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Enantioselective synthesis of chelidonine, a B/C-*cis*-11-hydroxyhexahydrobenzo-[*c*]phenanthridine alkaloid

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ABSTRACT

Both enantiomers of chelidonine, a B/C-*cis*-11-hydroxyhexahydrobenzo[*c*]phenanthridine alkaloid, were synthesized by manipulation of the B/C-dehydro ring juncture of benzo[*c*]phenanthridine skeleton using Sharpless asymmetric dihydroxylation and stereospecific catalytic hydrogenation after introduction of oxygen functions on the C ring as key reaction steps for the construction of stereogenic centers.

1. Introduction

Benzo[*c*]phenanthridine alkaloids,[1] showing interesting biological activities, such as anti-tumor[2] and anti-Leishmaniasis activities,[3] can be classified into two main categories of a B/C-*cis*-11-hydroxyhexahydro-type (a partially hydrogenated-type) and a fully aromatized-type alkaloid based on the oxidation stage of a basic skeleton;[4] e.g., chelidonine (**1**) and homochelidonine (**2**) as the former and sanguinarine (**3**) and chelerythrine (**4**) as the latter. Various types of synthetic methods have been reported for the construction of the benzo[*c*]phenanthridine skeleton;[5] however, only limited approaches have appeared on a partially hydrogenated-type, especially asymmetric version.[6]

We had already succeeded in establishing a general and practical synthetic method[7] for the fully aromatized-type alkaloids including chelerythrine (**4**)[8] through 2-aryl-1-tetralones, which was linearly derived from a chalcone, as key intermediates in the process of the examination of structure–activity relationship against tumor cells. On the other hand, for the structural determination of a naturally-occurring non-alkaloidal arnottin II (**5**)[9] co-existing with benzo[*c*]phenanthridine alkaloids, its racemic synthesis[10] had been also achieved using 2-benzofuranyl-1-tetralone **6**, the same key synthetic intermediate for **4**. The presence of a unique 2-spirolactonyl-3,4-dehydro-1-tetralone moiety in arnottin II (**5**) prompted us to undertake synthesis of homochelidonine (**2**) by the chemical conversion from **5** and, in the previous communication,[11] we presented the stereoselective synthesis of (±)-homochelidonine [(±)-**2**]. After then, we succeeded in the convergent asymmetric synthesis of (−)-arnottin II [(−)-**5**] by palladium (Pd)-catalyzed coupling of 3-bromobenzoate and 1-tetralone according to the Buchwald protocol[12] followed by Sharpless asymmetric dihydroxylation[13] of the formed four ring-fused dehydrolactone **7** using AD-mix.[14] This success encouraged us to enantioselectively synthesize chelidonine (**1**). An optically active chelidonine (**1**) could be simply synthesized by the use of the corresponding methylenedioxy analog of (−)-arnottin II [(−)-**5**] as a starting material in the established route for (±)-homochelidonine [(±)-**2**];[11] however, we challenged to independently approach to the enantioselective synthesis of chelidonine in order to compare the efficiency of both routes. In this paper we present the synthesis of both enantiomers of chelidonine [(+)- and (−)-**1**], which contains Sharpless asymmetric dihydroxylation of 4b,10b-dehydrolactam **8**, derived from a related tetracyclic lactone like **7**, and stereospecific catalytic hydrogenation of 4b,10b-dehydroamine 11,12-acetal **9** as key reaction steps for the construction of stereogenic centers in the chelidonine system.

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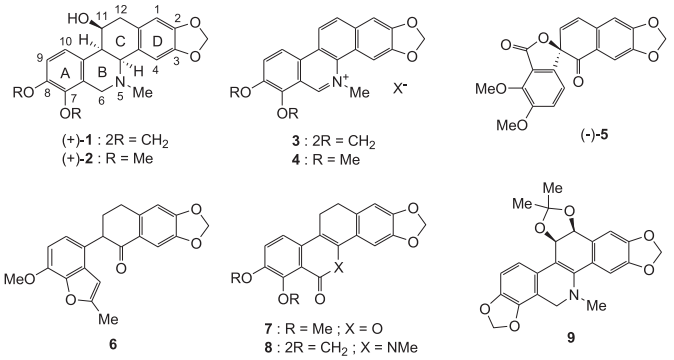
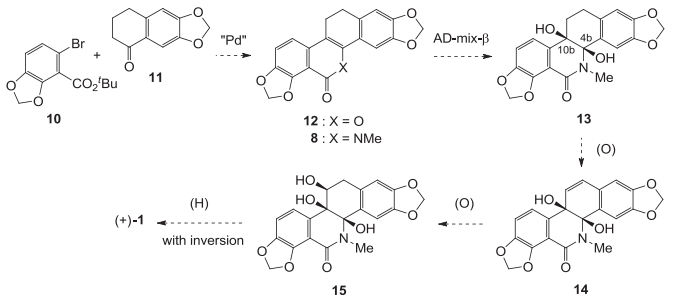


2. Results and discussion

Chelidonine (**1**) occurs in nature as (+)-, (−)-, and (±)-forms, but the majority is (+)-form, which has been isolated from some Papaveraceous plants since the first isolation from the root of *Chelidonium majus* L. by Probst in 1839.[15] (−)-Form was isolated from *Glaucium corniculatum* Curt, (Papaveraceae) in 1957[16] and the (±)-form was identified with diphylline in 1961 by Slavík's group.[17] The plain structure of **1** was finally proposed to be 4b,5,6,10b,11,12-hexahydro-11-hydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)benzo[*c*]phenanthridine skeleton by Späth and Küffner in 1931[18] after the original structural approaches by Gadamer in 1919.[19] The full structure of (+)-chelidonine [(+)-**1**] including (4b*S*,10b*R*,11*S*)-stereochemistries was concretely determined by X-ray crystallographic analysis of the *p*-bromobenzoate in 1979.[20]

Thus, although chelidonine chemistry has long history, limited total synthesis of (±)- and (+)-chelidonine [(±)- and (+)-**1**] has been reported. Oppolzer's group developed the unique synthetic method of the (±)-from, in which simultaneous electrocyclic and Diels–Alder reactions of ethynylbenzocyclobutene were designed for the construction of benzo[*c*]phenanthridine skeleton.[21] The (±)-from was alternatively synthesized by Cushman's groups through the acidic cyclization of diazoketone derivative obtained by the condensation of aryl imine and homophthalic anhydride.[22] On the other hand, recently, the enantioselective synthesis of naturally abundant (+)-chelidonine [(+)-**1**] was achieved by Lautens' group, in which Pd-catalyzed coupling reaction between arylboronic acid and azabicyclic benzoalkene in the presence of binaphthyl-type phosphine ligand was skillfully applied as a stereogenic key reaction.[23] This elegant strategy was successfully expanded to the enantioselective syntheses of the related B/C-*cis*-11-hydroxyhexahydrobenzo[***c***]phenanthridine alkaloids including (+)-homochelidonine [(+)-**2**].[24]

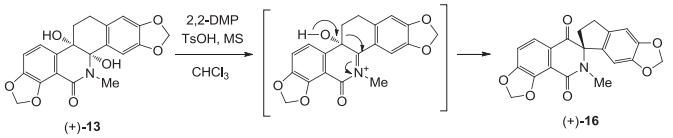
We primarily planned the synthetic strategy of (+)-chelidonine [(+)-**1**] based on our established syntheses of (±)-homochelidonine [(±)-**2**][11] and (−)-arnottin II [(−)-**5**][14] (Scheme 1). A tetracyclic dehydrolactone **12** is prepared by Pd-catalyzed coupling reaction of 6-bromo-2,3-methylenedioxybenzoate **10** and 1-tetralone **11** according to the procedure for (−)-**5** and is converted to the corresponding dehydrolactam **8** by replacement of the ring-oxygen atom of **12** with *N*-methyl group as a substrate for the possible construction of (4b*R*,10b*R*)-stereochemistries by Sharpless asymmetric dihydroxylation using AD-mix-β.[13,14] The newly created configurations in the 4b,10b-*cis*-dihydroxylactam **13** could control the next stereospecific introduction of a hydroxyl group to 11 position of the corresponding 11,12-dehydrolactam **14** with an (*S*)-configuration and, finally, (+)-chelidonine [(+)-**1**] could be afforded by hydrogenolysis of 4b,10b-benzylic hydroxy groups in 4b,10b,11-trihydroxylactam **15** with inversion.



Scheme 1. Outline of primary synthetic plan of (+)-chelidonine [(+)-**1**].

