A Convenient Racemic Synthesis of Two Isomeric Tetrahydropyridyl Alkaloids: Isoanatabine and Anatabine

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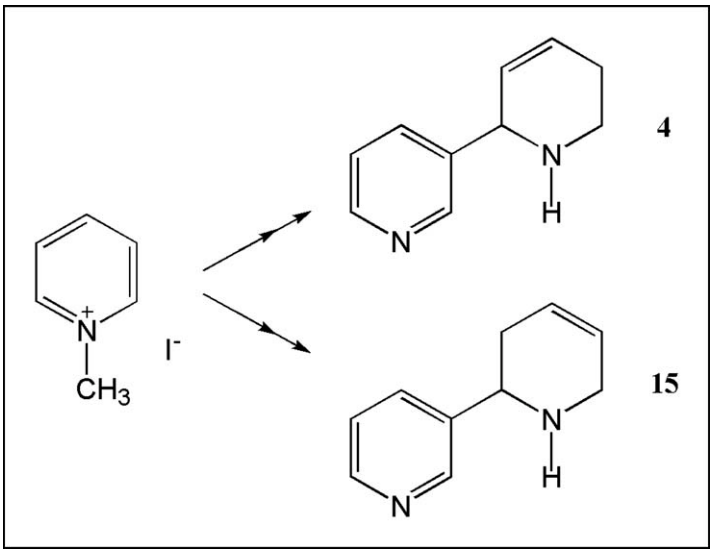

Anatabine is a major alkaloid in *Nicotiana tabacum* and its isomer, isoanatabine, was recently found in a marine worm. Reduction of 1-methylpyridinium iodide with sodium borohydride gave 1-methyl-3-piperideine, which was transformed with hydrogen peroxide into the *N*-oxide. Reaction of the *N*-oxide successively with trifluoroacetic anhydride and potassium cyanide gave 2-cyano-1-methyl-3-piperideine. Its reaction with 3-pyridylmagnesium chloride gave (±)-*N*-methyl-isoanatabine. This was transformed with *m*-chloroperbenzoic acid into the *N*-oxide which was *N*-demethylated with iron(II) sulfate, giving (±)-isoanatabine. The successive applications of literature procedures for the *N*-demethylation by decomposition of *N*-oxide contributed to the knowledge of the mechanism of this oxidative rearrangement. On the other hand, the reduction of 1-methylpyridinium iodide with sodium borohydride and with potassium cyanide present since the start of the reaction in a two layer ether-water system, gave 2-cyano-1-methyl-4-piperideine. This was transformed into (±)-anatabine by the same sequence of reactions used for the synthesis of (±)-isoanatabine.

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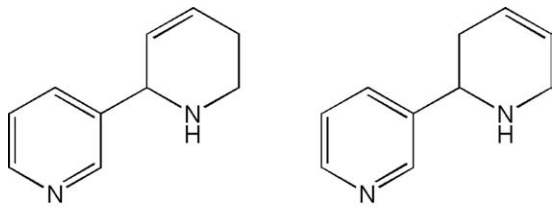
INTRODUCTION

In fresh tobacco leaves of the *Nicotina tabacum* species, the alkaloid mixture consists of 93% (*S*)-nicotine, 3.9% (*S*)-anatabine, 2.4% (*S*)-nornicotine, 0.5% (*S*)-anabasine, and several other pyridine alkaloids which are detected in lower amounts [1]. (*S*)-Nicotine and several of its minor metabolites have potent modulatory effects on nicotinic acetylcholine receptors in the central and peripheral nervous systems. Thus, a variety of nicotinic agonists are being developed for the treatment of neurodegenerative and mental diseases [2]. As part of a search for biologically active compounds acting upon these receptors, we synthesized anatabine and isomeric isoanatabine (Scheme 1), found in a marine worm [3,4].

To our knowledge, only the procedure of Flann *et al*. has been published for the synthesis of (±)-isoanatabine, i.e., 2-(3-pyridyl)-3-piperideine [5] (Scheme 2). This multistep procedure starts with 3-butyn-1-ol and synthesized 1-amino-4-trimethylsilyl-but-3-ene. The condensation of the latter with 3-pyridinecarboxaldehyde gave the aldimine, which with trifluoroacetic acid cyclized by 1,2-addition to the imine group of the trimethylsilylated vinylcarbon, giving (±)-isoanatabine.

On the other hand, several procedures have been developed for the synthesis of anatabine, i.e., 2-(3-pyridyl)-4-piperideine (Scheme 3). In general, they start from a 3-substituted pyridine and the piperideine ring is constructed at the substituent moiety. Quan *et al*. started

Scheme 1



Isoanatabine **Anatabine**

from 3-formylpyridine [6]. The formyl group was transformed with ethyl carbamate into diethyl *N*,*N*′-(3-pyridylmethyl)-biscarbamate. With boron trifluoride etherate, the biscarbamate was decomposed by heating in benzene into an intermediate imine which cyclized with 1,3-butadiene (Diels Alder reaction), giving the *N*-ethoxycarbonyl-anatabine and, after hydrolysis, (±)-anatabine.

Deo and Crooks started from 3-(aminomethyl)-pyridine [7]. This was transformed with benzophenone into a ketimine. Its reaction with LDA gave the carbanion of the activated methylene, which was then monoalkylated with *cis*-1,4-dichloro-2-butene. Hydrolysis made free the 1-amino group which cyclized by reaction with the 5-chloro substituent of the pent-3-ene, giving (±)-anatabine.

