112. Highly Stereoselective Total Syntheses of (±)-Chelidonine and of (±)-Norchelidonine by an Intramolecular *o*-Quinodimethane/Nitrostyrene-Cycloaddition

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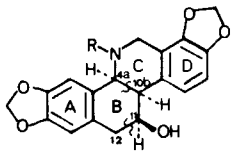
Summary

Conversion of 2-bromomethylstyrene **22** and benzocyclobutenyl carbamate **28** to the benzophenanthridine alkaloids (±)-chelidonine (**1**, five steps, 25% from **28**) and to (±)-norchelidonine (**2**, six steps, 24% from **28**) are described. The key step **29**→**31** involves a highly regio- and stereocontrolled intramolecular *Diels-Alder* reaction of the (*E*)-quinodimethane **30**.

Introduction. – (+)-Chelidonine, the main alkaloid of *Chelidonium majus*, was first isolated in 1839 [1]. Its constitution and relative configuration **1** were initially deduced on the basis of chemical [2] and spectroscopic evidence [3] and confirmed more recently by X-ray diffraction which also revealed the depicted absolute configuration [4]. Either enantiomer [5] as well as the racemate (diphylline) [6] and (–)-norchelidonine (**2**) [5b] [7] occur in different plants of the family *Papaveraceae.* Biogenetic studies suggest that **1** and related benzophenanthridine alkaloids arise in nature from protoberberines [8]. Chelidonine (**1**) is of pharmacological interest owing to its cytotoxic properties [9].

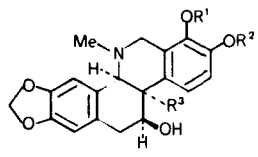
In 1971 we reported the first synthesis of (±)-chelidonine and (±)-norchelidonine [10]. Since then, different synthetic routes to chelidonine (**1**) [11] and to the related benzophenanthridines (±)-homochelidonine (**3**) [12] and (±)-corynoline (**4**) [13] have been devised. Our former approach to chelidonine constitutes the

Scheme 1



1 R=Me Chelidonine

2 R=H Norchelidonine

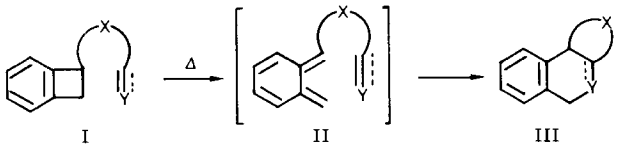


3 R^1=R^2 = Me, R^3 = H

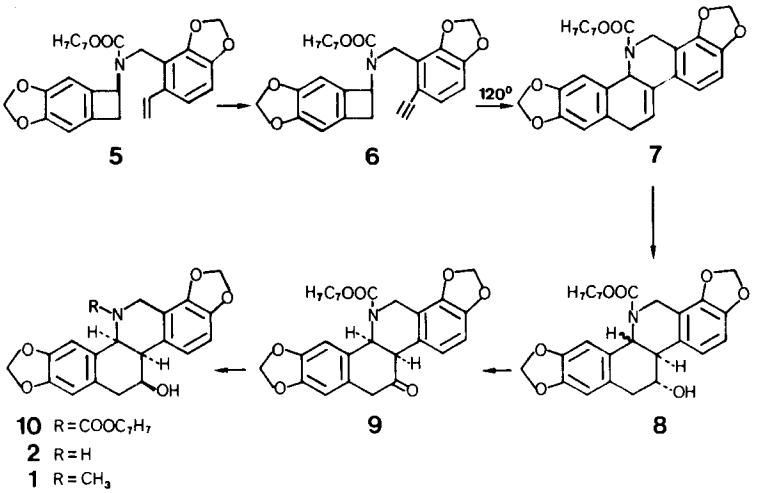
4 R^1,R^2 = $-CH_2-$, R^3 = Me

first application of the general sequence **I**→**II**→**III** [14] in natural product synthesis; this found further use in the construction of various complex polycyclic molecules, including steroids and other alkaloids[1]). Thus the key step **6**→**7** of our first synthesis *(Scheme 3)*, which involves an intramolecular *Diels-Alder* addition of a transient *o*-quinodimethane to the acetylenic bond, provided the skeleton of **1** in 73% yield. However, the poor yields of the transformations **5**→**6** and **8**→**9** diminish the attraction of this synthesis. Further, the non-stereoselective hydroboration (**7**→**8**) required chromatographic separation of the undesired *trans*-**8**. We therefore sought to establish the desired *cis* B/C-ring fusion early by conformational control in the cycloaddition step. Model studies had already shown that

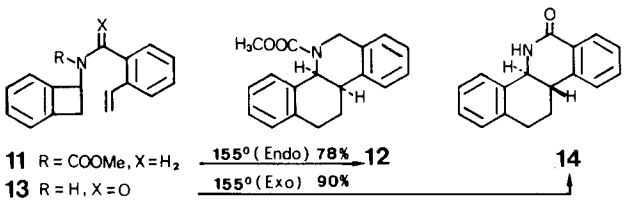
Scheme 2



Scheme 3

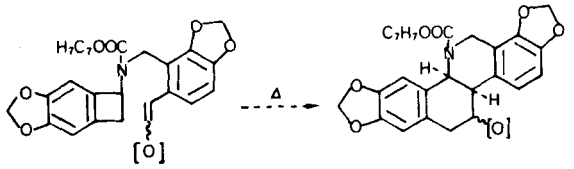


Scheme 4



[1]) Reviews [15], see also [16]. For further examples **II**→**III** using different methods to generate dienes **II**, see [17].