Actually, (+)- and (−)-4b,10b-dihydroxylactams [(+)- and (−)-**13**] were prepared as the outline shown in Scheme 1. Pd-Catalyzed coupling reaction between *tert*-butyl bromobenzoate **10**, which was prepared from a commercially available 6-bromo-2,3-methylenedioxybenzoic acid, and 1-tetralone **11** according to the reported conditions[14] provided a mixture of a major dehydrolactone **12** (78%) and a minor hydrolyzed carboxylic acid (3%), which was quantitatively converted to **12** by treatment with *p*-toluenesulfonic acid monohydrate (TsOH). Successive treatments of dehydrolactone **12** with 40% methylamine aqueous solution in dimethylformamide (DMF) at room temperature (rt) and with TsOH in benzene at 100 °C gave 4b,10b-dehydrolactam **8** in 89% yield. Application of the reaction conditions [AD-mix-α-$(DHQ)_2PHAL$ (or AD-mix-β-$(DHQD)_2PHAL$), $K_2OsO_4\cdot 2H_2O$, $MeSO_2NH_2$, and 50% ^{t}BuOH aq in CH_2Cl_2] established in the enantioselective synthesis of arnottin II (**5**) to the asymmetric dihydroxylation of 4b,10b-dehydrolactam **8** successfully afforded 4b,10b-dihydroxylactams [(+)-**13** with AD-mix-α in 86% yield (94% ee); (−)-**13** with AD-mix-β in 88% yield (85% ee)]; the stereogenic centers of (+)-**13** were assignable to be 4b*S*, 10b*S* based on the results in the synthesis of arnottin II (**5**).[14]

Thus, although both enantiomers of 4b,10b-dihydroxylactam **13** were in our hands, we decided to preliminarily use the (−)-enantiomer (−)-**13** with (4b*R*,10b*R*)-configurations as a chiral source for (+)-chelidonine [(+)-**1**] because stereochemical inversion of chiral centers on the B/C ring juncture was expected after introduction of hydroxy group at 11 position, as shown in Scheme 1. Before manipulation on the (−)-one, acetal protection of 4b,10b-dihydroxy functions in **13** was attempted for further modification of ring C using the (+)-enantiomer as a model substrate. Refluxing (+)-**13** with 2,2-dimethoxypropane (2,2-DMP) in the presence of catalytic TsOH and molecular sieves 4 Å (MS) unexpectedly provided (+)-3-spiroindanyl-4-oxoisoquinolone (+)-**16** without loss of optical activity. The new stereogenic center of a spiro product (+)-**16** could be reasonably deduced to be *S* by stereospecific conversion from (+)-**13** with (4b*S*,10b*S*)-configurations through pinacol-type rearrangement, as shown in Scheme 2.

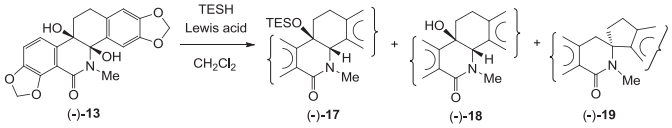


Scheme 2. Plausible pinacol-type rearrangement of (+)-4b,10b-dihydroxylactam (+)-**13** to (+)-3-spiroindanyl-4-oxoisoquinolone (+)-**16**.

Therefore, reduction of the 4b-hemiaminal function in (−)-4b,10b-dihydroxylactam (−)-**13** with acidic triethylsilane (TESH) was examined (Table 1). The use of slightly excess of TESH in the presence of half equivalent of ethereal boron trifluoride ($BF_3\cdot Et_2O$) at −40 °C[25] led to incomplete reduction, in which a silylated (−)-10b-hydroxylactam (−)-**17** (49% yield) was unexpectedly given with the recovery of starting (−)-**13** (51%) (run 1). A spiroindanylisoquinolone (−)-**19**, which was corresponded to the enantiomer of the 4-deoxo derivative of (+)-**16** in Scheme 2, was

mainly produced together with (−)-**17** when reaction was stirred with an equimolar $BF_3{\cdot}Et_2O$ until consumption of (−)-**13** (run 2). The use of large amounts of TESH improved the production of (−)-**17**, albeit contamination of other components (run 3). Interestingly, replacement of $BF_3{\cdot}Et_2O$ with boron trichloride (BCl_3) afforded a non-silylated (−)-10b-hydroxylactam (−)-**18** as a sole product in satisfactory yield (run 4), while a complex mixture was obtained in the case of titanium tetrachloride ($TiCl_4$) (run 5). On the other hand, (−)-10b-silyloxylactam (−)-**17** was effectively given, without rearrangement to the spiro system (−)-**19**, in the use of trifluoroacetic acid (TFA) as an acid source (runs 6 and 7), and (−)-**17** was finally obtained in 98% yield after optimization (run 8). However, as mentioned later, it was found that hydrogenolysis of the 4b-hemiaminal hydroxyl group occurred with undesired retention.

Table 1
Reduction of (−)-4b,10b-dihydroxylactam (−)-**13** with acidic TESH



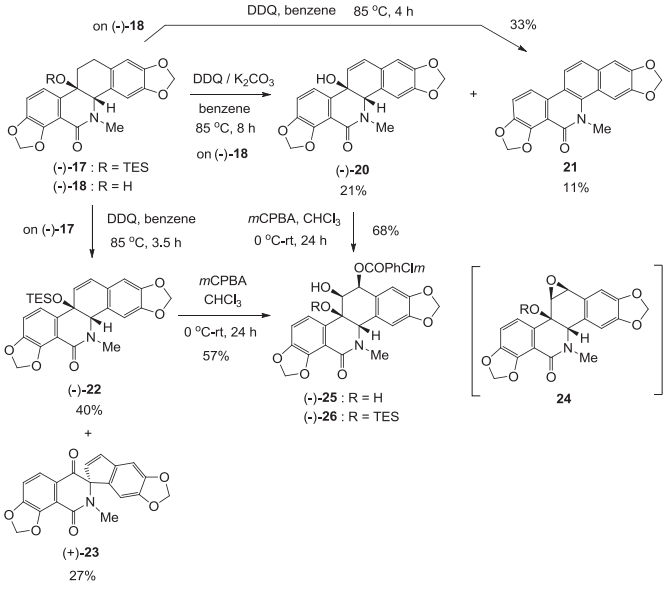
Run	TESH (equiv)	Acid (equiv)	Temp (°C)	Time (h)	Yield (%)			
					(−)-**17**	(−)-**18**	(−)-**19**	(−)-**13**
1[a]	4	$BF_3{\cdot}Et_2O$ (0.5)	−40	1	49	—	—	51
2[a]	4	$BF_3{\cdot}Et_2O$ (1)	−40	2	30	—	70	—
3[b]	30	$BF_3{\cdot}Et_2O$ (1)	−35	2	70	6	10	7
4[b]	30	BCl_3 (1)	−35	1	—	76	—	—
5	10	$TiCl_4$ (1)	−35	2	Complex mixture			
6[b]	10	TFA (1)	−35	2	76	9	—	—
7[b]	20	TFA (1.5)	−35	2	75	—	—	—
8[b]	30	TFA (1.7)	−35	2	98	—	—	—

[a] The product ratio was determined by ^1H NMR.
[b] Isolated yield.

Trials for the introduction of double bond between 11 and 12 positions in (−)-10b-hydroxylactam (−)-**18** with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) led to only isolation of oxysanguinarine **21** (33%). The aromatization was supposed to be triggered with acidic hydroquinone formed during reaction. Reaction in the presence of potassium carbonate (K_2CO_3) afforded a desired (−)-11,12-dehydro-10b-hydroxylactam (−)-**20** in 21% yield albeit co-production of an aromatized product **21** (11%). On the other hand, no aromatization was observed when (−)-10b-silyloxylactam (−)-**17** was used as a starting material even without base, in which a (−)-11,12-dehydro product (−)-**22** was given in 40% yield together with a pinacol-type rearranged (+)-3-spiroindenyl-4-oxoisoquinolone (+)-**23** (27%). Introduction of oxygen function to the double bond in both 10b-oxygenated 11,12-dehydrolactams (−)-**20** and (−)-**22** with *m*-chloroperbenzoic acid (*m*CPBA) afforded all *cis*-10b,11,12-trioxygenated lactams (−)-**25** and (−)-**26** as 12-benzoates, not 11,12-epoxy derivatives **24** (Scheme 3).

The same orientation of these three 10b,11,12-oxygen functions and 4b-hydrogen was confirmed by X-ray crystallographic analysis[26] of the (−)-trioxygenated derivative (−)-**25** derived from (−)-11,12-dehydro-10b-hydroxylactam (−)-**20** (Fig. 1); however, absolute configuration could not be determined because of the preferred crystallization of racemic crystals in the recrystallization from ethyl acetate. Insertion of the 12-benzoate residue was suggested to be controlled by S_N1 type opening of the pre-formed epoxide followed by attack from convex site.

Not only *cis*-orientation between 11-hydoxy group and 4b-hydrogen but also incorrect (*S*)-configuration of the 4b-hydrogen in (−)-10b,11,12-trioxygenated lactams (−)-**25** and (−)-**26** made us to



Scheme 3. DDQ dehydrogenation of (−)-10b-oxygenated lactams (−)-**17** and (−)-**18** and oxidation of (−)-11,12-dehydrolactams (−)-**20** and (−)-**22** formed with *m*CPBA.

alter (−)-4b,10b-dihydroxylactam (−)-**13** to the (+)-enantiomer as a chiral source in our strategy for (+)-chelidonine [(+)-**1**]. The same treatment of (+)-4b,10b-dihydroxylactam (+)-**13** with TESH in the presence of either TFA or BCl_3 gave a silylated (+)-**17** in 83% yield or a non-silylated (+)-10b-hydroxylactams (+)-**18** in 73% yield, respectively. DDQ dehydrogenation of (+)-10b-silyloxylactam (+)-**17** in the presence of K_2CO_3 improved the yield of (+)-11,12-dehydro-10b-silyloxylactam (+)-**22** (66%) compared to the case without base (40%), albeit inevitable co-production of the pinacol-type rearranged product (−)-**23** (23%). Monitoring the effect of other additives, such as magnesium sulfate ($MgSO_4$), cesium carbonate (Cs_2CO_3), and triethylamine (Et_3N), by ^1H NMR showed that K_2CO_3