Felpin *et al*. synthesized (*S*)-anatabine starting with the asymmetric addition of (+)-B-allyl-diisopinocampheylborane to 3-formylpyridine, giving the enantiomerically pure alcohol [8]. This was successively transformed into the mesylate, azide, and amine. The amino group previously transformed into carbamate was alkylated with allylbromide. Metathesis with the Grubb's ruthenium catalyst cyclized the two allyl groups into the *N*-carbamate protected (*S*)-anatabine, which was then deprotected.

Balasubramanian and Hassner synthesized (*S*)-anatabine starting from 3-pyridinecarboxaldehyde [9]. Its condensation with (*S*)-*p*-toluenesulfinamide gave an enantiomerically pure imine. After the enantioselective 1,2-addition to its imino group of the 4-carbanion of *cis*-1-hydroxy-4-phenylsulfonyl-but-2-ene (the dianion of which being obtained with LiHMDS), the amino group was deprotected. The Mitsunobu cyclization of the 1,5-unsaturated aminoalcohol generated the phenylsulfonyl substituted (*S*)-anatabine. Reductive elimination of the phenylsulfonyl substituent gave (*S*)-anatabine.

Ayers *et al*. synthesized (*S*)-anatabine starting with 3-(aminomethyl)-pyridine [10]. Its condensation with (+)-2-hydroxy-3-pinanone in the presence of boron trifluoride diethyl etherate gave an enantiomerically pure ketimine. The carbanion (generated with LDA) of the methylene α to the nitrogen of the imine group was enantioselectively monoalkylated with *cis*-1-bromo-4-(tetrahydropyran-2-yloxy)-but-2-en. The 4-tetrahydropyran and 2-hydroxy-3-pinanone groups were removed. The Mitsunobu cyclization of the unsaturated 1,5-aminoalcohol gave (*S*)-anatabine. The use of (−)-2-hydroxy-3-pinanone ketimine gave (*R*)-anatabine by the same procedure.

On the other hand, (*R*)-anatabine was synthesized starting with 1-(2,4-dinitrobenzene-1-yl)-pyridinium chloride and (*R*)-phenylglycinol [11].

The addition of lithium aluminum hydride to pyridine gives lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA) [12a]. The addition at 0°C of water to the solution of LDPA in pyridine, gives a mixture of 1,4-, 1,2-, and 2,5-dihydropyridines in a ratio of 26:37:38 [12b]. By conducting this hydrolysis under an atmosphere of oxygen, Yang and Tanner obtained (±)-anatabine with a yield of 59% [12c].

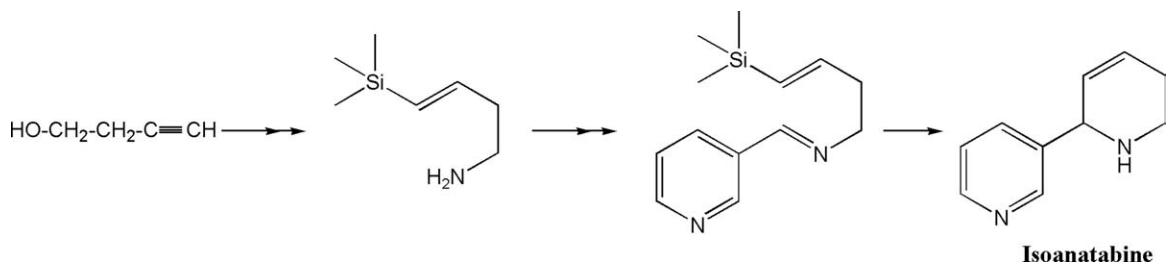
In this work, a short procedure has been developed for the synthesis of (±)-isoanatabine starting with 1-methylpyridinium iodide. By modifying the first reduction step, this procedure has been extended to the synthesis of (±)-anatabine.