Scheme 5

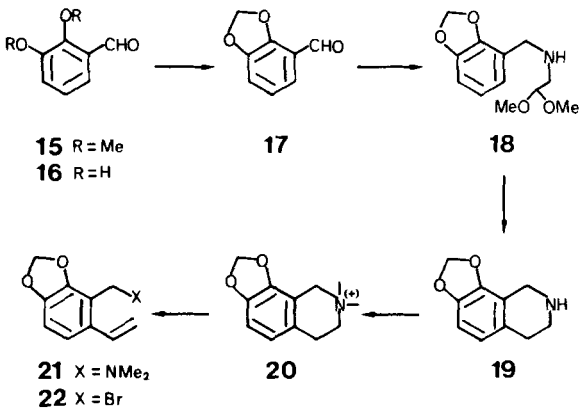


the carbamate **11** furnished selectively the *cis*-fused *endo*-adduct **12**. In contrast, the *trans*-annulated lactam **14** was obtained in 90% yield from the closely related amide **13**, under identical conditions [10]. Accordingly, we modified our synthetic approach to chelidonine *(Scheme 5)* through replacement of the acetylenic moiety by an olefinic dienophile, substituted with an oxygen or equivalent functionality. We report here in detail the implementation of this plan which led efficiently and with 100% stereoselectivity to (±)-chelidonine and to (±)-norchelidonine (preliminary description [18]). We decided to start with the styrene **5** and to functionalize the olefinic bond subsequently.

Preparation of the main building blocks *22* and *28*. – Following our procedure, the aldehyde **17**, obtained from **15** by successive demethylation [19] and methylenation [20], was subjected to reductive amination giving **18** which furnished the tetrahydroisoquinoline **19** on treatment with 6 N aq. HCl[2]).

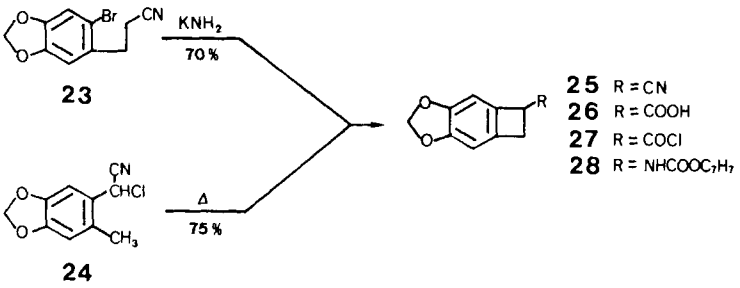
Exhaustive methylation **19**→**20** followed by *Hofmann* and *von Braun* degradations [22] (**20**→**21**→**22**) provided the benzyl bromide **22** (31% from **17**). On the other hand, the benzocyclobutenyl nitrile **25**, readily accessible by base treatment of **23** [23] or, alternatively, by flash pyrolysis of **24** [24], yielded on saponification the carboxylic acid **26** (64%). Treatment of **26** with oxalyl chloride gave the acid chloride **27** which, after azide exchange, *Curtius* rearrangement and trapping of the crude isocyanate with benzyl alcohol, afforded the carbamate **28** (83% from **26**).

Scheme 6

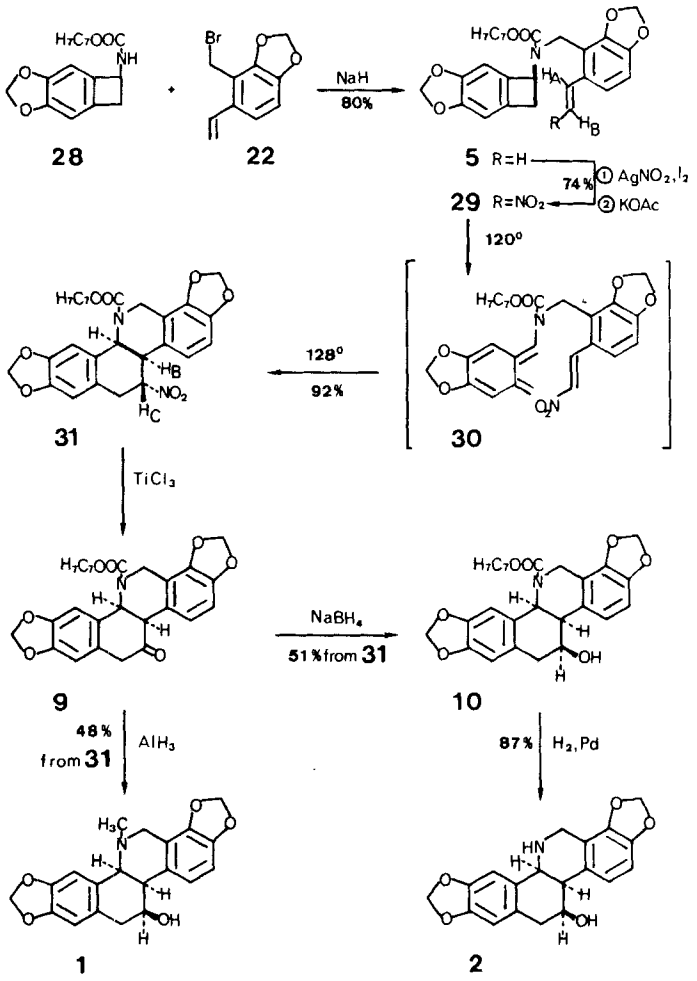


[2]) For the analogous preparation of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline see [21].