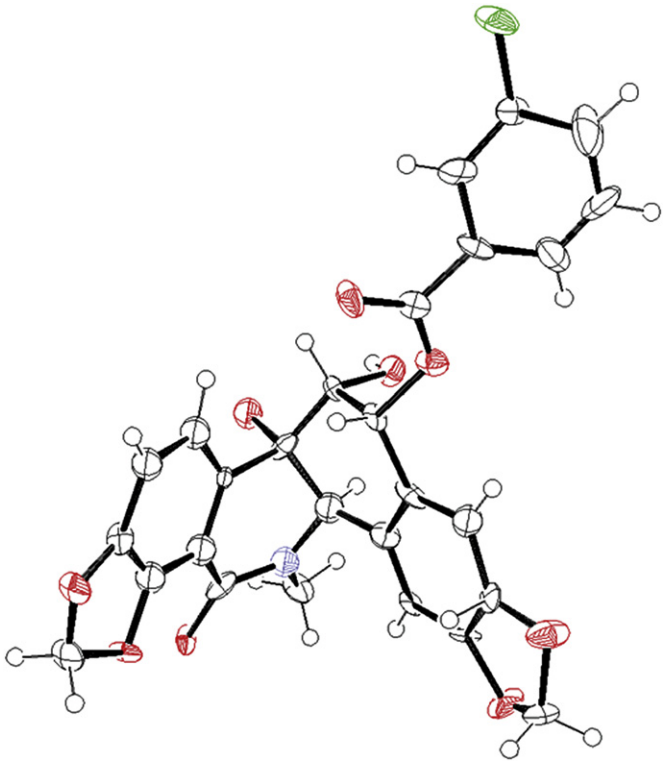
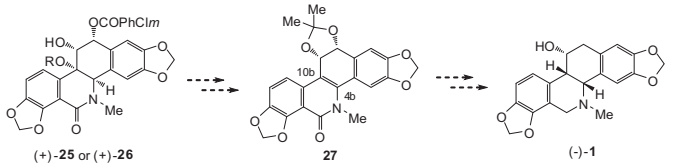


Fig. 1. ORTEP drawing of 10b,11-dihydroxylactam 12-benzoate **25**.

was the best. Oxidation of (+)-**22** with *m*CPBA gave (+)-11-hydroxy-10b-silyloxylactam 12-benzoate (+)-**26** in 87% yield, which was easily de-silylated with tetrabutylammonium fluoride (TBAF) to give (+)-**25** (refer, Table 1 and Scheme 3).

Deoxygenation of the 10b-hydroxy function in (+)-**25** or (+)-**26** was attempted under various conditions, but satisfactory results were not obtained. Therefore we turned our original strategy through direct reductive displacement of the 10b-oxygen function (Scheme 1) to construct new chiral centers by modification after introduction of double bond by dehydration (Scheme 4) and designed stereospecific construction of B/C ring juncture attributable to the bulkiness of 11,12-dioxygen functions in the hydrogenation of 4b,10b-dehydrolactam 11,12-acetal **27**, derivable from (+)-10b,11-oxygenated lactam 12-benzoates (+)-**25** or (+)-**26**, albeit the possible access to (−)-chelidonine [(−)-**1**].



Scheme 4. Alternative strategy toward chelidonine (**1**) synthesis by modification after introduction of double bond by dehydration.

Treatment of (+)-11-hydroxy-10b-silyloxylactam 12-benzoate (+)-**26** with 10% sodium hydroxide in tetrahydrofuran (THF) provided 10b,11,12-trihydroxylactam **28** through desilylation in addition to hydrolysis. Acetalization of **28** with 2,2-DMP gave an inseparable 3:1 mixture of possible bridged regioisomers **29**. The acetal mixture **29** was reacted with thionyl chloride ($SOCl_2$) in the presence of Et_3N, on assumption that the major isomer was a sterically less-hindered acetal **29a** carrying a free tertiary hydroxy group, to smoothly convert to a homogeneous product **30**; however, it was found to be easily either re-converted to the starting acetal mixture **29** on standing in air or converted to a methoxy-inserted product **31** in methanol solution. The structure of **31** was confirmed to be B/C-*cis*-10b-methoxylactam 11,12-acetal by spectral data including differential NOE measurement (Fig. 2a). These facts supported our assumption on the structures of acetal mixture **29** and suggested the production of a 10b-chlorine-substituted intermediate **30** in the treatment of **29** with $SOCl_2$. Successive treatment of a crude **30** with 1,8-diazabicylo[5.4.0]-7-undecene (DBU) for the introduction of double bond in the B/C ring juncture afforded a desired (+)-4b,10b-dehydrolactam 11,12-acetal **27** in 53% yield from acetal mixture **29** (Scheme 5).

Since trials for hydrogenation of 4b,10b-dehydrolactam 11,12-acetal **27** to the corresponding all-*cis*-lactam acetal **32** under hydride reductions ($NaBH_4$ in EtOH or acidic $NaB(CN)H_3$ in THF) and

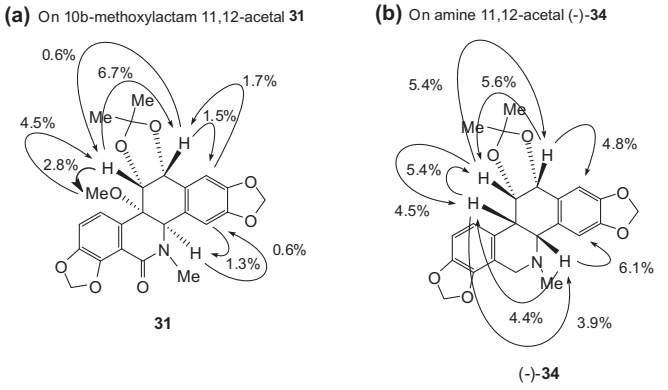
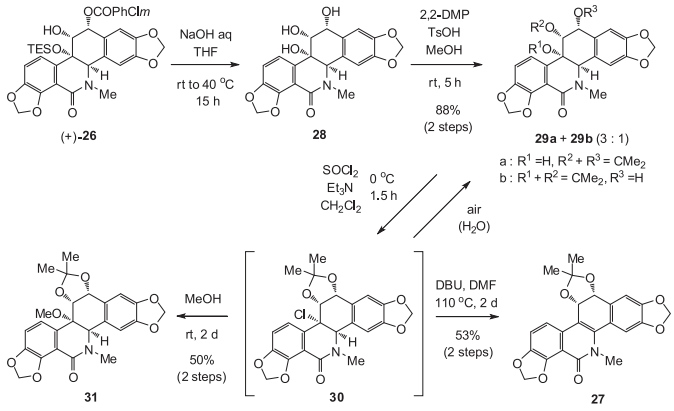
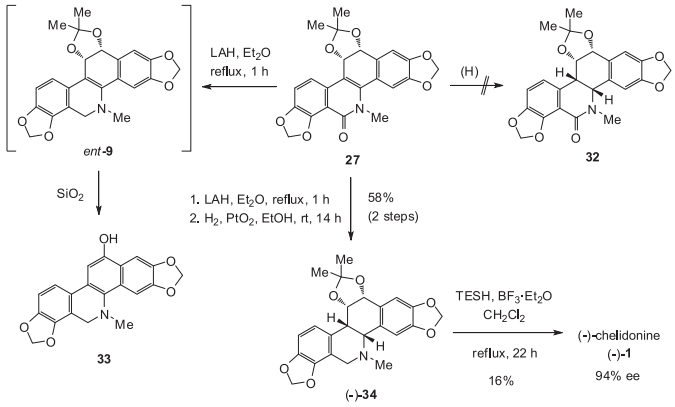


Fig. 2. NOE enhancements: (a) 10b-methoxylactam 11,12-acetal **31** and (b) (−)-amine 11,12-acetal (−)-**34**.



Scheme 5. Manipulation of (+)-11-hydroxy-10b-silyloxylactam 12-benzoate (+)-**26**.

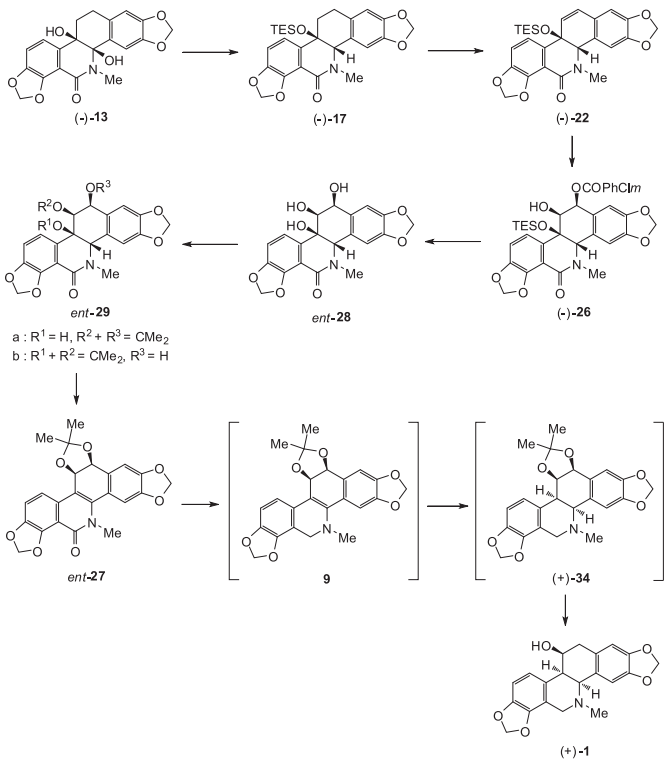
catalytic hydrogenation (H_2, 10% Pd/C in AcOH) were unsuccessful, the amide function in **27** was changed to more reactive amine one. Reduction of the lactam acetal **27** with lithium aluminum hydride (LAH) in diethyl ether (Et_2O) afforded 4b,10b-dehydroamine 11,12-acetal *ent*-**9**, which was easily aromatized to 12-hydroxydihydrosanguinarine **33** during purification with silica gel column chromatography. Therefore, a crude *ent*-**9** was subjected to next reaction without isolation. A desired (−)-amine 11,12-acetal (−)-**34** was provided in 58% yield by catalytic hydrogenation with platinum oxide. The same *cis*-orientation of four hydrogens at 4b,10b,11,12-positions in the product that in chelidonine (**1**) was determined by NOE enhancement (Fig. 2b). Finally, (−)-chelidonine [(−)-**1**] was synthesized by treatment of (−)-**34** with TESH in the presence of $BF_3 \cdot Et_2O$ albeit low yield (16%) (Scheme 6). The ee of (−)-**1** was estimated to be 94% ee by chiral HPLC.