RESULTS AND DISCUSSION

Synthesis of (±)-isonanatabine

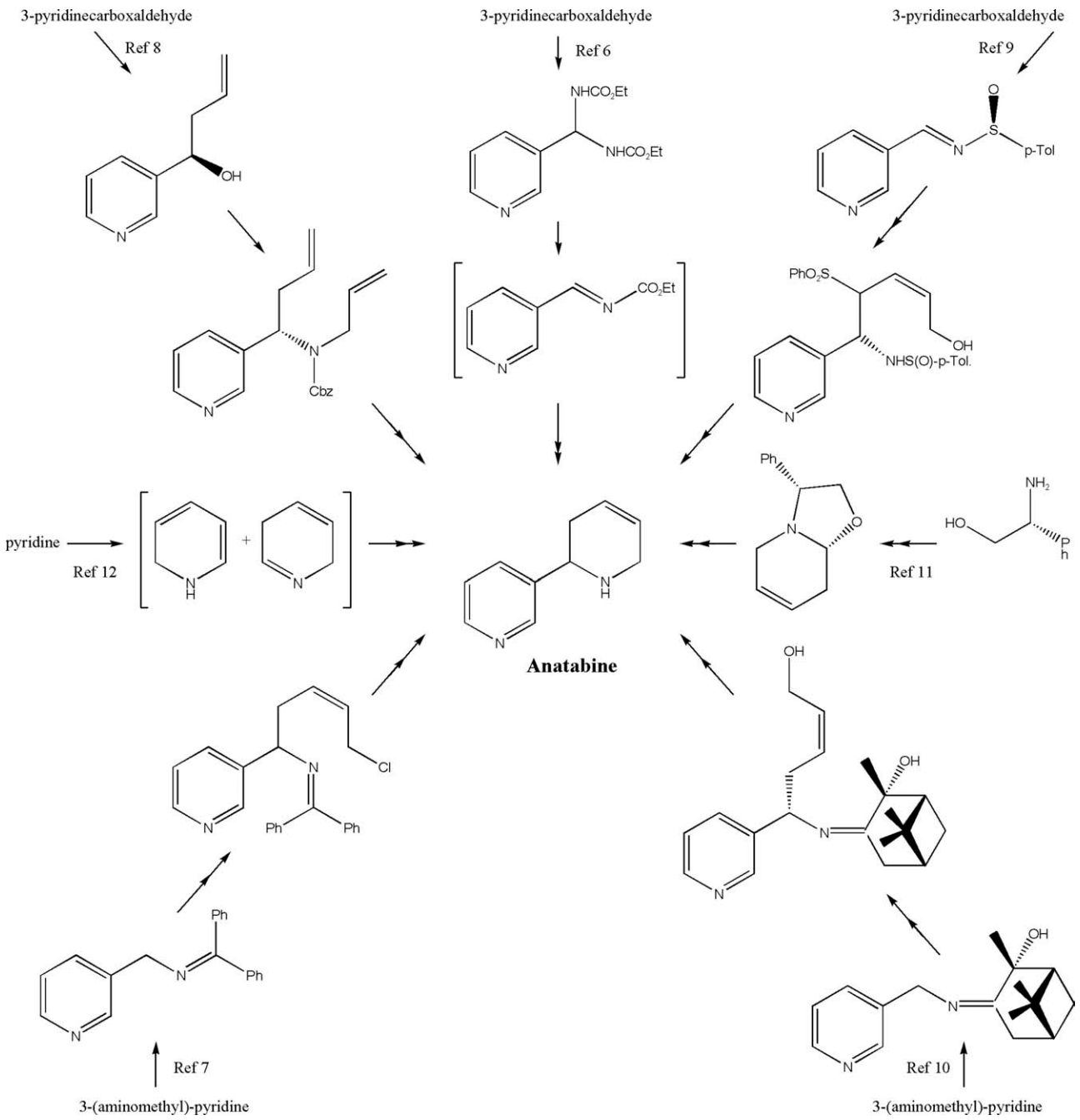
Synthesis of (±)-N-methyl-isoanatabine 3a and (±)-N-benzyl-isoanatabine 3b. Reaction of pyridine with methyl iodide in acetone gave 1-methylpyridinium iodide (Scheme 4). According to a described procedure, the reaction of 1-methylpyridinium iodide with sodium borohydride in methanol yielded 1-methyl-3-piperideine, which was not isolated [13]. Oxidation with hydrogen

Scheme 2

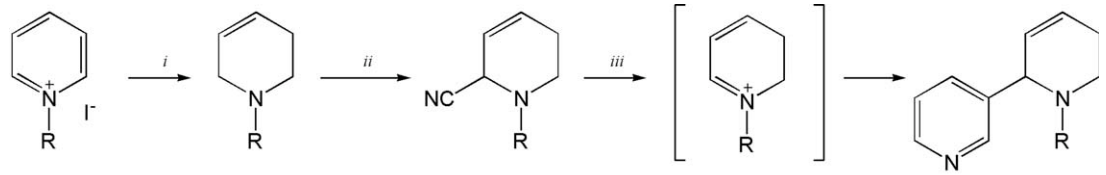


Isoanatabine

Scheme 3



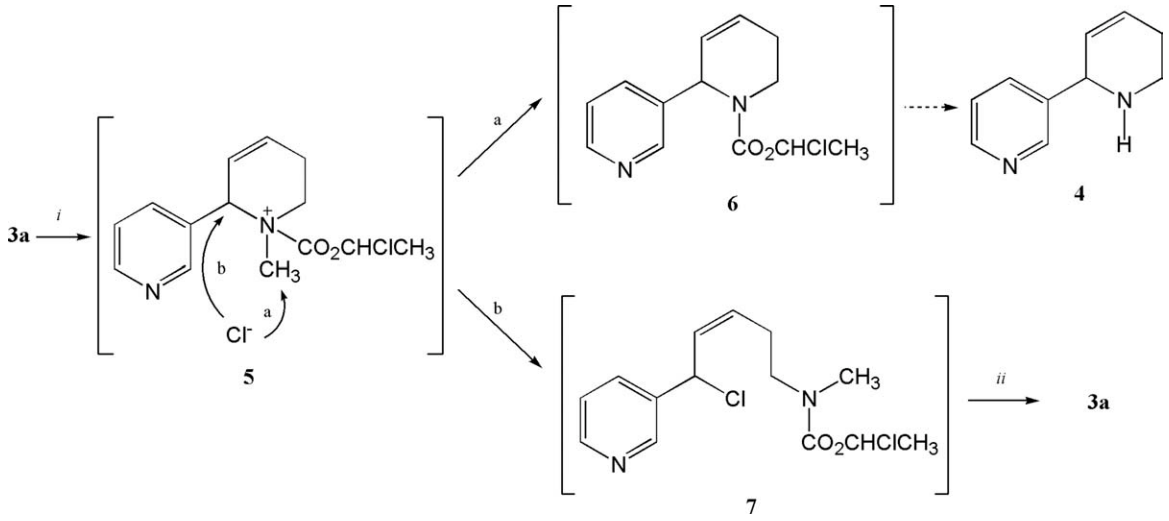
Scheme 4. Reagents and conditions: (*i*, *ii*) see refs. [13] and [14]. (*iii*) 3-PyrMgCl, THF/Et_2O, −10°C to rt, 16 h for **3a** (yield: 77%); 0°C to rt, 16 h for **3b** (yield: 67%).



a, R = CH_3
b, R = Bn

1 **2** **3**

Scheme 5. Reagents and conditions: (*i*) ACE-Cl, 1,2-dichloroethane, reflux, 16 h. (*ii*) 2.5% NaOH, EtOH/H_2O (9:1), 0°C (1 h) to rt (24 h), 75%.



peroxide gave 1-methyl-3-piperideine *N*-oxide. The *N*-oxide in methylene chloride was treated with trifluoroacetic anhydride. After 1 h, an aqueous solution of potassium cyanide was added while the pH of the aqueous layer was maintained at 4, giving (±)-2-cyano-1-methyl-3-piperideine **1a**.

