quenched by successive addition of Et_3N (1.6 mL) and a MeOH/H_2O solution (4/1, 1.6 mL); introduction was again along the side of the flask at $-95\,^{\circ}C$. The resulting mixture was then poured into a half-saturated aqueous solution of NH_4Cl (40 mL), the organic phase was separated, and the aqueous phase was extracted with ether (2×20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The diastereomeric α and β sidechain isomers were separated by chromatography and treated individually with aqueous HF (48%) in CH_3CN at 23 °C for 1.5 h to effect desilylation. The α isomer was dissolved in 10% KOH in MeOH and heated under reflux for 3 h under argon to generate the thermodynamically more stable β diastereomer **6**. After chromatography (silica gel), pure **6** (55 mg, 32%) was obtained as a colorless oil: $[\alpha]_D^{23}=+15.38$ ($c=1.45$ in $CHCl_3$); IR (neat): $\tilde{\nu}=3456$, 2938, 2855, 1708, 1451, 1389, 1028, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=$ 7.20–6.92 (4H, m), 3.20 (1H, dd, $J=4.8$, 11.6 Hz), 2.70–2.60 (1H, m), 2.48–1.00 (23H, m), 2.32 (3H, s), 0.97 (3H, s), 0.84 (3H, s), 0.82 (3H, s), 0.77 (3H, s), 0.70 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=212.2$, 142.6, 137.9, 129.3, 128.2, 126.5, 125.4, 78.9, 63.6, 60.8, 59.2, 55.4, 43.0, 42.5, 42.1, 40.6, 38.9, 38.3, 38.1, 35.1, 28.0, 27.4, 23.9, 23.0, 21.4, 18.0, 17.8, 17.3, 16.3, 15.5, 15.2, 14.2; HR-MS (CI) calcd for $[C_{32}H_{48}O_2+NH_4]^+$: 482.3998, found: 482.4004.

1: To freshly distilled CH_3SO_3H (0.18 mL) under argon was added P_2O_5 (29 mg) in one portion, and the mixture was stirred at 23 °C for 2 h until a homogeneous solution was obtained. Alcohol **8** (4.9 mg, 10.5 μmol) was dissolved in ether (0.1 mL plus 0.1 mL for rinsing) and added dropwise to the acid mixture through a cannula. The resulting cloudy mixture was stirred at 23 °C for 15 min, at which point thin-layer chromatography indicated complete conversion into a single spot suggestive of a very nonpolar substance. Crushed ice was then added, and the mixture was extracted with ether (3×10 mL). The ethereal extracts were washed with water, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Since ^1H NMR analysis indicated that two olefinic products (70%) were present in addition to the desired product **1** (30%), the mixture was treated with CH_3COOH (0.9 mL) and concentrated H_2SO_4 (0.1 mL) in the form of a suspension at 23 °C for 20 h. The acidic mixture was then diluted with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic solution was washed with saturated solution of $NaHCO_3$ and then brine, dried (Na_2SO_4), and concentrated in vacuo. The ^1H NMR spectrum of the residue now indicated a homogeneous final product, which was crystallized from CH_2Cl_2/MeOH to afford pure **1** (3.8 mg, 81%) as very fine thin plates: $[\alpha]_D^{23}=-35.38$ ($c=0.26$ in $CHCl_3$) [ref.[1] $[\alpha]_D^{23}=-38$ ($c=0.37$ in $CHCl_3$)]; m.p. 268–270 °C (ref.[1] m.p. 268–269 °C); IR (neat): $\tilde{\nu}=2942$, 2924 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2): $\delta=7.10$ (1H, d, $J=8.0$ Hz), 6.89 (1H, d, $J=$ 8.0 Hz), 6.81 (1H, s), 2.85 (1H, dd, $J=6.5$, 16.5 Hz), 2.76 (1H, dd, $J=7.1$, 11.4 Hz), 2.35 (1H, dt, $J=3.2$, 12.4 Hz), 2.23 (3H, s), 1.90–1.00 (23H, m), 1.14 (3H, s), 0.91 (3H, s), 0.86 (3H, s), 0.83 (6H, s), 0.80 (3H, s); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta=147.90$, 135.34, 134.65, 129.51, 126.74, 124.80, 61.58, 61.50, 56.88, 56.24, 42.50, 42.11, 42.08, 41.14, 40.13, 38.10, 38.07, 38.06, 37.81, 33.53, 33.38, 31.22, 26.23, 21.45, 20.81, 19.06, 18.70, 18.27, 18.20, 17.57 (two peaks in $CDCl_3$: 17.52, 17.49), 17.43, 16.29; HR-MS (EI) calcd for $[C_{33}H_{50}]^+$: 446.3913, found: 446.3921. All data matched those of the authentic natural product. The synthetic material coeluted with the authentic natural product on thin-layer chromatography: $R_f=0.41$ (hexane), 0.67 (benzene/pentane, 1/10).