Scheme 6. Synthesis of (−)-chelidonine [(−)-**1**] from 4b,10b-dehydrolactam 11,12-acetal **27**.

Naturally abundant (+)-chelidonine [(+)-**1**] was similarly synthesized from (−)-4b*R*,10b*R*-dihydroxylactam (−)-**13**, obtained in the Sharpless dihydroxylation of 4b,10b-dehydrolactam **8** using AD-mix-β, according to the above-mentioned reaction sequence [(−)-**13**→(−)-**17**→(−)-**22**→(−)-**26**→*ent*-**28**→*ent*-**29**→*ent*-**27**→**9**→(+)-**34**→(+)-**1**], as summarized in Scheme 7. The synthetic specimen was given in total 1.2% yield from a tetracyclic lactone **12** and 98% ee of (+)-**1** was achieved by recrystallization of 11-hydroxy-10b-silyloxylactam 12-benzoate (−)-**26** from hexane and ethyl acetate.

In conclusion, both enantiomers of chelidonine were synthesized by Sharpless asymmetric dihydroxylation of tetracyclic 4b,10b-dehydrolactam and stereospecific catalytic hydrogenation of 4b,10b-dehydrolactam 11,12-acetal as key reaction steps for the construction of stereogenic centers. This example is the second success of



Scheme 7. Summary for the synthesis of (+)-chelidonine [(+)-**1**] from (−)-4b,10b-dihydroxylactam (−)-**13**.

enantioselective synthesis of chelidonine; however, its synthetic efficiency is not necessarily satisfactory because of low yields in the last reaction stages, albeit these drawbacks could be overcome by further elaboration. Thus, we have to conclude at this stage that the first enantioselective total synthesis by Lautens' group is superior to ours, even if our racemic synthesis of homochelidonine from 2-spirolactonyl-1-tetralone would be successfully expanded to alternative enantioselective synthesis of chelidonine. However, we would like to further challenge to establish a more effective synthetic route for these alkaloids using our original strategy in the future.

3. Experimental

3.1. General

All melting points were measured on Yanagimoto MP-SI melting point apparatus and are uncorrected. IR spectra were recorded with ATR on a JASCO FT/IR-300E spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-ECP-400 unless otherwise stated. MS spectra were measured on JEOL JMS-HX110A for FABMS and JEOL JMS-T100LP for ESIMS. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. For column chromatography were used Kanto silica gel 60 (37564-85) for SiO_2, Woelm Pharma alumina (B-super 1) for Al_2O_3, and Fujisilicia NH silica gel (100–200 mesh) for NH–SiO_2. For TLC was used Merck DC-Fertigplatten Kieselgel 60 F_{254} (5715). For preparative TLC were used Merck silica gel 60 F_{254}, 0.5 nm (105744) (PTLC) and Fijisilicia NH-TLC plate (NH-PTLC). Chiral HPLC was recorded on JASCO PU-1580/MD-1510.

*3.1.1. tert-Butyl 2-bromo-3,4-methylenedioxybenzoate (**10**).* A mixture of $MgSO_4$ (5.5 g, 46 mmol) and concd H_2SO_4 (0.6 mL, 12 mmol) in CH_2Cl_2 (80 mL) was stirred at room temperature (rt) for 20 min under argon, and 2-bromo-3,4-methylenedioxybenzoic acid (2.48 g, 10 mmol) and ^{t}BuOH (6 mL, 65 mmol) were added. The whole was stirred at rt for 24 h, diluted with satd $NaHCO_3$ aq (80 mL), stirred for 1 h, and extracted with $CHCl_3$ (30 mL×3). The organic solutions were washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=60:1) gave **10** (2.8 g, 92%) as a colorless oil. IR ν_{max} cm^{-1}: 1722 (C=O). ^{1}H NMR (400 MHz): δ (ppm) 1.61 (s, 9H), 6.05 (s, 2H) 6.70 (d, J=8.3 Hz, 1H), 7.03 (d, J=8.3 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 28.1, 83.4, 102.3, 110.4, 110.6, 118.2, 125.8, 147.1, 147.5, 162.9. HRFABMS m/z: 299.9970 (calcd for $C_{12}H_{13}{}^{79}BrO_4$: 299.9997), 301.9968 (calcd for $C_{12}H_{13}{}^{81}BrO_4$: 301.9978).

*3.1.2. 2,3; 7,8-Bis(methylenedioxy)-11,12-dihydrobenzo[d]naphtho[1,2-b]pyran-6(5H)-one (**12**).* A solution of 2-bromobenzoate **10** (1.51 g, 5.0 mmol) in toluene (10 mL) was added to a mixture of 1-tetralone **11** (1.43 g, 7.5 mmol), $Pd_2(dba)_3$ (183 mg, 0.20 mmol), Xantphos (225 mg, 0.44 mmol), Cs_2CO_3 (3.82 g, 12 mmol), and $Na_2S_2O_5$ (95 mg, 0.50 mmol) in Schlenk tube under argon and the whole was stirred at 100 °C for 20 h. After dilution with $CHCl_3$ (600 mL), the mixture was stirred at rt for 1 h and the insoluble materials were filtered off through a Celite pad. The filtrate was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was triturated with AcOEt to afford lactone **12** (1.32 g, 78%) as yellow solids. The aqueous washings were acidified with 2 N HCl aq (2 mL) and extracted with $CHCl_3$ (20 mL×3). The organic solutions were washed with H_2O and brine, dried ($MgSO_4$), and evaporated to afford carboxylic acid **15** (48 mg, 3%) as white solids, which were dissolved in benzene (3 mL). The solution was refluxed with TsOH (2.6 mg, 0.014 mmol) for 1 h using Dean–Stark apparatus, diluted with $CHCl_3$ (10 mL), washed with H_2O, 1 N NaOH and brine, dried (Na_2SO_4), and evaporated to afford additional **12** [48 mg (total 1.37 g, 81%)] as yellow solids after trituration with AcOEt. Mp: >300 °C. IR ν_{max} cm^{-1}: 1715 (C=O). ^{1}H NMR (400 MHz): δ (ppm) 2.80–2.84 (m, 2H), 2.90–2.93 (m, 2H), 5.98 (s, 2H), 6.26 (s, 2H), 6.71 (s, 1H), 7.04 (d, J=8.4 Hz, 1H), 7.21 (d, J=8.4 Hz, 1H), 7.36 (s, 1H). ^{13}C NMR (100 MHz): δ (ppm) 21.9, 27.6, 101.3, 103.2, 103.7, 105.6, 107.8, 108.3, 114.7, 115.1, 122.8, 130.9, 131.7, 146.7, 146.9, 147.6, 148.1, 149.3, 158.7. HRFABMS m/z: 336.0621 (calcd for $C_{19}H_{12}O_6$: 336.0634). Anal. Calcd for $C_{19}H_{12}O_6$: C, 67.86; H, 3.60. Found: C, 67.54; H, 3.63.

*3.1.3. 5-Methyl-2,3; 7,8-bis(methylenedioxy)-11,12-dihydrobenzo[c]phenanthridin-6(5H)-one (**8**).* A mixture of dehydrolactone **12** (380 mg, 1.13 mmol) and 40% $MeNH_2$ aq (12 mL, 137 mmol) in DMF (12 mL) was stirred at rt for 6 h under argon. The separated precipitate (ppt) was collected by filtration and washed with AcOEt and MeOH to give colorless solids (332 mg). The filtrate was extracted with AcOEt (15 mL×3). The organic extracts were washed with H_2O, satd NH_4Cl aq and brine, dried ($MgSO_4$), and evaporated. After the residue (110 mg) was combined with the ppt, the whole was dissolved in benzene (20 mL) and refluxed for 1 h with TsOH (19 mg, 0.097 mmol) using Dean–Stark apparatus. Filtration of the separated ppt followed by washing with AcOEt and MeOH afforded 4b,10-dehydrolactam **8** (349 mg, 89%) as yellow solids. Mp: >300 °C. IR ν_{max} cm^{-1}: 1639 (C=O). ^{1}H NMR (400 MHz): δ (ppm) 2.71–2.77 (m, 4H), 3.67 (s, 3H), 5.99 (s, 2H), 6.24 (s, 2H), 6.80 (s, 1H), 6.91 (s, 1H), 7.16 (d, J=8.2 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 24.4, 29.1, 37.5, 101.2, 102.7, 106.5, 108.3, 110.8, 113.3, 115.3, 115.9, 124.2, 130.8, 132.7, 136.2, 146.1, 146.6, 146.7, 147.3, 162.0. HRFABMS m/z: 349.0934 (calcd for $C_{20}H_{15}NO_5$: 349.0950).