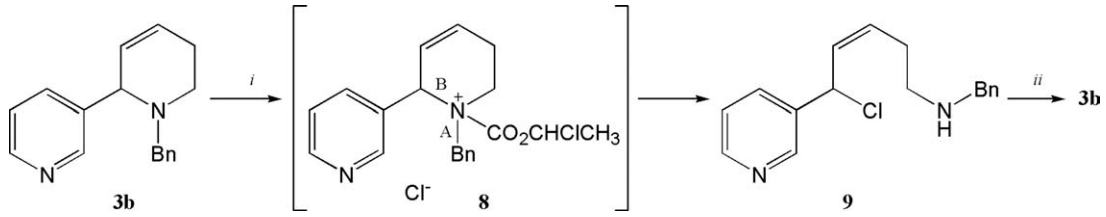
Alkylation of the α-amino nitrile **1a** with 3-pyridylmagnesium chloride (or 3-pyridylmagnesium bromide) was made according to the Bruylants reaction, i.e., the reaction of an α-tertiary-amino nitrile with a Grignard reagent [15]. The metal of the Grignard reagent probably mediates the formation of the conjugated iminium **2a**, on which subsequently adds the Grignard reagent. The stability and the reactivity of the iminium **2a** is the most likely reason why the Grignard reagent substitutes the CN in the α-aminonitrile **1a**, generating 1-methyl-2-(3-pyridyl)-3-piperideine **3a**, i.e., (±)-*N*-methyl-isoanatabine, rather than adding to it. The THF solution containing 5 equiv of the Grignard reagent was added at −10°C to a solution of the α-amino nitrile **1a**, also in THF. After stirring the mixture at room temperature overnight, **3a** was obtained with a yield of 77%. For the preparation of 3-pyridylmagnesium chloride, 1 equiv of 3-bromopyridine was added to 1 equiv of *i*-propylmagnesium chloride in THF at room temperature, and the mixture was stirred for 1 h [16].

The 3-pyridylmagnesium bromide was also used for the alkylation of α-amino nitrile **1a**. In this case, **3a** was obtained with a lower yield of 65%. The procedure previously described in the literature for the synthesis of 3-pyridylmagnesium bromide was modified [17]. The ratio of the reagents was changed and the reaction generating $MgBr_2$ was made in ether instead of THF, $MgBr_2$ being more soluble in ether than in THF as $MgBr_2$ forms a complex with ether. In this way, the transfer of the solution of $MgBr_2$ through a cannula under argon to the solution of 3-pyridyllithium was easier.

(±)-1-Benzyl-2-cyano-3-piperideine **1b** was synthesized according to the procedure of Bonin *et al*. [14]. This procedure is similar to the one used for the synthesis of **1a**, except for some modifications. Sodium borohydride was reacted with 1-benzyl-pyridinium bromide (obtained by reaction of benzyl bromide with pyridine in toluene [18]) in ethanol, giving the 1-benzyl-1,2,5,6-tetrahydropyridine, which was isolated with a yield of 75%. Its solution in dichloromethane was reacted with *m*-chloroperbenzoic acid, giving 1-benzyl-1,2,5,6-tetrahydropyridine-*N*-oxide isolated with a yield of 80%. To the solution of the *N*-oxide in dichloromethane was added trifluoroacetic anhydride; after 1 h at room temperature, an aqueous solution of potassium cyanide was added, during which the pH was maintained at 4. 1-Benzyl-2-cyano-3-piperideine **1b** was obtained with a yield of 57%. The subsequent alkylation of the α-amino nitrile **1b** with 3-pyridylmagnesium chloride was made according to the Bruylants reaction, generating (±)-1-benzyl-2-(3-pyridyl)-3-piperideine **3b**, i.e., (±)-*N*-benzyl-isoanatabine. The solution of the Grignard reagent in THF was added at 0°C to the solution of the α-amino nitrile **1b** in THF. The (±)-*N*-benzyl-isoanatabine **3b** was obtained with a yield of 67%.

Attempts at N-demethylation and N-debenzylation by a chloroformate of the (±)-N-methyl- and (±)-N-benzyl-isoanatabines. To obtain (±)-isoanatabine **4**, the *N*-demethylation of **3a** was attempted by reacting **3a** with a chloroformate [19a]. The mixture of **3a** and 1 equiv of α-chloroethyl chloroformate (ACE-Cl) in 1,2-dichloroethane was refluxed for 16 h (monitored by TLC). After evaporation of the solvent, the residue was refluxed in methanol for 1 h, giving a mixture of unidentified

Scheme 6. Reagents and conditions: (*i*) ACE-Cl, CH_2Cl_2, 0°C to rt, 16 h. (*ii*) 2.5% NaOH, EtOH/H_2O (9:1), 0°C (1 h) to rt, 5 h, 78%.



products. To solve the problem, the mixture of **3a** and ACE-Cl in 1,2-dichloroethane was refluxed for 16 h, but instead of the intermediate carbamate **6**, the *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-methyl-carbamic acid 1-chloro-ethyl ester **7** was isolated and analyzed (Scheme 5). Thereafter, **7** was treated with 2.5% sodium hydroxide in aqueous ethanol, and (±)-*N*-methyl-isoanatabine **3a** was recovered with a yield of 75% relative to the starting amount of **3a**.