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[10] We are indebted to Dr. Pierre Albrecht (Université Louis Pasteur, Strasbourg) for an authentic specimen of **1**.
[11] Prepared from (6*S*)-6,7-oxidogeranyl bromide as described previously for the farnesyl[3] and geranylgeranyl[4] homologues.

A Short Synthesis of (±)-Matrine**

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Matrine (**1**) is the main alkaloid found in *Sophora flavenscens* Ait. and belongs to a family of about two dozen members with the same basic tetracyclic skeleton (Figure 1).[1] Some of these compounds (such as allomatrine, sophoridine,

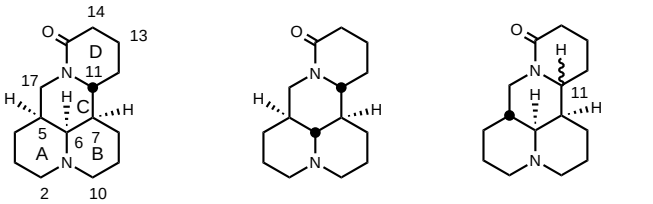

Figure 1. Some alkaloids of the matrine family.

and darvasamine) differ only in the relative stereochemistry at the ring junctions; others contain one or more double bonds (leontalbinine, sophoramine) or a hydroxyl group (sophoranol or 5α-hydroxymatrine). Matrine has been claimed to have antiulcerogenic and anticancer activities, but information on these biological aspects is still scant.[1] Here we describe a short, convergent synthesis of (±)-matrine involving a radical cascade reaction of a xanthate as the key step.

The three earlier total syntheses of matrine[2] rely on traditional ionic chemistry; the most recent by Chen and coworkers[2a] is biomimetic in its conception and is based on an

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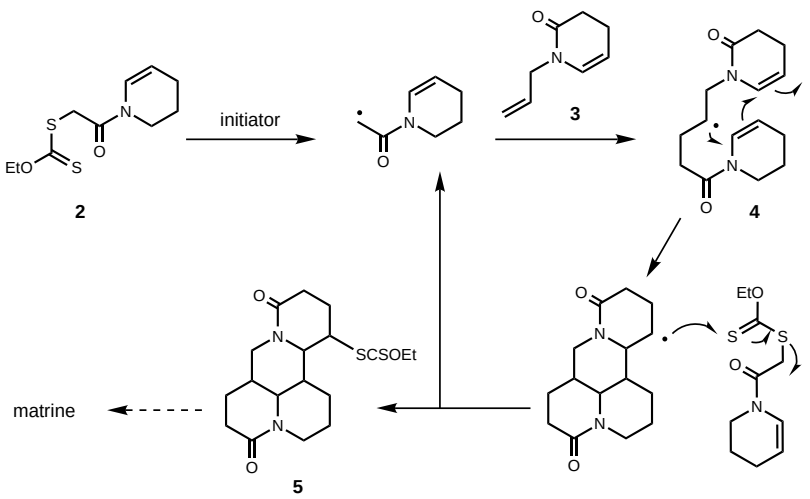


Scheme 1. Radical cascade reaction for the one-step construction of the matrine skeleton.