*3.1.4. (+)-4b,10b-Dihydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one [(+)-**13**].* A mixture of AD-mix-α (8.48 g), $K_2OsO_4{\cdot}2H_2O$ (48 mg, 0.129 mmol), and $(DHQ)_2PHAL$ (480 mg, 0.615 mmol) in 50% ^{t}BuOH aq (60 mL) was stirred at rt for 15 min, at 0 °C for 86 h after addition of $MsNH_2$ (186 mg, 1.96 mmol) and a suspension of 4b,10-dehydrolactam **8** (408 mg, 1.17 mmol) in CH_2Cl_2 (60 mL), and at rt

for 1 h after addition of Na_2SO_3 (13.5 g), and then extracted with CH_2Cl_2 (30 mL×4). The organic solutions were washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give (+)-4b,10-dihydroxylactam (+)-**13** (383 mg, 86%) as colorless solids after trituration with CH_2Cl_2. Mp: 243–245.5 °C. IR ν_{max} cm^{-1}: 3278 (OH), 1646 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.90–2.00 (m, 1H), 2.14–2.19 (m, 1H), 2.59–2.66 (m, 1H), 2.73 (br s, 3H), 2.81–2.89 (m, 1H), 5.11 (s, 1H, exchangeable), 5.98 (dif. s, 2H), 6.07 (s, 1H, exchangeable), 6.07 (dif. s, 2H), 6.65 (s, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.06 (br s, 1H), 7.07 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 25.8, 29.5, 72.7, 87.4, 101.0, 102.0, 107.9, 110.9, 117.4, 130.1, 145.4, 146.8, 147.2, 147.9, 161.3. HRFABMS m/z: 384.1087 (calcd for $C_{20}H_{18}NO_7$: 384.1083). $[\alpha]_D^{24}$ +115 (c 0.05, MeOH) (94% ee).

*3.1.5. (−)-4b,10b-Dihydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one [(−)-**13**].* A mixture of AD-mix-β (11.5 g), $K_2OsO_4{\cdot}2H_2O$ (72 mg, 0.195 mmol), and $(DHQD)_2PHAL$ (636 mg, 0.816 mmol) in 50% ^{t}BuOH aq (80 mL) was stirred at rt for 15 min, at 0 °C for 84 h after addition of $MsNH_2$ (273 mg, 2.87 mmol) and a suspension of 4b,10-dehydrolactam **8** (558 mg, 1.60 mmol) in CH_2Cl_2 (80 mL), and at rt for 1 h after addition of Na_2SO_3 (16 g), and then extracted with CH_2Cl_2 (100 mL×4). The organic solutions were washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Trituration of the residue with CH_2Cl_2 afforded (−)-4b,10-dihydroxylactam (−)-**13** (536 mg, 87%) as colorless solids. Mp: 212.5–215 °C. IR ν_{max} cm^{-1}: 3256 (OH), 1647 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.87–2.00 (m, 1H), 2.12–2.16 (m, 1H), 2.59–2.66 (m, 1H), 2.73 (br s, 3H), 2.81–2.89 (m, 1H), 5.11 (s, 1H), 5.96 (s, 1H), 5.97 (s, 1H), 6.07–6.08 (m, 3H), 6.65 (s, 1H), 7.02–7.08 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 25.6, 29.3, 72.4, 87.2, 100.9, 101.8, 107.7, 110.7, 117.2, 129.9, 145.2, 146.6, 147.0, 147.7, 161.1. HRFABMS m/z: 384.1065 (calcd for $C_{20}H_{18}NO_7$: 384.1083). $[\alpha]_D^{24}$ −104 (c 0.05, MeOH) (85% ee).

*3.1.6. (+)-Spiro[2,3-dihydro-2-methyl-7,8-methylenedioxy-2H-isoquinoline-1,4-dione-3,1′-5′,6′-methylenedioxyindane] [(+)-**16**].* A suspension of (+)-4b,10-dihydroxylactam (+)-**13** (19 mg, 0.05 mmol), TsOH (1 mg, 0.005 mmol), MS 4 Å (75 mg), and 2,2-DMP (0.1 mL, 0.81 mmol) in $CHCl_3$ (10 mL) was refluxed for 1 h under argon. The mixture was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=1:1) gave (+)-spiroindanyloxoisoquinolone (+)-**16** (17 mg, 94%) as colorless solids. Mp: 90–95 °C. IR ν_{max} cm^{-1}: 1643 (C=O). ^1H NMR (400 MHz): δ (ppm) 2.43 (ddd, J=13.8, 9.2, 7.4 Hz, 1H), 2.72 (ddd, J=13.8, 9.2, 3.5 Hz, 1H), 3.02 (ddd, J=15.5, 9.2, 3.5 Hz, 1H), 3.14 (ddd, J=15.5, 9.2, 7.4 Hz, 1H), 5.91 (d, J=1.3 Hz, 1H), 5.97 (d, J=1.3 Hz, 1H), 6.29 (s, 1H), 6.30 (s, 1H), 6.37 (s, 1H), 6.74 (s, 1H), 7.08 (d, J=8.2 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 30.3, 30.9, 37.1, 80.0, 101.5, 103.3, 103.6, 105.3, 111.9, 115.0, 123.5, 124.4, 134.2, 137.9, 147.6, 147.7, 149.1, 154.9, 159.9, 192.8. HRFABMS m/z: 366.0965 (calcd for $C_{20}H_{16}NO_6$: 366.0978). $[\alpha]_D^{20}$ +103 (c 0.043, $CHCl_3$).

*3.1.7. TESH reduction of (−)-4b,10b-dihydroxylactam (−)-**13** in the presence of $BF_3{\cdot}Et_2O$ (run 2 in Table 1).* A 0.16 mol solution of TESH in CH_2Cl_2 (1.3 mL, 0.2 mmol) was added to a suspension of (−)-4b,10-dihydroxylactam (−)-**13** (19 mg, 0.05 mmol) in CH_2Cl_2 (5 mL). An 8 mmol solution of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (6.3 mL, 0.05 mmol) was added to the above mixture at −40 °C under argon and the whole was stirred at the same temperature for 2 h. After poured to ice (10 mL), the mixture was extracted with CH_2Cl_2 (5 mL×5). The organic solutions were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=1:1) gave (−)-10b-silyloxylactam (−)-**17** (9 mg, 30%) and (−)-spiroindanylisoquinolone (−)-**19** (13 mg, 70%) as colorless solids, respectively. (i) (−)-5-*Methyl*-2,3;7,8-*bis*(*methylenedioxy*)-10*b*-*triethylsilyloxy*-4*b*,10*b*,11,12-*tetrahydrobenzo*[*c*]*phenanthridin*-6(5*H*)-*one* [(−)-**17**]. *See* 3.1.9. (ii) (−)-*Spiro*[3,4-*dihydro*-2-*methyl*-7,8-*methylenedioxy*-2*H*-*isoquinoline*-1-*one*-3,1′-5′,6′-*methylenedioxyindane*] [(−)-**19**]. Mp: 126–128 °C. IR ν_{max} cm^{-1}: 1645 (C=O). ^1H NMR (400 MHz): δ (ppm) 2.09 (dt, J=12.6, 7.4 Hz, 1H), 2.47 (dt, J=12.8, 6.4 Hz, 1H), 2.88 (t, J=7.4 Hz, 1H), 3.14 (s, 3H), 3.14 (d, J=12.6 Hz, 1H), 3.75 (d, J=12.6 Hz, 1H), 5.94 (br s, 1H), 5.97 (br s, 1H), 6.07 (br s, 1H), 6.15 (br s, 1H), 6.30 (d, J=8.3 Hz, 1H), 6.54 (s, 1H), 6.75 (s, 1H), 6.76 (d, J=8.3 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 29.7, 34.9, 39.2, 51.9, 57.9, 101.2, 102.2, 104.6, 105.2, 110.8, 112.5, 117.8, 137.5, 137.6, 138.9, 146.9, 147.8, 147.9, 162.5. HRFABMS m/z: 352.1214 (calcd for $C_{20}H_{18}NO_5$: 352.1185). $[\alpha]_D^{24}$ −144 (c 0.054, $CHCl_3$).

*3.1.8. TESH reduction of (−)-4b,10b-dihydroxylactam (−)-**13** in the presence of BCl_3 (run 4 in Table 1): (−)-10b-Hydroxy-5-methyl-2,3;7,8-bis(methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one [(−)-**18**].* A 1 mol solution of BCl_3 in CH_2Cl_2 (0.2 mL, 0.20 mmol) was dropwise added to a mixture of (−)-4b,10-dihydroxylactam (−)-**13** (77 mg, 0.20 mmol) and TESH (0.96 mL, 6.0 mmol) in CH_2Cl_2 (30 mL) at −35 °C under argon and stirred at the same temperature for 1 h. After dilution with H_2O (80 mL), the separated organic layers were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=3:7 to AcOEt) gave (−)-10b-hydroxylactam (−)-**18** (56 mg, 76%) as colorless solids. Mp: 263–264 °C. IR ν_{max} cm^{-1}: 3423 (OH), 1633 (C=O). ^1H NMR (400 MHz): δ (ppm) 2.23 (ddd, J=13.9, 11.2, 7.0 Hz, 1H), 2.62 (ddd, J=13.9, 6.5, 2.4 Hz, 1H), 2.74 (ddd, J=17.2, 11.2, 6.5 Hz, 1H), 2.87 (ddd, J=17.2, 6.5, 2.4 Hz, 1H), 3.43 (s, 3H), 3.76 (br s, 1H), 4.52 (s, 1H), 5.84 (s, 1H), 5.86 (s, 1H), 5.90 (s, 1H), 5.98 (s, 1H), 6.42 (s, 1H), 6.59 (s, 1H), 6.79 (d, J=7.8 Hz, 1H), 6.92 (d, J=7.8 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 27.2, 31.3, 37.2, 69.0, 69.3, 101.0, 102.2, 106.3, 108.0, 110.7, 111.9, 117.0, 128.4, 128.5, 132.4, 146.5, 147.1, 147.8, 148.8, 161.8. HRFABMS m/z: 368.1111 (calcd for $C_{20}H_{18}NO_6$: 368.1134). $[\alpha]_D^{24}$ −132 (c 0.03, $CHCl_3$).