The opening of the piperideine ring when **3a** is reacted with α-chloroethyl chloroformate can be explained by the intermediate formation of the quaternary ammonium salt **5** followed by the attack of the chloride ion at the benzylic carbon, following the pathway b instead of the attack at the methyl group (pathway a). This corresponds to the benzyl effect, i.e., the benzyl cleavage is preferred over the methyl loss on account of the great stability of the benzyl carbocation. The general rule indicates that the group that cleaves is the one that gives the most stable carbocation and the most reactive halide (e.g., benzyl or allyl); for simple alkyl groups, the smallest are the most readily cleaved [19]. A similar reactivity to that of **3a** is observed with nicotine. When nicotine is reacted with chloroformates, the pyrrolidine ring is opened and the δ-chlorocarbamates are obtained [20].

An assay was made for the *N*-debenzylation of **3b** by its reaction with α-chloroethyl chloroformate in dichloromethane at room temperature, as it is known that the benzyl group needs lower temperatures to be cleaved.

In the intermediate quaternary ammonium salt **8**, it was hoped that the breaking of the *N*-Bn (bond A) would be favored over the breaking of the *N*-(C-2 of the 3-piperideine) bond (bond B), generating (±)-isoanatabine **4** (Scheme 6). The reverse however occurred and 1-chloro-1-(3-pyridyl)-5-benzylamino-pent-2-ene **9** was formed. This could be due to the fact that the B bond breaking in **8** generates at the 2-C of the 3-piperideine a more stable carbocation because it is simultaneously a benzyl and allyl cation. The A bond breaking would generate a carbocation benzyl lacking the further allyl stabilization.

The treatment of **9** with 2.5% sodium hydroxide in aqueous ethanol permitted recovery of the starting (±)-*N*-benzyl-isoanatabine **3b** with a yield of 78%.

Attempted N-debenzylation of (±)-N-benzyl-isoanatabine 3b with CAN. Yamaura *et al*. observed that the *N*-(4-methoxybenzyl) group on 2,5-piperazinediones can be oxidatively removed with $(NH_4)_2Ce(NO_3)_6$ (CAN), but not the unsubstituted benzyl group [21]. However, Bull *et al*. observed that the treatment of a range of *N*-unsubstituted benzyl tertiary amines with CAN at room temperature results in *N*-debenzylation to afford the corresponding secondary amine [22]. Therefore, the oxidative *N*-debenzylation of **3b** with CAN was assayed. A solution of **3b** and 2 equiv of CAN in 5:1 acetonitrile:water was stirred for 2 h at rt. Only the starting material **3b** was obtained. In another assay, 4 equiv of CAN were added to a solution of **3b** in 5:1 acetonitrile:water, and the solution was stirred 24 h at rt. Again only the starting **3b** was recovered. The concentration of CAN in the reaction mixture of each of these assays was greater than 0.25*M* as it is known that no oxidation is obtained at lower concentration [21]. A further assay was made with **3b** and 4 equiv of CAN, and stirring at 50°C overnight; isoanatabine **4** was not obtained but **3b** was completely transformed into a lot of unidentified products. The use of tetrahydrofuran instead of acetonitrile and higher concentrations of CAN at room temperature also led to the recovering of the starting (±)-*N*-benzyl-isoanatabine **3b**.

N-Demethylation of the (±)-N-methyl-isoanatabine 3a by decomposition of its N-oxide 10 (nonclassical Polonovski reaction). Several possible methods for *N*-demethylation of **3a** were tested, starting from the *N*-oxide of **3a**, **10**. The *N*-oxide **10** was obtained by reaction of (±)-*N*-methyl-isoanatabine **3a** with *m*-chloroperoxybenzoic acid (1.1 equiv) in CH_2Cl_2 at 0°C to avoid the possible epoxidation of the double bond [23]. The usual work up, i.e., treatment of the reaction mixture by aq. NaOH to pH 10–11 and then extraction by $CHCl_3$ led to the isolation of the *N*-oxide only in low yield. The low yield was probably due to the high solubility of the *N*-oxide at basic pH. This problem was overcame by concentrating the reaction mixture and pouring the concentrate

over alumina and chromatographing. In this way, the (±)-*N*-methyl-isoanatabine-*N*-oxide **10** was obtained with a yield of 91% as a mixture of diastereomers in a 6:4 ratio (undefined stereochemistry). The diastereomers were not separated and were used in next step as a mixture.

The nonclassical Polonovski reaction for the *N*-demethylation of the *N*-oxide of (±)-*N*-methyl-isoanatabine **3a** was investigated [24a]. The desired reaction is the catalyzed decomposition of the tertiary amine *N*-oxide through an internal oxidation into the secondary amine, the *N*-methyl being oxidized to formaldehyde. When the reaction is catalyzed by an iron salt, the mechanism is believed to involve two successive one-electron transfers involving Fe(II)/Fe(III) redox reactions [24b,c]. Cations, free radicals and radical-cations ions stabilized as iminium ions and radicals, are considered as intermediates. Often the catalyst (the iron salt or complex, selenium dioxide, etc.) is engaged in stoichiometric amounts. The *N*-demethylation of the hydrochloride salts of the *N*-oxides of opiate alkaloids (codeine, codeine methyl ether, thebaine, thevinone, etc.) was realized with $FeSO_4 \cdot 7H_2O$ in methanol; the *N*-oxide of codeine gave norcodeine with a yield of 49%, in mixture with codeine, i.e., the product of *N*-deoxygenation [25]. When the same reaction was made using a porphyrin chelate of iron(II), the yield of norcodeine was increased to 91% [26]. The same reaction has been applied to the *N*-demethylation of the *N*-oxides of piperidines, benzomorphans, and morphinans using iron(II) chloride [27].

