0×10^3 MDA-MB-231 cells/well were inoculated into 96-well microplates. Both cells were cultured in RPMI1640 medium supplemented with 10% fetal bovine serum, and 1 mM sodium pyruvate for NCI-H460 cells. Following overnight culture, serially diluted samples (0.016, 0.08, 0.4, 2, 10, 50 μg mL^{-1}) were added into the wells. After a 3-day culture, cells were stained with 0.05% methylene blue dissolved in 10 mM Tris buffer (pH 8.5) for 30 min, and then thoroughly washed with distilled water. The stained dye was extracted with 3% hydrochloric acid, and OD660 was measured with microplate reader Benchmark Plus (Bio-Rad, USA) to determine cell growth inhibition.

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