*3.1.9. TESH reduction of (−)-4b,10b-dihydroxylactam (−)-**13** in the presence of TFA (run 8 in Table 1): (−)-5-methyl-2,3;7,8-bis(methylenedioxy)-10b-triethylsilyloxy-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one [(−)-**17**] (run 8 in Table 1).* To a mixture of (−)-4b,10-dihydroxylactam (−)-**13** (539 mg, 1.41 mmol) and TESH (4.8 mL, 30.1 mmol) in CH_2Cl_2 (88 mL) was added a 1.31 M solution of TFA in CH_2Cl_2 (1.8 mL, 2.35 mmol) at −35 °C over 30 min under argon. The resultant mixture was stirred at the same temperature for 2 h, diluted with satd $NaHCO_3$ aq (10 mL), and extracted with CH_2Cl_2 (100 mL×3). The organic solutions were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=4:1) gave (−)-10b-silyloxylactam (−)-**17** (660 mg, 98%) as colorless solids. Mp: 86–88.5 °C. IR ν_{max} cm^{-1}: 1652 (C=O). ^1H NMR (400 MHz): δ (ppm) 0.28–0.38 (m, 6H), 0.81 (t, J=7.9 Hz, 9H), 2.19–2.27 (m, 1H), 2.65–2.71 (m, 1H), 2.75–2.80 (m, 1H), 2.84–2.90 (m, 1H), 3.44 (s, 3H), 4.42 (s, 1H), 5.82 (d, J=1.3 Hz, 1H), 5.85 (d, J=1.5 Hz, 1H), 5.97 (d, J=1.3 Hz, 1H), 6.15 (d, J=1.5 Hz, 1H), 6.38 (s, 1H), 6.59 (s, 1H), 6.79 (d, J=8.0 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 5.93, 6.87, 27.7, 32.9, 37.7, 70.1, 71.4, 100.9, 102.3, 106.0, 107.7, 109.9, 113.3, 117.7, 127.9, 128.8, 131.3, 146.5, 147.0, 148.0, 149.1, 161.7. HRFABMS m/z: 482.1971 (calcd for $C_{26}H_{32}NO_6Si$: 482.1999). $[\alpha]_D^{24}$ −127 (c 0.10, $CHCl_3$).

*3.1.10. DDQ oxidation of (−)-10b-hydroxylactam (−)-**18**.* A suspension of (−)-10b-hydroxylactam (−)-**18** (32 mg, 0.09 mmol), DDQ (22 mg, 0.1 mmol), and K_2CO_3 (1.2 mg, 0.01 mmol) in benzene (1 mL) was heated at 60 °C for 8 h and the solvent was evaporated.

After addition of $CHCl_3$ (15 mL), the mixture was successively washed with H_2O, 1 N NaOH, H_2O, and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=4:1) gave (−)-11,12-dehydro-10b-hydroxylactam (−)-**20** (7 mg, 21%) and oxysanguinarine (**21**) (4 mg, 11%) as colorless solids, respectively. (i) (−)-10*b-Hydroxy*-5-*methyl*-2,3; 7,8-*bis*(*methylenedioxy*)-4*b*,10*b*-*dihydrobenzo*[*c*]*phenanthridin*-6(5*H*)-*one* [(−)-**20**]. Mp: 257–260 °C. IR ν_{max} cm^{-1}: 3342 (OH), 1639 (C=O). ^1H NMR (400 MHz): δ (ppm) 3.42 (s, 3H), 4.80 (s, 2H), 5.84–5.87 (m, 4H), 6.33 (d, *J*=9.9 Hz, 1H), 6.40 (d, *J*=9.9 Hz, 1H), 6.51 (s, 1H), 6.57 (s, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.80 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 36.4, 69.6, 70.6, 101.2, 102.2, 105.5, 107.4, 110.6, 112.1, 117.5, 126.8, 127.4, 128.8, 131.7, 133.4, 147.0, 147.1, 147.3, 148.8, 161.7. HRFABMS *m*/*z*: 366.0994 (calcd for $C_{20}H_{15}NO_6$: 366.0978). $[\alpha]_D^{24}$ −10 (*c* 0.107, $CHCl_3$). (ii) 5-*Methyl*-2,3; 7,8-*bis*(*methylenedioxy*)*benzo*[*c*]*phenanthridin*-6(5*H*)-*one* (*oxysanguinarine*) (**21**). Mp: >300 °C (lit.[27] Mp 360–362 °C). IR ν_{max} cm^{-1}: 1649 (C=O). ^1H NMR (400 MHz): δ (ppm) 3.91 (s, 3H) 6.10 (s, 2H), 6.27 (s, 2H), 7.16 (s, 1H), 7.24 (d, *J*=8.6 Hz, 1H), 7.53 (d, *J*=8.8 Hz, 1H), 7.57 (s, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.98 (d, *J*=8.8 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 40.8, 101.5, 102.5, 102.9, 104.7, 110.9, 113.2, 115.4, 117.3, 118.7, 121.1, 123.5, 131.8, 135.6, 147.1, 147.5, 147.7, 147.8, 162.7. LREIMS *m*/*z*: 347 (M^+).

*3.1.11. DDQ oxidation of (−)-10b-silyloxylactam (−)-**17**.* A mixture of (−)-10b-silyloxylactam (−)-**17** (521 mg, 1.08 mmol), K_2CO_3 (403 mg, 2.91 mmol), and DDQ (411 mg, 1.81 mmol) in benzene (20 mL) was refluxed for 7 h under argon and the separated ppt was filtered off through a Celite pad. After evaporation of the filtrate, the residue was successively purified by Al_2O_3 column chromatography (toluene/acetone=30:1) and SiO_2 column chromatography (hexane/AcOEt=4:1 to 1:1) to afford (−)-11,12-dehydro-10b-silyloxylactam (−)-**22** (518 mg, 63%) as colorless solids and (+)-spiroindenyloxoisoquinolone (+)-**23** (125 mg, 32%) as yellow solids. (i) (−)-5-*Methyl*-2,3;7,8-*bis*(*methylenedioxy*)-10*b*-*triethylsilyloxy*-4*b*,10*b*-*dihydrobenzo*[*c*]*phenanthridin*-6(5*H*)-*one* [(−)-**22**]: Mp: 78–79.5 °C. IR ν_{max} cm^{-1}: 1652 (C=O). ^1H NMR (400 MHz): δ (ppm) 0.39 (q, *J*=7.8 Hz, 6H) 0.85 (t, *J*=7.8 Hz, 9H), 3.37 (s, 3H), 4.71 (s, 1H), 5.86 (s, 1H), 5.87 (s, 1H), 6.00 (s, 1H), 6.16 (s, 1H), 6.25 (d, *J*=9.9 Hz, 1H), 6.37 (d, *J*=9.9 Hz, 1H), 6.50 (s, 1H), 6.61 (s, 1H), 6.71 (d, *J*=8.1 Hz, 1H), 6.78 (d, *J*=8.1 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 5.93, 6.87, 36.4, 70.1, 72.9, 101.2, 102.3, 105.8, 107.3, 110.0, 113.5, 118.1, 126.5, 127.1, 129.1, 131.8, 132.8, 146.9, 147.3, 147.3, 149.3, 161.6. HRFABMS *m*/*z*: 480.1850 (calcd for $C_{26}H_{30}NO_6Si$: 480.1842). $[\alpha]_D^{24}$ −36 (*c* 0.188, $CHCl_3$). (ii) (+)-*Spiro*[2,3-*dihydro*-2-*methyl*-7,8-*methylenedioxy*-2*H*-*isoquinoline*-1,4-*dione*-3,1′-5′,6′-*methylenedioxyindene*] [(+)-**23**]: mp: 147–150 °C. IR ν_{max} cm^{-1}: 1697 (C=O). ^1H NMR (400 MHz): δ (ppm) 2.85 (s, 3H), 5.99 (d, *J*=1.2 Hz, 1H), 6.03 (d, *J*=1.2 Hz, 1H), 6.11 (d, *J*=1.2 Hz, 1H), 6.14 (d, *J*=1.2 Hz, 1H), 6.18 (d, *J*=10.1 Hz, 1H), 6.52 (s, 1H), 6.57 (d, *J*=8.0 Hz, 1H), 6.76 (d, *J*=8.0 Hz, 1H), 6.89 (s, 1H), 7.48 (d, *J*=10.1 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 26.8, 75.8, 102.1, 103.0, 107.1, 109.8, 111.1, 112.7, 113.9, 123.0, 124.6, 134.4, 137.2, 143.7, 146.1, 148.3, 149.3, 150.6, 167.3, 194.3. HRFABMS *m*/*z*: 364.0835 (calcd for $C_{20}H_{14}NO_6$: 364.0821). $[\alpha]_D^{20}$ +121 (*c* 0.126, $CHCl_3$).