For the nonclassical Polonovski reaction of the *N*-oxides of tertiary amine catalyzed with iron salts in water or in nonpolar solvents, the ease of alkyl conversion to the corresponding carbonyl compound decreases in the order $C_6H_5CH_2 > CH_3 > RCH_2 > R_2CH$; this is the decreasing order for the ease of the breaking of the bond between the *N*-oxide nitrogen atom and one of the three alkyl groups linked to this nitrogen [24b,c]. This reactivity order for the rearrangement was assigned among others to the acidity of the protons on the carbon adjacent to the nitrogen atom; the greater stability of the intermediate benzyl carbocation, benzyl radical and benzyl radical-carbocation also explains the reactivity order and that benzyl cleavage is preferred over methyl loss (benzyl effect). For the *N*-demethylation of the *N*-oxides of opiates (codeine, codeine methyl ether, thebaine, thevinone, etc.) cited earlier, there was no benzyl group linked to the nitrogen atom; there was no competition from the benzyl effect and the *N*-demethylation was obtained with a good yield [25]. The *N*-oxide of *N*-methyl-isoanatabine and the *N*-oxide of the *N*-benzyl-isoanatabine are subjected to the benzyl effect. The failure of the trials for their *N*-demethylation and *N*-debenzylation with a chloroformate showed their high sensitivity to the benzyl effect and prompted to select assays able to avoid this benzyl effect.

Another secondary reaction that competes with the *N*-demethylation is the deoxygenation of the *N*-oxide, which is catalyzed by the iron salt or chelate. It generates back the tertiary amine from which was made the *N*-oxide. Moreover, the deoxygenation of the *N*-oxide may be accompanied by the oxidation (oxidative dehydrogenation) of the *N*-demethylated product or of the *N*-methylated one. Other secondary degradative reactions occur when the reaction temperature is too high.

Selective *N*-demethylation of the *N*-oxides of tertiary aminofumagillols to the corresponding secondary aminofumagillols has been made by heating the *N*-oxide with selenium dioxide in ethanol [28]. The *N*-oxides of tertiary aminofumagillols do not sustain the concurrence of the benzyl effect. However, they contain two epoxy and the α,β-unsaturated ester sensitive functionalities. These remained intact during the reaction.

Therefore, our first attempt at the *N*-demethylation of **10** by means of the nonclassical Polonovski reaction utilized SeO_2. A mixture of **10** and 1.5 equiv of SeO_2 in 95% ethanol was heated to reflux for 4 h under an atmosphere of argon. (±)-*N*-methyl-isoanatabine **3a** was formed with a yield of 65%, indicating that only *N*-deoxygenation occurred.

Several studies have been reported for the *N*-demethylation of the *N*-oxides of tertiary amines subjected to the benzyl effect, by means of their decomposition catalyzed by iron salts (generally engaged in stoichiometric amounts) in aqueous solutions containing large amounts of tartaric or citric acids (present as such or as their salts). The $FeSO_4$-catalyzed dealkylation of the *N*-oxide of *N*,*N*-dimethyl-benzylamine showed the importance of the benzyl effect relatively to the *N*-demethylation. When the *N*-oxide of *N*,*N*-dimethyl-benzylamine in an aqueous solution at pH 1–2 containing iron(II) sulfate was heated, benzaldehyde was produced with a yield of 85%, no *N*-demethylation being obtained [24b,c]. Under the same conditions at pH 1, the *N*-oxide of *N*,*N*-dimethyl-butylamine gave mainly formaldehyde and *N*-methyl-butylamine. On the other hand at pH 6–7, when the mixture in water of the *N*-oxide of *N*,*N*-dimethyl-benzylamine, L-(+)-tartaric acid and $FeSO_4 \cdot 7H_2O$ (or of $Fe(NO_3)_3 \cdot 9H_2O$) was heated, a mixture of formaldehyde (the product of *N*-demethylation) and benzaldehyde (2.3:1) was formed [24b,29]. At pH 6–7, the Fe^{+2}/Fe^{+3} system is as a complex with the anion of tartaric acid. The *N*-oxide would occupy some coordination positions of this complex [30]. The rearrangement of the *N*-oxide would then occur at the coordination positions of the complex so the regioselectivity of the rearrangement would be directed by the geometry of the complex and thus by steric factors. This would explain the

production of formaldehyde and thus the *N*-demethylation, what did not occur when the iron ions were not chelated.

In previous experiments on the dealkylation of amine oxides, it was observed that reaction mixtures of iron (III) and tartaric or oxalic acid (reducing acids) generated iron(II) *in situ*, and that iron(II) was the initiator of the rearrangement [24b,c]. That iron(II) and not iron(III) was the initiator of the reaction was shown by experiments with iron(III) salts coordinated to nonreducing acids (sulfuric, succinic) [24b,c]. Under these conditions, the Polonovski reaction did not occur. When as little as 3% iron(II) sulfate was added to the reaction medium, secondary amine production began. On the other hand, iron(II) was converted to iron(III) during the course of the rearrangement; this was mainly due to the oxidation of iron(II) by the amine-oxide with formation of the tertiary amine (the secondary reaction of the amine-oxide: deoxygenation).

Noscapine (also called narcotine) has been converted by *N*-demethylation to nornarcotine in 35% overall yield *via* the noscapine *N*-oxide and in spite of the concurrence of a benzyl effect [31]. Therefore, the mixture of noscapine-*N*-oxide·HCl and iron(III) citrate, in water acidified to pH 1–2, was heated. Nicotine-*N*-oxide also suffers the competition of the benzyl effect during its *N*-demethylation by the nonclassical Polonovski reaction. A mixture in water at pH 6 of nicotine-*N*-oxide, $Fe(NO_3)_3$, L-(+)-tartaric acid and sodium carbonate was heated [32]. Nornicotine was obtained with a yield of 56%, besides several other alkaloids arising from the transformation of nicotine: myosmine (6.9%), *N*-methylmyosmine (2.1%), and nicotine (3.0%).