Scheme 7



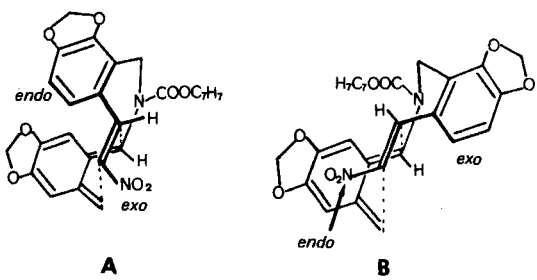
Scheme 8



Conversion of the styrene *5* to (±)-chelidonine (*1*) and to (±)-norchelidonine (*2*) *(Scheme 8).* – Combination of the main components **28** and **22** was accomplished by successive treatment of carbamate **28** with NaH and bromide **22** in DMF at r.t. to give the *N*-alkylated product **5** (80%). We then directed our efforts to the regio- and stereoselective functionalization of **5**. For this purpose, the nitro group was intended to serve as a masked oxygen substituent. Modifying the procedure of *Hassner et al.* [25], I_2 and $AgNO_2$ were added slowly to a solution of the styrene **5** in ether. After the disappearance of **5**, the reaction mixture was treated with KOAc at r.t. to give the (*E*)-nitrostyrene **29** (56%, 74% based on recovered **5**) as the only isolable product. The *trans*-disposition of H_A and H_B in **29** follows clearly from the ^{1}H-NMR. coupling (J_{AB} = 13.5 Hz). In the key step of the synthesis, the nitrostyrene **29** was heated in xylene at 128° for 75 min to give after crystallization the *cis*-fused adduct **31** (92%). No other regio- or stereoisomers were detectable by ^{1}H-NMR. analysis of the mother liquor. The next objective was the replacement of the nitro group by a hydroxy group with inversion of configuration. Employing the method of *McMurry & Melton* [26], successive treatment of **31** with sodium methylate and buffered aq. $TiCl_3$ furnished under mild conditions the unstable ketone **9**. Concomitant reduction of the ketone and carbamate groups of crude **9** with AlH_3 provided directly (±)-chelidonine, identical with a natural sample of (±)-**1** (48% from **31**). During the reduction **9**→**1** hydride attack has proceeded with high selectivity from the sterically less hindered face; this holds also for the previously observed reduction **9**→**10** using $NaBH_4$ (51% from **31**). The benzyloxycarbonyl group of **10** was either reduced with AlH_3, yielding (±)-**1** (56%) or hydrogenolyzed with Pd/C, H_2 to furnish (±)-norchelidonine (**2**) 87%, identified by spectral comparison (UV., IR., ^{1}H-NMR., MS.) with (–)-**2** of natural origin.

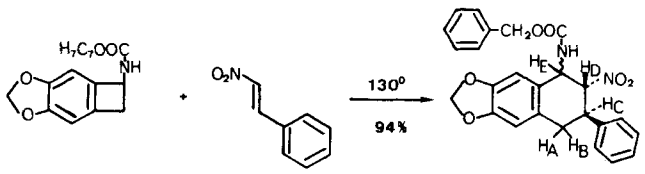
Discussion of the thermal reaction *29*→*30*→*31*. – The high regiochemical control and the absence of products derived from a hypothetical (*Z*)-quinodimethane are consistent with an irreversible cycloaddition of the intermediate (*E*)-quinodimethane **30** to the internal olefinic bond [15a]. Accordingly, a strong preference for transition state **A** (*exo*-NO_2) over transition state **B** (*endo*-NO_2) must be responsible for the striking stereoselectivity. This result contrasts sharply with that of the thermal addition of the benzocyclobutenylcarbamate **28** to ω-nitrostyrene (**32**); the bimolecular addition takes place in the *opposite* direction providing a 2:1-

Scheme 9



A **B**

Scheme 10



stereoisomeric mixture of **33** as shown by ^{1}H-NMR. decoupling experiments. It thus follows again that intra- *vs.* intermolecular cycloadditions are dramatically superior in terms of regio- and stereochemical control.[3])

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Experimental Part

General. All reactions were carried out under Ar using a magnetic stirring bar. Anh. solvents were obtained by distillation over drying agents (in parenthesis) as follows: diethyl ether (Et_2O, KH), tetrahydrofuran (THF, K metal), hexamethylphosphoramide (HMPA, CaH), *t*-butanol (Na metal), CH_2Cl_2(P_2O_5). Workup means washing the org. phase with sat. aq. NaCl, drying ($MgSO_4$) and removal of solvent by distillation *in vacuo* (*i.v.*) using a rotatory evaporator. Column chromatography was carried out on SiO_2 (*Merck*, Kieselgel *60*, 0.063–0.2). For medium pressure chromatography SiO_2 (*Woelm ICN* 0.032–0.063 mm) and a *FMI RP* pump were used. Melting points (m.p.) were determined on a *Kofler* hot stage and are uncorrected. Temperatures are expressed as degrees *Celsius*. – UV. spectra: in 94% EtOH, λ_{max} in nm (logε). – IR. spectra: $CHCl_3$ unless otherwise specified, $\tilde{\nu}_{max}$ in cm^{-1}. – ^{1}H-NMR. spectra in $CDCl_3$ at 100 MHz, unless otherwise specified, standard tetramethylsilane δ(ppm) = 0; abbreviations: *s* singlet, *d* doublet, *t* triplet, *m* multiplet, *J* spin-spin coupling constant (Hz), W_H = signal width at half height (Hz), irr. = position of decoupling irradiation. – Mass spectra (MS.): signals are given in *m/z* (rel.-%). Instruments: UV.: *Beckman DK 2;* IR.: *Perkin-Elmer 257* or *Pye-Unicam Sp 1100;* ^{1}H-NMR.: *Varian XL 100* or *Bruker WH 360;* MS.: *Varian CH-4* or *SM-1.*