*3.1.12. (−)-12-(3-Chlorobenzoyloxy)-10b,11-dihydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,5,6,10b,11,12-hexahydrobenzo[c]phenanthridin-6(5H)-one [(−)-**25**].* To a solution of (−)-11,12-dehydro-10b-hydroxylactam (−)-**20** (19 mg, 0.052 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (9 mg, 0.055 mmol) at 0 °C under argon, and the whole was stirred at 0 °C for 2 h and at rt for 16 h. After dilution with CH_2Cl_2 (5 mL) and H_2O (2 mL), the separated organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=4:1 to 3:2) gave (−)-10b,11-dihydroxylactam 12-benzoate (−)-**25** (16 mg, 57%) as colorless solids. Mp: 181–183 °C. IR ν_{max} cm^{-1}: 3377 (OH), 1712 (C=O), 1635 (C=O). ^1H NMR (400 MHz): δ (ppm) 3.42 (s, 1H), 3.52 (s, 3H), 5.02 (s, 1H), 5.11 (d, *J*=3.1 Hz, 1H), 5.49 (s, 1H), 5.84 (d, *J*=1.1 Hz, 1H), 5.88 (d, *J*=1.1 Hz, 1H), 5.91 (d, *J*=1.1 Hz, 1H), 5.92 (d, *J*=1.1 Hz, 1H), 6.10 (d, *J*=3.1 Hz, 1H), 6.62 (s, 1H), 6.67 (s, 1H), 6.80 (d, *J*=8.1 Hz, 1H), 7.11 (d, *J*=8.1 Hz, 1H), 7.43 (dd, *J*=7.9, 7.9 Hz, 1H), 7.58 (br d, *J*=7.9 Hz, 1H), 8.03 (br d, *J*=7.9 Hz, 1H), 8.11 (t, *J*=1.8 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 38.0, 64.9, 70.7, 71.4, 72.5, 101.5, 102.3, 105.4, 107.5, 111.2, 111.8, 117.2, 124.4, 128.0, 129.9, 129.9, 130.7, 131.3, 133.6, 134.8, 147.7, 148.6, 149.1, 161.9, 165.4. HRFABMS *m*/*z*: 538.0895 (calcd for $C_{27}H_{21}{}^{35}ClNO_9$: 538.0905). $[\alpha]_D^{24}$ −59 (*c* 0.087, $CHCl_3$).

*3.1.13. (−)-12-(3-Chlorobenzoyloxy)-11-hydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-10b-triethylsilyloxy-4b,5,6,10b,11,12-hexahydrobenzo[c]phenanthridin-6(5H)-one [(−)-**26**].* A solution of (−)-11,12-dehydro-10b-silyloxylactam (−)-**22** (328 mg, 0.683 mmol) and *m*CPBA (227 mg, 0.987 mmol) in CH_2Cl_2 (18 mL) was stirred at 0 °C for 2 h and at rt for 25 h, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (30 mL×3). The organic solutions were washed with satd $NaHCO_3$ aq and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=4:1 to 2:1) gave (−)-11-hydroxy-10b-silyloxylactam 12-benzoate (−)-**26** (312 mg, 70%) as colorless solids. Mp: 145–148 °C. IR ν_{max} cm^{-1}: 3387 (OH), 1714 (C=O), 1648 (C=O). ^1H NMR (400 MHz): δ (ppm) 0.29–0.42 (m, 6H), 0.84 (t, *J*=8.0 Hz, 9H), 2.87 (s, 1H), 3.49 (s, 3H), 4.89 (s, 1H), 5.06 (d, *J*=3.8 Hz, 1H), 5.89 (s, 1H), 5.92 (s, 1H), 6.01 (s, 1H), 6.13 (d, *J*=3.8 Hz, 1H), 6.20 (s, 1H), 6.66 (s, 2H), 6.92 (d, *J*=8.1 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 7.44 (t, *J*=8.2 Hz, 1H), 7.59 (d, *J*=8.2 Hz, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz): δ (ppm) 5.67, 6.89, 38.1, 65.4, 71.2, 72.4, 74.3, 101.5, 102.6, 105.7, 107.3, 110.7, 113.5, 118.6, 124.0, 128.0, 129.1, 129.3, 129.87, 129.91, 131.3, 133.6, 134.8, 147.8, 148.3, 148.6, 150.0, 161.5, 165.4. HRFABMS *m*/*z*: 652.1750 (calcd for $C_{33}H_{35}{}^{35}ClNO_9Si$: 652.1770). $[\alpha]_D^{24}$ −74 (*c* 0.127, $CHCl_3$). Evaporation of mother liquor in the recrystallization of the above solids from hexane/AcOEt afforded optically pure crystals. Mp: 135.5–138 °C. $[\alpha]_D^{20}$ −83 (*c* 0.308, $CHCl_3$) (98% ee).

*3.1.14. 11,12-Isopropylidenedioxy-10b-methoxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one (**31**).* A solution of the acetal mixture **29** (23 mg, 0.05 mmol), $SOCl_2$ (0.008 mL, 0.110 mmol), and Et_3N (0.05 mL, 0.36 mmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 2 h under argon. After evaporation the residue was dissolved in MeOH (3 mL), stirred at rt for 2 days under argon, and evaporated. The residue was dissolved in $CHCl_3$ (30 mL), washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=2:1 to 1:2) gave 10b-methoxylactam 11,12-acetal **31** (12 mg, 50%) as pale brown solids. Mp: 116–120.5 °C. IR ν_{max} cm^{-1}: 1648 (C=O). ^1H NMR (400 MHz): δ (ppm) 1.26 (s, 3H), 1.53 (s, 3H), 3.15 (s, 3H), 3.47 (s, 3H), 4.79 (s, 1H), 5.08 (d, *J*=5.7 Hz, 1H), 5.26 (d, *J*=5.7 Hz, 1H), 5.89 (s, 1H), 5.89 (s, 1H), 6.00 (s, 1H), 6.13 (s, 1H), 6.59 (s, 1H), 6.66 (s, 1H), 6.74 (d, *J*=8.4 Hz, 1H)., 6.77 (d, *J*=8.4 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 26.5, 27.5, 37.4, 50.5, 62.7, 72.3, 75.6, 76.2, 101.3, 102.6, 105.1, 108.7, 109.3, 110.0, 113.0, 118.1, 127.4, 127.5, 128.5, 147.6, 148.3, 148.6, 149.8, 161.5. HRESIMS *m*/*z*: 476.13466 (calcd for $C_{24}H_{23}NNaO_8$: 476.13214).

*3.1.15. (−)-11,12-Isopropylidenedioxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,5,6,10b,11,12-hexahydrobenzo[c]phenanthridine [(−)-**34**].* A mixture of (+)-4b,10-dehydrolactam 11,12-acetal **27** (21 mg, 0.05 mmol) and LAH (12 mg, 0.32 mmol) in Et_2O (3 mL) was refluxed for 1 h, quenched by addition of 10% NaOH aq (1 mL), and extracted with AcOEt (15 mL×3) after addition of H_2O (10 mL). The organic solutions were washed with satd NH_4Cl aq and brine,

dried (K_2CO_3), and evaporated to give pale brown residue. A mixture of the residue and PtO_2 (11 mg, 52 wt %) in EtOH (2 mL) was stirred at rt for 14 h under hydrogen atmosphere (1 atm) and the catalyst was filtered off through a Celite pad. After evaporation of the filtrate the residue was purified by NH–SiO_2 column chromatography (hexane/AcOEt=3:1) to give (−)-amine 11,12-acetal (−)-**34** (12 mg, 58%) as colorless prisms. Mp: 62.5–64 °C. IR ν_{max} cm^{-1}: no characteristic absorption. ^1H NMR (400 MHz): δ (ppm) 1.32 (s, 3H), 1.33 (s, 3H), 2.12 (s, 3H), 2.84–2.93 (m, 1H), 3.32–3.46 (m, 2H), 4.05 (d, J=16.8 Hz, 1H), 4.72 (dd, J=7.0, 7.0 Hz, 1H), 5.23 (d, J=7.0 Hz, 1H), 5.96 (s, 1H), 5.97 (s, 1H), 5.99 (s, 2H), 6.68 (d, J=7.9 Hz, 1H), 6.72 (d, J=7.9 Hz, 1H), 6.76 (s, 1H), 6.92 (s, 1H). ^{13}C NMR (100 MHz): δ (ppm) 24.6, 25.7, 42.5, 43.9, 53.5, 62.8, 75.6, 76.2, 101.1, 101.2, 106.6, 108.8, 110.6, 111.3, 118.8, 119.9, 127.8, 129.6, 132.5, 143.1, 145.3, 147.2, 147.5. HRFABMS m/z: 410.1611 (calcd for $C_{23}H_{24}NO_6$: 410.1604). $[\alpha]_D^{20}$ −12.5 (c 0.072, $CHCl_3$).

*3.1.16. (−)-10b,11,12-Trihydroxy-5-methyl-2,3; 7,8-bis (methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one (ent-**28**).* A mixture of (−)-11-hydroxy-10b-silyloxylactam 12-benzoate (−)-**26** (102 mg, 0.157 mmol) and 10% NaOH aq (0.8 mL, 2.00 mmol) in THF (9 mL) was stirred at rt for 11 h and at 40 °C for 5 h, and diluted with a mixed solution of $CHCl_3$ and MeOH (3/1, 40 mL). The organic solutions were washed satd NH_4Cl aq and brine, dried ($MgSO_4$), and evaporated to afford a crude (−)-10b,11,12-trihydroxylactam *ent*-**28** as colorless solids (56 mg, 89%). Mp: 226–229 °C. IR ν_{max} cm^{-1}: 3414 (OH), 3387 (OH), 1635 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.32 (s, 3H), 4.40–4.45 (m, 1H), 4.50–4.53 (m, 1H), 5.07 (d, J=8.2 Hz, 1H), 5.43 (d, J=2.7 Hz, 1H), 5.61 (s, 1H), 5.90 (s, 1H), 5.93 (s, 2H), 6.09 (s, 1H), 6.54 (s, 1H), 6.78 (s, 1H), 6.93 (d, J=8.0 Hz, 1H), 6.95 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 38.2, 64.1, 67.8, 71.5, 72.6, 102.2, 101.3, 104.9, 107.6, 10.8, 113.0, 118.1, 129.3, 131.1, 132.6, 147.0, 147.1, 147.3, 148.4, 161.1. HRFABMS m/z: 400.1035 (calcd for $C_{20}H_{18}NO_8$: 400.1032). $[\alpha]_D^{21}$ −84 (c 0.104, MeOH).