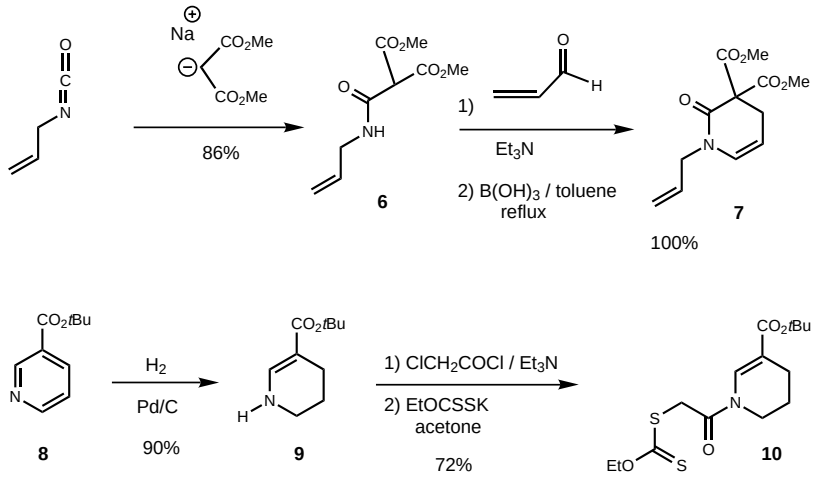
elegant intramolecular Mannich reaction. In contrast, our approach (Scheme 1), hinges on the possibility of building the tetracyclic framework by two consecutive radical cyclizations. Six-membered ring closure via radical intermediates is usually slower and therefore more difficult to accomplish than the formation of five-membered rings.[3] Earlier work on simpler bicyclic perhydroquinolizidines by Beckwith et al.[4] revealed that premature reduction can occur in competition with the desired cyclization when the radical is generated with tributyltin hydride; slow (syringe pump) addition of the stannane was necessary. We hoped to avoid such a shortcoming by exploiting the inherently long lifetime of radicals created by the xanthate transfer process.[5]

Initially, the most direct route to matrine seemed to conduct the radical cascade starting with the two relatively unsubstituted substrates **2** and **3**, exactly as shown in Scheme 1. However, in a preliminary study, **2** and **3** were prepared and tested with little success: Neither the regiochemistry (the radical derived from xanthate **2** did not selectively attack the terminal double bond in **3** and even appeared to react with the double bond in its own precursor **2**) nor the relative stereochemistry could be controlled. Complex mixtures were thus invariably obtained. But even if these difficulties were overcome, we would still be faced by the issue of selectively reducing the lactam in ring A of adduct **5** without affecting the lactam in ring D. In view of the very close similarity of the two lactams, this was certainly not a trivial matter. After some further model studies, a better route which addressed most of these problems eventually emerged.

First, the olefinic partner **7** was selected. The two geminal ester functionalities should protect the carbonyl group of the lactam against reduction later in the synthesis and shield the endocyclic double bond to a certain extent, making it less susceptible to radical attack. Its synthesis was straightforward (Scheme 2): Addition of the anion of dimethyl malonate to commercially available allyl isocyanate cleanly gave amide **6**. The reaction of malonate anions with isocyanates was studied by Dieckmann et al. early this century,[6a] but has not found much use since despite its obvious importance.[6b] Amide **6** smoothly underwent Michael addition to acrolein in the presence of triethylamine, and the intermediate aminal was dehydrated without prior purification by heating with boric acid in toluene to afford the desired cyclic enamide **7** in 86% overall yield. The xanthate component **10** was also easily prepared in 64% overall yield from *tert*-butyl nicotinate (**8**) through catalytic hydrogenation to enamine **9**,[7] chloroacetylation, and finally reaction with potassium ethyl xanthate in acetone (Scheme 2).