Preparation of 2-bromomethyl-3,4-methylenedioxystyrene (22, *Scheme 6*). – *2,3-Dihydroxybenzaldehyde* (**16**). A solution of 2,3-dimethoxybenzaldehyde (**15**) (5 g, 30 mmol) in CH_2Cl_2 (150 ml) was added over 1 h to a solution of BBr_3 (16.5 g, 66 mmol) in CH_2Cl_2 (50 ml) at −78°. The mixture was allowed to warm to r.t. and kept at RT. for 24 h. Addition of water, extraction with ether (4×), reextraction of the org. phase with 0.5 N aq. NaOH, acidification of the resulting aq. phase followed by extraction with ether (4×), washing (H_2O), drying ($MgSO_4$) and evaporation of the ether phase furnished the aldehyde **16** (3.5 g, 85%), m.p. 103–104°. – IR.: 3540, 2840, 1660, 1465, 1390, 1275, 1015. – ^{1}H-NMR.: 5.60 (*s*, 1 H, disappears on exchange with D_2O); 6.6–7.2 (3 H); 9.85 (*s*, 1 H); 11.0 (*s*, 1 H, disappears on exchange with D_2O). – MS.: 138 (100, $C_7H_6O_3^+$), 137 (71), 120 (21), 109 (14), 92 (35), 81 (35), 64 (21).

2,3-Methylenedioxybenzaldehyde (**17**). A mixture of **16** (25 g, 180 mmol), KF (49.3 g, 830 mmol) and DMF (500 ml) was heated at 50° for 20 min. Then CH_2Br_2 (44.5 g, 250 mmol) was added at r.t.

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[3]) For reviews see [27].

and the mixture was heated at 120° for 3 h. After filtration of the mixture the filtrate was shaken with water/ether. Extraction of the aq. phase with ether (8×), washing of the combined org. phases with water and 0.5 N aq. NaOH and final workup gave the product **17** (oil, 20.97 g, 78%). – IR.: 2900, 2740, 1690, 1635, 1462, 1260, 1080, 1060, 930. – ^{1}H-NMR.: 6.03 (*s*, 2 H); 6.65–7.35 (3 H); 10.05 (*s*, 1 H). – MS.: 150 (100, $C_8H_6O_3^+$), 149 (77), 121 (15), 120 (7), 119 (7), 92 (100), 91 (92).

*2,3-Methylenedioxy-*N*-(2,2-dimethoxyethyl)benzylamine* (**18**). A mixture of the aldehyde **17** (19.15 g, 127 mmol), aminoacetaldehyde dimethyl acetal (13.35 g, 127 mmol), PtO_2 (200 mg) and dry EtOH (220 ml) was stirred under H_2 (1 atm.) for 24 h. Filtration of the reaction mixture through *Celite* and evaporation of the filtrate furnished the amine **18** (oil, 31.12 g, 100%). – IR. (CCl_4): 2900, 2830, 1460, 1355, 1250, 1192, 1130, 1058. – ^{1}H-NMR.: 1.82 (*s*, 1 H); 2.75 (*d*, J = 6, 2 H); 3.36 (*s*, 6 H); 3.80 (*s*, 2 H); 4.50 (*t*, J = 5, 1 H); 5.95 (*s*, 2 H); 6.6–6.9 (3 H)). – MS.: 239 (7, $C_{12}H_{17}NO_4^+$), 208 (6), 207 (7), 176 (8), 164 (85), 150 (23), 133 (100).

7,8-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**19**). A solution of the acetal **18** (31.12 g, 127 mmol) in 6 N aq. HCl (750 ml) was stirred at r.t. for 24 h. After addition of Pd/C (10%, 10 g) the mixture was stirred under H_2 (1 atm) for 14 days. Filtration of the mixture through *Celite*, and concentration of the filtrate *i.v.* to a volume of 200 ml gave the crystalline hydrochloride of **19** (15.69 g). Concentration of the mother liquors to a volume of 50 ml and addition of EtOH yielded another crop (4.23 g) of **19** · HCl (total yield: 19.92 g, 73%). An aq. solution of **19** · HCl (1 g) was basified with KOH to give after extraction with CH_2Cl_2 and evaporation of the dried extracts the free amine **19** (solid, 770 mg). – IR. (CH_2Cl_2): 2995, 1462, 1360, 1052, 971, 930, 815. – ^{1}H-NMR.: 1.74 (br. *s*, 1 H); 2.6–2.9 (2 H); 3.0–3.25 (2 H); 4.0 (*s*, 2 H); 5.94 (*s*, 2 H); 6.5–6.85 (2 H). – MS.: 177 (45, $C_{10}H_{11}NO_2^+$), 176 (16), 149 (12), 148 (100), 118 (2), 91 (7).