*3.1.17. A mixture of 10b-hydroxy-11,12-isopropylidenedioxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,10b,11,12-tetrahydrobenzo[c] phenanthridin-6(5H)-one (ent-**29a**) and 12-hydroxy-10b,11-isopropylidenedioxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,10b, 11,12-tetrahydrobenzo[c]phenanthridin-6(5H)-one (ent-**29b**).* A mixture of (−)-10b,11,12-trihydroxylactam *ent*-**28**, (56 mg, 0.14 mmol), 2,2-DMP (3 mL, 24.5 mmol), and TsOH (15 mg, 0.08 mmol) in MeOH (10 mL) was stirred at rt for 6 h under argon, diluted with satd $NaHCO_3$ aq (1 mL) and H_2O (10 mL), and extracted with $CHCl_3$ (30 mL×3). The organic solutions were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=1:3) gave an acetal mixture *ent*-**29** (55 mg, 80%) as colorless solids. Mp: 142.5–159 °C. IR ν_{max} cm^{-1}: 3388 (OH), 1647 (C=O). ^1H NMR (400 MHz): δ (ppm) 1.26 (s, 3H), 1.29 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H), 2.70 (s, 3H), 3.14 (s, 1H), 3.50 (s, 3H), 4.32 (s, 1H), 4.48 (s, 1H), 4.61 (d, J=7.8 Hz, 1H), 4.73 (s, 1H), 5.08, (d, J=5.8 Hz, 1H), 5.15 (d, J=7.8 Hz, 1H), 5.20 (d, J=5.8 Hz, 1H), 5.87 (s, 2H), 5.88 (s, 1H), 5.95 (s, 1H), 6.02 (s, 1H), 6.04 (s, 1H), 6.11 (s, 1H), 6.18 (s, 1H), 6.54 (s, 1H), 6.65 (s, 1H), 6.71 (d, J=7.9 Hz, 1H), 6.74 (d, J=10.4 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.97 (d, J=10.4 Hz, 1H), 7.06 (s, 2H). HRESIMS m/z: 462.1163 (calcd for $C_{23}H_{21}NNaO_8$: 462.1165).

*3.1.18. (−)-11,12-Isopropylidenedioxy-5-methyl-2,3; 7,8-bis (methylenedioxy)-11,12-dihydrobenzo[c]phenanthridin-6(5H)-one (ent-**27**).* A solution of the acetal mixture *ent*-**29** (108 mg, 0.245 mmol), $SOCl_2$ (0.06 mL, 0.826 mmol), and Et_3N (0.55 mL, 3.95 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 2 h under argon and evaporated. A mixture of the residue and DBU (0.90 mL, 6.02 mmol) in DMF (5 mL) was stirred at 110 °C for 2 days, diluted with H_2O (20 mL), and extracted with $CHCl_3$ (30 mL×3). The organic solutions were washed with satd NH_4Cl aq and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt=2:1 to 1:1) gave (−)-4b,10b-dehydrolactam 11,12-acetal *ent*-**27** (52 mg, 50%) as pale brown solids. Mp: 62.5–64.5 °C. IR ν_{max} cm^{-1}: 1651 (C=O). ^1H NMR (400 MHz): δ (ppm) 1.22 (s, 3H), 1.59 (s, 3H), 3.70 (s, 3H), 5.22 (d, J=5.9 Hz, 1H), 5.31 (d, J=5.9 Hz, 1H), 6.03 (s, 2H), 6.22 (s, 1H), 6.25 (s, 1H), 6.95 (s, 1H), 7.15 (s, 1H), 7.21 (d, J=8.5 Hz, 1H), 7.36 (d, J=8.5 Hz, 1H). ^{13}C NMR (100 MHz): δ (ppm) 26.6, 27.6, 38.2, 71.9, 73.6, 101.6, 102.8, 106.5, 107.6, 108.4, 109.5, 110.7, 113.9, 116.0, 121.5, 130.6, 130.7, 137.1, 147.0, 147.0, 147.2, 147.7, 162.4. HRFABMS m/z: 421.1148 (calcd for $C_{23}H_{19}O_7N$: 421.1162). $[\alpha]_D^{20}$ −96 (c 0.286, $CHCl_3$).

*3.1.19. (+)-11-Hydroxy-5-methyl-2,3; 7,8-bis(methylenedioxy)-4b,5,6, 10b,11,12-hexahydrobenzo[c]phenanthridine {(+)-chelidonine [(+)-**1**]}.* A mixture of (−)-4b,10-dehydrolactam-11,12-acetal *ent*-**27** (50 mg, 0.123 mmol) and LAH (35 mg, 0.927 mmol) in Et_2O (7.5 mL) was stirred at 50 °C for 1 h under argon, cooled to 0 °C, and diluted with 10% NaOH aq (3 mL) and H_2O (5 mL). The resultant mixture was stirred at 0 °C for 10 min and extracted with AcOEt (30 mL×3). The organic solutions were washed with brine, dried (K_2CO_3), and evaporated to afford a crude 4b,10b-dehydroamine 11,12-acetal **9** as a pale brown oil (46 mg). A mixture of the crude **9** and PtO_2 (23 mg, 45 wt %) in EtOH (2 mL) was stirred at rt for 14 h under hydrogen atmosphere (1 atm), and the catalyst was filtered off through a Celite pad and washed with $CHCl_3$. The combined organic solutions were evaporated and purified by NH–SiO_2 column chromatography (hexane/acetone=20:1) to give a crude (+)-amine 11,12-acetal (+)-**34** as colorless solids (16 mg). A mixture of the crude (+)-**34**, TESH (0.05 mL, 0.313 mmol), and $BF_3 \cdot Et_2O$ (0.09 mL, 0.073 mmol) in CH_2Cl_2 (1 mL) was stirred at 50 °C for 22 h under argon, diluted with H_2O (10 mL) and 10% NaOH aq (3 mL), and extracted with AcOEt (15 mL×3). The organic solutions were washed with brine, dried (K_2CO_3), and evaporated. Purification of the residue by NH–PTLC (hexane/AcOEt=1:1) gave (+)-chelidonine [(+)-**1**] (4 mg, 9%) as colorless solids. Mp: 112–114.5 °C (lit.[28] Mp: 135–136 °C).[29] IR ν_{max} cm^{-1}: 3733 (OH). ^1H NMR (400 MHz): δ (ppm) 2.28 (s, 3H), 2.97–3.02 (m, 1H), 3.09 (dd, J=17.5, 4.3 Hz, 1H), 3.21–3.25 (m, 1H), 3.43 (d, J=15.6 Hz, 1H), 3.55–3.61 (m, 1H), 4.09 (d, J=15.6 Hz, 1H), 4.21–4.27 (m, 1H), 5.94 (s, 1H), 5.94 (s, 1H), 5.96 (s, 1H), 6.00 (s, 1H), 6.65 (s, 1H), 6.67 (s, 1H), 6.75 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 7.64 (br s, 1H). ^{13}C NMR (100 MHz): δ (ppm) 39.6, 41.9, 42.4, 53.9, 62.9, 72.3, 101.0, 101.3, 107.5, 109.5, 111.9, 116.8, 120.4, 125.4, 128.8, 131.1, 143.0, 145.2, 145.5, 148.1. HRFABMS m/z: 354.1336 (calcd for $C_{20}H_{20}NO_5$: 354.1341). $[\alpha]_D^{19}$ +69 (c 0.078, $CHCl_3$) (98% ee) [lit.[28] $[\alpha]_D^{20}$ +117.2 (c 2, $CHCl_3$)].[29]

Supplementary data

NMR charts of new compounds (**10**, **12**, **8**, **13**, **16**–**20**, **22**, **23**, **25**–**29**, **31**, and **34**) characterized and known compounds (**21** and **1**), chiral HPLC charts of **13**, **26**, and **1**, and X-ray data of the compound **25** (CIF). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.091.

References and notes

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26. Crystal data for compound of **25**: $C_{54}H_{42}Cl_2N_2O_{19}$; M=1093.80 g mol^{-1}, triclinic, *P*-1, colorless prismatic measuring 0.50×0.30×0.02 mm, T=150 K, a=10.1948(17) Å, b=15.044(2) Å, c=16.932(3) Å, α=75.969(2)°, β=81.109(3)°, γ=70.707(3)°, V=2370.1(7) Å^3, Z=2, D_{calcd}=1.533 Mg m^{-3}, μ=0.224 mm^{-1}, GOF on F^2=0.981, R_1=0.0674, wR_2=0.1715 [$I>2\sigma(I)$], R_1=0.1199, and wR_2=0.2044 (all data). CCDC-821745.
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29. Chiral HPLC of the synthetic (+)-chelidonine (S-25 in SD) showed the presence of impurity albeit reasonable ^{1}H and ^{13}C NMR charts (S-22 in SD), resulting in lowering the data of melting point and $[\alpha]_D$.