N-demethylation of (±)-*N*-methyl-isoanatabine **3a** by decomposition of its *N*-oxide **10** was attempted under the conditions used by Craig *et al*. for the *N*-demethylation of nicotine [32]. The pH of a mixture in water of **10**, 3 equiv of $Fe(NO_3)_3$, and 30 equiv of L-(+)-tartaric acid was adjusted to 6.3 by adding a solution of sodium carbonate. After heating at 80°C for 40 min, (±)-isoanatabine **4** was obtained but only with a low yield of 9%. The major compound isolated was the (±)*N*-methyl-anatabine **3a**, obtained with a yield of 49%, indicating that deoxygenation of the *N*-oxide was the main reaction.

The results obtained in the two preceding assays suggested that heating could induce the deoxygenation of **10** generating (±)-*N*-methyl-isoanatabine **3a**. Therefore, a method was searched for the decomposition of the *N*-oxide at room or lower temperature.

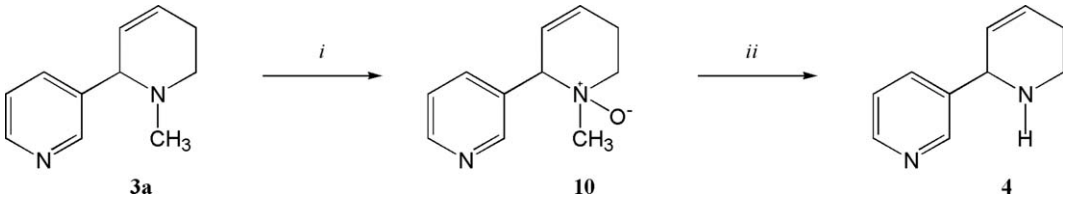
The secondary amine 5-dimethylamino-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine is a metabolite of a new vasopressin V2 receptor antagonist [33]. The *N*-demethylation of its *N*-oxide was sensitive to the competition from the benzyl effect. However, the *N*-demethylation of the *N*-oxide was obtained by stirring a mixture of *N*-oxide, meso-(tetraphenylporphinato)iron(III) chloride, Fe(TPP)Cl, and imidazole in dichloromethane at room temperature. The product of *N*-demethylation was obtained with a yield of 68%, accompanied by 25% of the deoxygenation product of the *N*-oxide. When imidazole was replaced by tetrazole, the secondary amine was produced with a yield of 86%, and the product of deoxygenation was no more detected. This showed the influence of the additives imidazole or tetrazole. They could make some association with the *N*-oxide and the iron porphyrin, orienting in this way the decomposition of the *N*-oxide toward the *N*-demethylation, and overcoming the benzyl effect. In the *N*-demethylation of the *N*-oxides of the *N*,*N*-dimethyl-benzylamine [24b,c] noscapine [31] and nicotine [32] cited earlier, the chelation of the iron ions by the tartaric and citric acids and their salts present in large excess, would explain the orientation by steric effects of the rearrangement of the *N*-oxide toward the *N*-demethylation. The increase of the yield of the *N*-demethylation of the *N*-dimethyl benzazepine *N*-oxide by the use of the additives imidazole or tetrazole corroborated that hypothesis.

Therefore, *N*-demethylation of (±)-*N*-methyl-isoanatabine **3a** was assayed in the conditions used by Kawano *et al*. [33]. The mixture of **10**, 1 equiv of Fe(TPP)Cl and 1 equiv of tetrazole in dichloromethane was stirred at room temperature during 16 h in the dark. The *N*-oxide **10** was recovered untransformed with a yield of 80%. The assay was repeated but without the addition of tetrazole; again the *N*-oxide **10** was recovered untransformed.

The *N*-demethylation of the galanthamine-*N*-oxide is sensitive to the competition from the benzyl effect [34]. However, the *N*-demethylation has been obtained with a yield of 76% by stirring at 10°C the *N*-oxide in methanol containing iron(II) sulfate. No cleavage at the benzylic carbon was observed. The selective demethylation of the galanthamine-*N*-oxide in the presence of iron salts indicated the preference for oxidation at the methyl center of the *N*-methyl substituted amine oxide. This is at the opposite of the general rule which gives the preference to the oxidation of the benzylic carbon. The bulky structure of galanthamine would induce the *N*-demethylation by a steric effect, the *N*-methyl being deprotected to oxidation outside of the bulky structure.

The *N*-demethylation of the *N*-oxide of the alkaloid glaucine suffers also from the competition of the benzyl effect [35]. However, the *N*-demethylation has been performed under the same conditions as for galanthamine without addition of a complexing agent. The *N*-oxide of glaucine was treated in methanol with iron(II) sulfate at 10°C. Norglaucine was formed with a yield of 52%. It

Scheme 7. Reagents and conditions: (*i*) *m*-CPBA, CH_2Cl_2, 0°C, 1.5 h, 91%. (*ii*) $FeSO_4 \cdot 7H_2O$, CH_3OH, 10°C, 1.5 h, 55%.



was accompanied by the formation for 13% of the product of the benzyl effect, which was further reduced. When the reaction temperature was 50°C or when the reagent was changed to ferrous chloride, only the product due to the benzyl effect was formed.