We now examined the key radical cyclization. Heating a mixture of **7** (3 equiv) and **10** (1 equiv) in benzene (0.3 M in **10**) in the presence of a small amount of lauroyl peroxide as the initator gave three major compounds: the two tetracyclic derivatives **12** and **13** in a combined yield of 18% (in a ratio of 3:1 in favor of **12**, which has the relative stereochemistry of matrine; **13** has the allomatrine skeleton) and the bicyclic intermediate **11** (30%); the radical arising from the first addition transferred a xanthate group before undergoing cyclization (Scheme 3). Since some starting xanthate (15–20%) was recovered, the corrected yield for the various adduct is in fact a little higher. Compound **11** is itself a xanthate, and merely reexposing it to lauroyl peroxide converted it into the same mixture of the two tetracyclic isomers **12** and **13** in 80% yield. This is an enormous advantage of the xanthate transfer method: The radical can always be regenerated in order to force an otherwise reluctant cyclization, unlike the organotin hydride process where reduction of the radical by the stannane is fast and irreversible.

Four new bonds (including the quite difficult *intermolecular* C–C bond) and five contiguous chiral centers have thus been created in one operation with reasonable efficiency and fair stereoselectivity. It is the first cyclization that provides the stereochemistry shown in Scheme 4. The transition state with



Scheme 2. Synthesis of precursors **7** and **10** for the cascade radical reaction.

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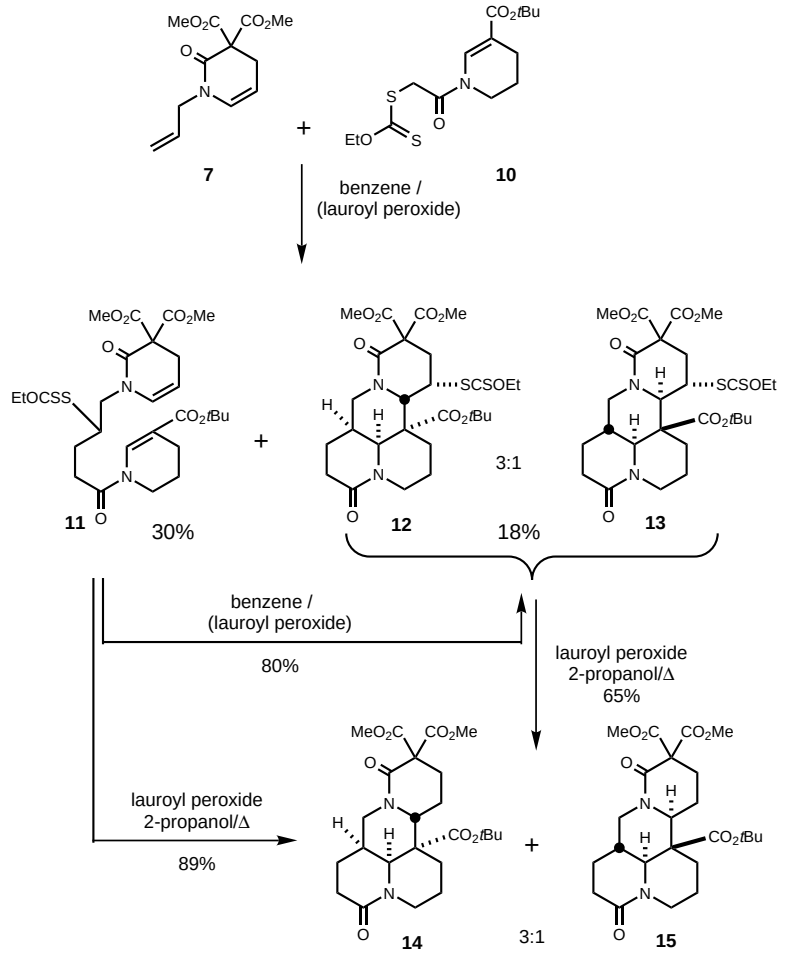
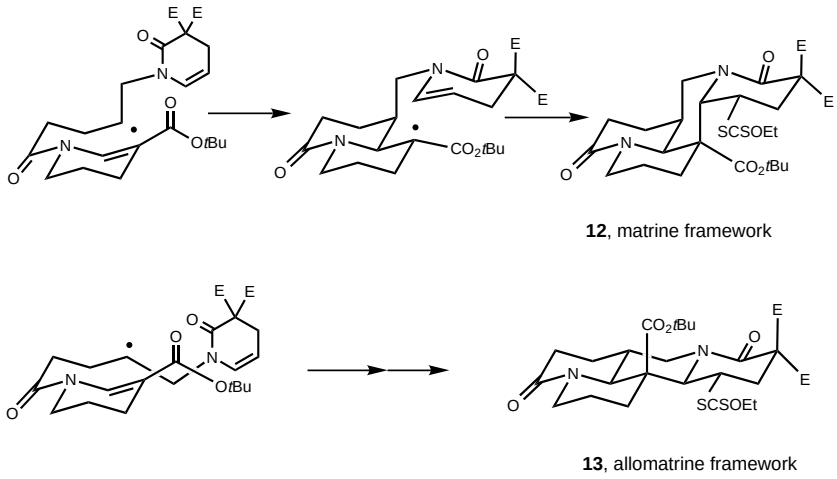
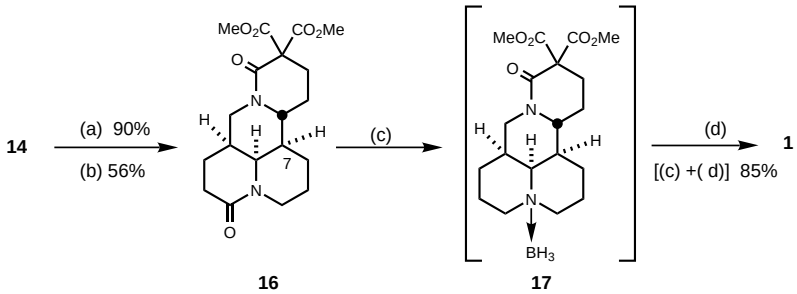