N,N-*Dimethyl-(5,6-methylenedioxy-2-vinyl)benzylamine* (**21**). MeI (16.3 g, 115 mmol) was added dropwise to a stirred suspension of the free isoquinoline **19** (7.94 g, 46 mmol) in 2.5 N aq. NaOH (20.3 ml, 50.6 mmol) at 0°. The mixture was kept at r.t. for 1.5 h and then heated under reflux for 4 h and finally cooled to 0°. The precipitated crystals gave after washing (H_2O) and drying the *N,N*-dimethylisoquinolinium iodide **20** (14.19 g, 95%, m.p. 272–274°) which was directly converted to **21**. A hot solution of $AgNO_3$ (12.56 g, 88 mmol) in water (100 ml) was mixed with aq. 3 N NaOH (29.33 ml, 88 mmol) at 80°. The precipitated silver oxide was separated by filtration, washed with water and added to a suspension of **20** (7.1 g, 21.3 mmol) in water (40 ml). Heating of the mixture at 100° for 2 h, filtration of the hot reaction mixture, evaporation of the filtrate *i.v.* and distillation of the oily residue at 81–83°/0.1 Torr afforded the amine **21** (3.03 g, 69.5%). – IR. (CH_2Cl_2): 2930, 2890, 2810, 2760, 1617, 1503, 1455, 1362, 1345, 1235, 1065, 1030, 995, 938, 845, 812. – ^{1}H-NMR.: 2.26 (*s*, 6 H); 3.44 (*s*, 2 H); 5.1–5.74 (2 H); 5.96 (*s*, 2 H); 6.65–7.35 (3 H). – MS.: 205 (100, $C_{12}H_{15}NO_2^+$), 190 (47), 162 (47), 161 (38), 160 (35), 131 (29), 104 (47).

2-(Bromomethyl)-3,4-methylenedioxystyrene (**22**). Cyanogen bromide (1.03 g, 9.8 mmol) in ether (10 ml) was added dropwise to a solution of the amine **21** (2.0 g, 9.8 mmol) in ether (10 ml) at −10°. The reaction mixture was kept at r.t. for 1 h and then filtered. Washing of the filtrate successively with 1 N HCl and water followed by workup gave the crystalline bromide **22** (1.51 g, 64%), m.p. 78–80°. – IR. (CH_2Cl_2): 2995, 1615, 1500, 1475, 1350, 1052, 928, 822. – ^{1}H-NMR.: 4.56 (*s*, 2 H); 5.24–5.8 (2 H); 6.04 (*s*, 2 H); 6.7–7.2 (3 H). – MS.: 242 (22, $C_{10}H_9BrO_2^+$), 240 (25), 162 (10), 161 (80), 131 (60), 103 (100), 77 (42).

Preparation of benzyl *N*-(4,5-methylenedioxybenzocyclobuten-1-yl)carbamate (***28***, *Scheme 7*). – *4,5-Methylenedioxybenzocyclobutene-1-carboxylic acid* (**26**). A mixture of the nitrile **25** (1.4 g, 8.09 mmol) and a sat. solution of powdered KOH in EtOH (8 ml) was heated under reflux for 30 min. After addition of water the reaction mixture was washed with ether (3×) then acidified with 5 N HCl and extracted with CH_2Cl_2. Evaporation of the dried extracts, trituration of the residue with ether, filtration and addition of petroleum ether to the filtrate yielded the crystalline acid **26** (1.0 g, 64%), m.p. 138–142°. – IR. (CH_2Cl_2): 3470, 3400–2400, 1700, 1450, 1128, 1038, 943. – ^{1}H-NMR. (60 MHz): 3.35 (*d*, J = 4, 2 H); 4.20 (*t*, J = 4, 1 H); 5.90 (*s*, 2 H); 6.69 (*s*, 1 H); 6.75 (*s*, 1 H); 8.90 (br. *s*, 1 H).

$C_{10}H_8O_4$ (192.16) Calc. C 62.50 H 4.20% Found C 62.80 H 4.50%

(4,5-Methylenedioxybenzocyclobuten-1-yl)carbonyl chloride (**27**). Oxalyl chloride (1 g, 7.8 mmol) was added dropwise to a solution of the acid **26** (0.5 g, 2.6 mmol) in CH_2Cl_2 (20 ml). The mixture

was kept at r.t. for 18 h and then evaporated. Distillation of the residue at 111°/0.06 Torr furnished **27** (oil, 0.52 g, 95%). – IR. (CH_2Cl_2): 2930, 2880, 1795, 1458, 1310, 1130, 1038, 998, 945, 860. – ^{1}H-NMR.: 3.42 (*d*, *J* = 4, 2 H); 4.53 (*t*, *J* = 4, 1 H); 5.93 (*s*, 2 H); 6.68 (*s*, 1 H); 6.83 (*s*, 1 H). – MS.: 212 (8, $C_{10}H_7{}^{37}ClO^+$), 210 (25, $C_{10}H_7{}^{35}ClO^+$), 175 (27), 147 (100), 117 (8), 89 (27).

Benzyl N-*(4,5-methylenedioxybenzocyclobuten-1-yl)carbamate* (**28**). A solution of **27** (5.95 g, 28 mmol) in acetonitrile (15 ml) was added to a solution of NaN_3 (8.19 g, 126 mmol) in water (30 ml) at 0°. The mixture was vigorously shaken for 5 min and then extracted with CH_2Cl_2 (3 × 40 ml). The org. phase was washed with sat. aq. $NaHCO_3$ (2 ×), dried ($MgSO_4$), diluted with toluene (80 ml) and heated thus removing the CH_2Cl_2 by distillation. The distillation was stopped as soon as the vapors have reached 90° and the mixture kept at 90° for 1 further hour. Addition of benzyl alcohol (3.32 g, 30.88 mmol) and triethylamine (0.56 g, 5.6 mmol) to the resulting solution at r.t., keeping the mixture at r.t. for 48 h, filtration and recrystallization (ether) of the precipitated solid gave **28** (7.36 g, 87%), m.p. 175–176°. – IR. (KBr): 3310, 3035, 2935, 1695, 1545, 1460, 1305, 1265, 1129, 1055, 942, 862, 755, 700. – ^{1}H-NMR.: 2.84 (*d*, *J* = 14, 1 H); 3.54 (*d* × *t*, *J* = 14 and 2, 1 H, irr. at 5.16 → *d*, *J* = 14); 5.16 (br. *s*, 4 H); 5.90 (*s*, 2 H); 6.65 (*s*, 1 H); 6.70 (*s*, 1 H); 7.40 (*s*, 5 H). – MS.: 297 (45, $C_{17}H_{15}O_4N^+$), 252 (9), 238 (9), 206 (28), 162 (100), 147 (8).