Scheme 3. Key radical cascade reaction and reductive cleavage of the xanthate group.



Scheme 4. Stereochemistry of the radical cyclization.



Scheme 5. Final steps of the synthesis. a) CF_3CO_2H, CH_2Cl_2; b) $(COCl)_2$, CH_2Cl_2; *N*-hydroxy-4-methylthiazolinethione, Et_3N; *tert*-dodecanethiol, cyclohexane, reflux, (cat. azobisisobutyronitrile); c) $BH_3 \cdot Me_2S$, THF; d) 2 M HCl, reflux.

the pseudo-axial disposition of the side chain is slightly less congested than the alternative with a pseudo-equatorial conformation, even though the latter would ultimately lead to the thermodynamically more stable all-*trans* allomatrine structure. The difference between the energies of the two transition states must be small, since the ratio of the two isomeric products is only 3:1. The relative configurations were determined by NMR spectroscopy, especially in relation to a model adduct for which an X-ray structure was secured, and eventually confirmed by the final conversion into matrine. The transfer of the xanthate in the last propagation step takes place reversibly to give the least hindered, thermodynamically more stable, equatorial xanthate group at C-12.

Although reductive cleavage of the xanthate group can be effected with tributylstannane[8] or "nickel boride" (formed in situ from $NiCl_2$ and $NaBH_4$),[9] we elected to use a combination of lauroyl peroxide and isopropyl alcohol.[10] Portion-wise addition of lauroyl peroxide (total 1.3 molar equiv) to a solution of the mixture of tetracyclic adducts **12** and **13** at reflux afforded the corresponding derivatives **14** and **15** in 65% yield and in the same 3:1 ratio (Scheme 3). The advantage of this method is that hydrogen atom transfer from isopropyl alcohol is relatively slow, and exposure of the uncyclized intermediate **11** to the same reaction conditions provided the cyclized and reduced mixture of **14** and **15** directly and in excellent yield (89%, Scheme 5).

Chromatographic separation of **14** and **15** is easier than that of the xanthate precursors and was carried out preparatively at this stage. The remaing steps consisted of removing the extra functionalities present in **14**. Treatment with trifluoroacetic acid caused selective cleavage of the *tert*-butyl ester group at C-7 in 90% yield. The free carboxylic acid was then reductively removed with the ester method by Barton et al.[11] to give intermediate **16** in an overall yield of 56%. Not unexpectedly, delivery of the hydrogen atom from the thiol took place from the least hindered convex face (Scheme 4). Finally, reduction of the lactam in ring A was accomplished cleanly with $BH_3 \cdot Me_2S$ in THF; the lactam in ring D was completely protected by the two

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neighboring ester groups. The resulting crude tertiary amine, which could be isolated as the borane complex **17**, was simply heated with dilute hydrochloric acid to effect both hydrolysis and decarboxylation of the geminal diester moiety. (±)-Matrine was obtained as the hydrochloride salt in 85% overall yield. The ^{1}H and ^{13}C spectra (400 MHz) of the free base in deuterated benzene was identical to those described by Chen et al.[2a]

The short, convergent approach to matrine we implemented here highlights the utility of several radical processess, especially the cascade reaction mediated by the xanthate group. In principle, the *tert*-butyl ester group can be replaced by a bulkier group to improve selectivity or, perhaps even better, by a chiral amide unit, which would allow an asymmetric synthesis of matrine and its congeners.[12]

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Micelle-Bound Metalloporphyrins as Highly Selective Catalysts for the Epoxidation of Alkenes**

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The synthesis and the study of metalloporphyrins as catalysts for the oxidation of organic substrates is an active area of research.[1] Much effort has been devoted to the construction of systems able to mimic the activity of metalloenzymes such as the family of cytochrome P_{450} dependent monooxygenases. Their reactivity, in terms of turnover number, and regio- and stereoselectivity, can be finely modulated by the presence of substituents on the macrocycle. Encouraging results were obtained when the reactions were performed in the ordered microenvironment offered by vesicles, liposomes, and monolayers,[2] and when dendritic polymers were introduced along the periphery of the pyrrolic macrocycle.[3] Guilard et al. reported recently on the synthesis and the spectroscopic characterization of some metalloporphyrin derivatives that are able to form micellar aggregates.[4] The use of an organized medium[5] is known to strongly affect the rate and the selectivity of many organic reactions[6] as well as some metal-catalyzed reactions.[7] With this aim we began a study on the synthesis and the reactivity of porphyrin derivatives bearing a suitable, appended functionality making them soluble in the micellar phase.[8] We report here the results obtained in the application of these porphyrins as catalysts for the epoxidation of selected alkenes carried out in the presence of surfactants.

Porphyrin **1a** was synthesized and demethylated according to literature methods (Scheme 1).[9] Williamson coupling of the intermediate 5-(*p*-hydroxyphenyl)-10,15,20-triphenylporphyrin with triethyleneglycol monochloride and 1-bromopropyl-3-trimethylammonium bromide gave the porphyrins **2a** and **3a**, respectively, in good yield. The metalloporphyrins **1b**, **2b**, and **3b** were obtained by standard procedures,[10] purified by column chromatography and crystallization, and characterized (^{1}H NMR, UV/Vis, and FAB-MS). Detailed experimental procedures along with the spectroscopic and analytical data will be reported elsewhere. The metalated porphyrins **2b** and **3b** are fairly soluble in aqueous media.

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