Conversion of the building blocks *22* and *28* to (±)-chelidonine (*1*) and to (±)-norchelidonine (*2*) *(Scheme 8).* – *Benzyl* N-*(4,5-methylenedioxybenzocyclobuten-1-yl)*-N-*(5,6-methylenedioxy-2-vinylbenzyl)carbamate* (**5**). The carbamate **28** (1.85 g, 6.2 mmol) was added dropwise to a stirred suspension of NaH (washed with pentane, 180 mg, 7.5 mmol) in DMF (5 ml) at −15°. The mixture was stirred at 0° until the evolution of H_2 has finished. Then the bromide **22** (1.81 g, 7.5 mmol) in DMF (20 ml) was added to the resulting solution and the mixture kept at 20° for 18 h. Dilution of the mixture with CH_2Cl_2 (100 ml), successive washing with 5% aq. citric acid and sat. aq. $NaHCO_3$, followed by workup and chromatography (toluene/EtOAc 9:1) furnished the alkylated carbamate **5** (viscous oil, 2.24 g, 80%). – IR. (CH_2Cl_2): 2880, 1692, 1450, 1410, 1270, 1128, 1060, 1040, 945. – ^{1}H-NMR.: 3.02 (*d* × *d*, *J* = 14 and 2.5, 1 H); 3.27 (*d* × *d*, *J* = 14 and 5, 1 H); 4.54 (*d*, *J* = 16, 1 H); 4.74 (*d*, *J* = 16, 1 H); 4.98–5.58 (2 H); 5.20 (*s*, 2 H); 5.44 (*m*, 1 H); 5.6–5.9 (4 H); 6.29 (*s*, 1 H); 6.5–7.1 (4 H); 7.33 (*s*, 5 H). – High-resolution-MS. ($C_{27}H_{23}NO_6$): Calc. 457.1525, Found 457.1507.

Benzyl N-*(4,5-methylenedioxybenzocyclobuten-1-yl)*-N-*{5,6-methylenedioxy-2-[(E)-2-nitrovinyl]benzyl}carbamate* (**29**). Iodine (40 mg, 0.16 mmol) was added portionwise over 2 h in the dark to a stirred mixture of the styrene **5** (32 mg, 0.07 mmol), $AgNO_2$ (13.5 mg, 0.086 mmol) and ether (5 ml). After addition of further $AgNO_2$ (10 mg, 0.06 mmol) the mixture was stirred at r.t. for 4.5 h, then KOAc (100 mg, 1.0 mmol) was added and the mixture stirred at r.t. for 1.5 h. After filtration, washing of the filtrate with 5% aq. $Na_2S_2O_3$ and water, and workup, chromatography (toluene/EtOAc 9:1) afforded unchanged **5** (8 mg) and the less polar nitrostyrene **29** (yellow oil, 19.5 mg, 56% (74% based on recovered **5**). – IR. (CH_2Cl_2): 2905, 1700, 1618, 1515, 1465, 1345, 1308, 1135, 1068, 1040, 1020, 950, 915. – ^{1}H-NMR.: 2.95 (*d* × *d*, *J* = 14 and 2.5, 1 H); 3.33 (*d* × *d*, *J* = 14 and 5, 1 H); 4.60 (*d*, *J* = 16, 1 H); 4.80 (*d*, *J* = 16, 1 H); 5.26 (*s*, 2 H); 5.60 (*m*, 1 H); 5.65–6.0 (4 H); 6.27 (*s*, 1 H); 6.56 (*s*, 1 H); 6.74 (*d*, *J* = 8.5, 1 H); 7.08 (*d*, *J* = 8.5, 1 H); 7.36 (*s*, 5 H); 7.38 (*d*, *J* = 13.5, 1 H); 8.25 (*d*, *J* = 13.5, 1 H). – MS.: 502 (22, $C_{27}H_{22}N_2O_8^+$), 456 (33), 364 (61), 346 (100), 320 (41), 318 (33), 316 (28).

(4bR, 10bS*, 11S*)-5-Benzyloxycarbonyl-2, 3, 7, 8-bis(methylenedioxy)-11-nitro-4b, 5, 6, 10b, 11, 12-hexahydrobenzo[c]phenanthridine* (**31**). A solution of the nitrostyrene **29** (300 mg, 0.60 mmol) in xylene (35 ml) was heated under Ar at 128° for 75 min. Evaporation of the solution and crystallization (CH_2Cl_2/ether) of the residue furnished the pure cycloadduct **31** (267 mg). The evaporated mother liquors which contained only **29** and **31** (^{1}H-NMR.; 35 mg) were heated in xylene (3 ml) at 128° for 15 min to give after chromatography (toluene/EtOAc 9:1) unchanged **29** (4 mg) and a further crop of recrystallized adduct **31** (total yield: 276 mg, 92%), m.p. 174–175°. – IR. (CH_2Cl_2): 2898, 1705, 1555, 1505, 1488, 1350, 1110, 1052, 1040, 940, 912, 878, 808. – ^{1}H-NMR.: 2.95 (*d* × *d*, *J* = 18 and 4, 1 H); 3.37 (*d* × *d*, *J* = 18 and 1.5, 1 H); 3.98 (*d* × *d*, *J* = 17.5 and 1, 1 H); 4.2 (*d* × *d*, *J* = 6 and 3, 1 H, irr. at 5.72 → *d*, *J* = 3); 5.04 (*d*, *J* = 17.5, 1 H); 5.28 (*s*, 2 H); 5.34 (*m*, 1 H, irr. at 2.95 → simplified *m*); 5.73 (*d*, *J* = 6, 1 H, irr. at 4.25 → *s*); 5.85–6.1 (4 H); 6.50 (*s*, 1 H); 6.65 (*s*, 1 H); 6.7–6.9 (2 H); 7.4 (*m*, 5 H). – MS.: 502 (14, $C_{27}H_{22}N_2O_8^+$), 456 (31), 455 (16), 365 (18), 364 (52), 347 (22), 346 (100), 320 (49), 318 (45), 316 (30).

(4bR, 10bS*)-5-Benzyloxycarbonyl-2, 3, 7, 8-bis(methylenedioxy)-4b, 5, 6, 10b, 11, 12-hexahydrobenzo[c]phenanthridin-11-one* (**9**). Sodium methylate (16 mg, 0.3 mmol) was added to a solution of the

nitro-carbamate **31** (100 mg, 0.2 mmol) in THF/MeOH (4:3, 7 ml) at 0°. After 30 min a buffered ($p_H = 5$) aq. solution of $TiCl_3$ [8 ml, 3.5 mmol, prepared from 15% aq. $TiCl_3$ (15 ml), ammonium acetate (2.3 g) and water (6.5 ml)] was added at 0° under Ar. Keeping the reaction mixture at 4° for 24 h, shaking with CH_2Cl_2/water and workup gave the crude unstable ketone **9** which was converted directly to **1** and to **2** as described below. For characterization **9** was chromatographed (toluene/EtOAc 9:1) to give pure **9** (oil, 40 mg, 43%). – IR. (CH_2Cl_2): 3000, 1735, 1705, 1508, 1488, 1470, 1327, 1110, 1050, 942. – ^{1}H-NMR.: 3.45 (*d*, *J* = 19, 1 H); 3.74 (*d*, *J* = 19, 1 H); 4.10 (*m*, 1 H); 4.22 (*d*, *J* = 18, 1 H); 5.12 (*d*, *J* = 18, 1 H); 5.35 (*s*, 2 H); 5.98 (*m*, 5 H); 6.4–6.8 (4 H); 7.2–7.6 (5 H). – MS.: 471 (100, $C_{27}H_{21}NO_7^+$), 410 (9), 380 (30), 352 (14), 336 (82), 320 (31), 319 (85), 308 (25), 306 (17).

(4bR,10bS*,11R*)-5-Benzyloxycarbonyl-2,3,7,8-bis(methylenedioxy)-4b,5,6,10b,11,12-hexahydrobenzo[c]phenanthridin-11-ol* (**10**). $NaBH_4$ (40 mg, 1.05 mmol) was added over 45 min to a stirred solution of the crude ketone **9**, prepared from the nitro-carbamate **31** (100 mg, 0.2 mmol) in dioxane/MeOH 1:1 (4 ml) at −15°. The mixture was kept at 0° for 1.5 h then diluted with CH_2Cl_2 to give on workup, chromatography (toluene/EtOAc 3:1) and crystallization the alcohol **10** (48 mg, 51%), m.p. 213–215°. – IR.: 3600, 2895, 1695, 1505, 1485, 1465, 1325, 1265, 1110, 1052, 998, 940. – ^{1}H-NMR.: 2.35 (br. *s*, 1 H, disappears on exchange with D_2O); 2.7–3.0 (2 H); 3.65 (*m*, 1 H); 3.94 (*d*, *J* = 17, 1 H); 4.45 (*m*, 1 H, simplifies on exchange with D_2O); 5.01 (*d*, *J* = 17, 1 H); 5.32 (*s*, 2 H); 5.72 (*d*, *J* = 6, 1 H); 5.8–6.0 (4 H); 6.47 (*s*, 1 H); 6.65 (*s*, 1 H); 6.71 (*d*, *J* = 8.5, 1 H); 7.2–7.6 (5 H); 7.7 (*d*×*d*, *J* = 8.5 and 1, 1 H). – MS.: 473 (3, $C_{27}H_{23}NO_7^+$), 455 (13), 382 (11), 364 (14), 346 (29), 338 (100), 320 (94), 304 (15), 290 (19), 262 (9).

(±)-Chelidonine (**1**). Method A: 1N AlH_3 [29] in THF (4 ml, 4 mmol) was added dropwise to a solution of the crude ketone **9**, prepared from **31** (40 mg, 0.08 mmol), in THF (1 ml) at −30°. The mixture was allowed to warm up to 0° over 45 min, kept at 0° for 30 min and then warmed up to r.t. over 45 min. Addition of sat. aq. $MgSO_4$, extraction with CH_2Cl_2, workup, chromatography (toluene/isopropanol/sat. aq. NH_4OH 95:5:0.2) and crystallization (EtOH) furnished pure (±)-chelidonine (**1**, 13.5 mg, 48% from **31**), m.p. 217–218°. – UV.: 236 (3.92), 288.5 (3.89). – IR. (KBr): 3430, 2880, 2770, 1491, 1465, 1423, 1393, 1370, 1305, 1268, 1245, 1190, 1081, 1067, 1046, 1033, 961, 933, 890, 872, 846, 786, 761, 485. – ^{1}H-NMR.: 2.27 (*s*, 3 H); 3.01 (*t*, *J* = 6, 1 H, irr. at 4.26 → *d*, *J* = 6); 3.1–3.3 (2 H); 3.45 (*d*, *J* = 15.5, 1 H); 3.59 (*m*, 1 H); 4.13 (*d*, *J* = 15.5, 1 H); 4.26 (*m*, 1 H); 5.8–6.2 (4 H); 6.5–7.0 (4 H); 7.65 (br. *s*, 1 H). – MS.: 353 (83, $C_{20}H_{19}NO_5^+$), 335 (83), 320 (39), 304 (100), 294 (33), 176 (100), 163 (67), 162 (56), 148 (67).

The synthetic and natural (±)-**1** showed no depression of their m.p. upon admixture and displayed identical IR. spectra.

Method B: a solution of AlH_3 [28] in THF (0.8 ml, 0.15 mmol) was added dropwise to a stirred solution of the alcohol **10** (5 mg, 0.01 mmol) in THF (0.3 ml) at 0°. Stirring of the mixture at r.t. for 3.5 h, followed by addition of sat. aq. $MgSO_4$, workup and crystallization (EtOH) provided pure (±)-chelidonine (**1**, 2.1 mg, 56%).

(±)-Norchelidonine (**2**). A mixture of the carbamate **10** (37 mg, 0.078 mmol), 10% Pd/C (35 mg) and EtOH (25 ml) was stirred under H_2 (1 atm) for 3 h. Filtration of the mixture, evaporation of the filtrate and crystallization of the residue ($CHCl_3$/ether) furnished (±)-norchelidonine (**2**, 23 mg, 87%), m.p. 213–217°. – UV.: 236 (3.92), 288.5 (3.89). – IR. (CH_2Cl_2): 3680, 3250, 2900, 1505, 1488, 1468, 1390, 1360, 1235, 1075, 1050, 1000, 968, 943, 865. – ^{1}H-NMR.: 2.97 (*t*, *J* = 3, 1 H); 3.05–3.2 (2 H); 4.04 (br. *d*, *J* = 3, 1 H, irr. at 2.97 → br. *s*); 4.18 (*d*, *J* = 2.5, 2 H); 4.35 (*m*, 1 H); 5.8–6.1 (4 H); 6.6–6.95 (4 H); OH, NH-signals not clearly recognizable. – MS.: 339 (100, $C_{19}H_{17}NO_5^+$), 338 (24), 321 (69), 320 (54), 315 (28), 314 (69), 294 (48), 293 (40), 274 (20), 174 (35), 162 (50), 148 (50), 148 (68). The UV., IR., ^{1}H-NMR. and mass spectra of synthetic (±)-**2** are identical to those of natural (−)-norchelidonine.

Thermal cycloaddition of benzyl N-(4,5-methylenedioxybenzocyclobuten-1-yl)carbamate (**28**) *to ω-nitrostyrene* (**32**) *(Scheme 10).* A mixture of the carbamate **28** (298 mg, 1 mmol), ω-nitrostyrene (**32**, 149 mg, 1 mmol) and xylene (50 ml) was heated at 130° for 1 h. Evaporation of the mixture and chromatography of the residue furnished a 2:1 (^{1}H-NMR.) stereoisomer mixture **33** (solid, 419 mg, 94%) which melts at 80–90°. – IR. (CCl_4): 3450, 3040, 3005, 1739, 1565, 1490, 1402, 1380, 1330, 1242, 1045, 945, 875, 702. – ^{1}H-NMR. (360 MHz): signals of the major isomer: 2.95 (*d*×*d*, *J* = 17.5 and 9, 1 H, irr. at 3.75 → *d*, *J* = 17.5); 3.12 (*d*×*d*, *J* = 17.5 and 6, 1 H, irr. at 3.75 → *d*, *J* = 17.5, no change on irr. at 5.28 and at 5.44); 3.75 (*m*, 1 H, irr. at 5.28 → *d*×*d*, *J* = 6 and 9); 5.13 (*s*, 2 H); 5.2 (br., 1 H); 5.28

(*m*, 1 H, irr. at 3.75 → simplified *m*); 5.44 (*m*, 1 H, no change on irr. at 3.75); 5.97 (*m*, 2 H); 6.57 (*s*, 1 H); 6.81 (*s*, 1 H); 7.1-7.5 (10 H); characteristic signals of the minor isomer: 3.04 (*d* × *d* × *d*, *J* = 17.5, 5 and 2.5, 1 H, irr. at 3.75 → *d* × *d*, *J* = 17.5 and 2.5, no change on irr. at 5.28 and 5.44); 3.15 (*m*, 1 H; irr. at 3.75 → br., *d*, *J* = 17.5, no change on irr. at 5.28 and 5.44); 3.65 (*m*, 1 H, irr. at 5.28 → simplified *m*). – MS.: 446 (12, $C_{25}H_{22}N_2O_6^+$), 416 (14), 399 (78), 372 (52), 355 (72), 308 (100), 264 (52), 171 (17), 149 (14).

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