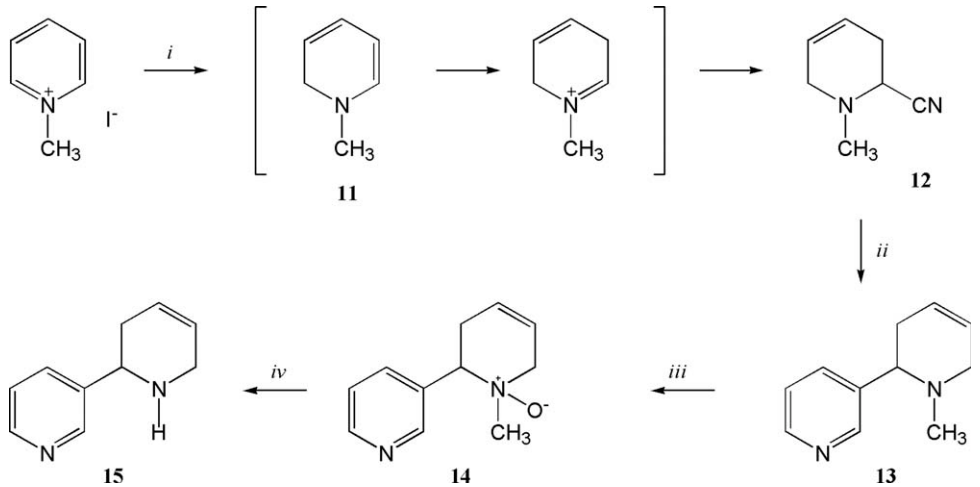
N-demethylation of the (±)-*N*-methyl-isoanatabine **3a** by decomposition of its *N*-oxide **10** was tested under the same conditions as the *N*-oxides of galanthamine [34] and glaucine [35] (Scheme 7). A mixture of **10** and 2 equiv of $FeSO_4 \cdot 7H_2O$ in methanol was stirred for 1.5 h at 10°C. The (±)-isoanatabine **4** was obtained with a yield of 55%. It was accompanied by the formation of 23% of (±)-*N*-methyl-isoanatabine **3a**, the product of deoxygenation. As with galanthamine and glaucine, the structure of the *N*-oxide **10** of isoanatabine would induce by a steric effect the *N*-demethylation without requiring an additive. The *N*-methyl would be more accessible to oxidation because of its greater exposure. For the *N*-demethylation by decomposition of the *N*-oxide, the search by the successive applications of described procedures thus contributes, by the analysis of the generated products, to the knowledge of the mechanism and of the experimental parameters orienting the selectivity of the oxidative rearrangement of the nonclassical Polonovski reaction.

Synthesis of (±)-anatabine. The procedure for the synthesis of (±)-isoanatabine **4** was extended to the synthesis of (±)-anatabine **15** (Scheme 8). (±)-2-Cyano-1-methyl-4-piperideine **12** is the isomer of (±)-2-cyano-1-methyl-3-piperideine **1a**. The sequence of transformations applied to compound **1a** for the synthesis of (±)-isoanatabine **4** could in principle be applied to **12** for the preparation of (±)-anatabine **15**. Therefore, a procedure for the synthesis of compound **12** was developed. Like for compound **1a** it started with the reduction of 1-methylpyridinium iodide with $NaBH_4$, but the experimental conditions were changed to obtain the double bond in the right position. A two phases solvent system was used [36]. To an aqueous solution of 4 equiv of potassium cyanide was added 1.5 equiv of hydrochloric acid at 0°C. This aqueous phase was layered with the same volume of ether. 1-Methylpyridinium iodide was added followed by 1.2 equiv of $NaBH_4$. After 5 h at room temperature, compound **12** was obtained with a yield of 95%.

The presence of the solution of potassium cyanide in water underlayering the ether phase since the beginning of the reduction of 1-methylpyridinium iodide by $NaBH_4$ permitted to limit the reduction to the formation of 1-methyl-1,2-dihydro-pyridine which in acidic condition was trapped by potassium cyanide, generating compound **12**.

The isomerization of (±)-2-cyano-1-methyl-4-piperideine **12** into (±)-2-cyano-1-methyl-3-piperideine **1a**

Scheme 8. Reagents and conditions: (*i*) $NaBH_4$, KCN, HCl, H_2O/Et_2O, 0°C to rt, 5 h, 95%. (*ii*) 3-PyrMgCl, THF, −10°C to rt, 16 h, 83%. (*iii*) *m*-CPBA, CH_2Cl_2, 0°C, 1.5 h, 88%. (*iv*) $FeSO_4 \cdot 7H_2O$, CH_3OH, 10°C, 3 h, 44%.



was attempted [37a,b]. If it succeeded, the aminonitrile **12** could be another starting point for the synthesis of (±)-isoanatabine **4**. The isomerization was attempted by heating **12** in 6*N* HCl. Thereafter, the solution was made basic by addition of potassium cyanide. However, the aminonitrile **12** was recovered untransformed.

The same sequence of transformations applied to compound **1a** for the synthesis of isoanatabine **4**, was applied to compound **12** for the preparation of anatabine **15**. The 3-pyridylmagnesium chloride was reacted with the α-amino nitrile **12** in THF, giving the *N*-methyl-anatabine **13** with a yield of 83%. Compound **13** was oxidized by *m*-CPBA in dichloromethane, giving the *N*-methyl-anatabine-*N*-oxide **14** with a yield of 88% as a mixture of two diastereomers in a 7:3 ratio. The diastereomers can be separated by chromatography on alumina.

The *N*-demethylation of **14** was made on the mixture of diastereomers by their decomposition at 10°C in methanol containing 2 equiv of $FeSO_4 \cdot 7H_2O$ leading to the anatabine **15** with a yield of 44%. It was accompanied by the formation of 44% of *N*-methyl-anatabine **13**, product of deoxygenation of the *N*-oxide **14** which could be recovered from the reaction mixture.

EXPERIMENTAL

General. ESI-HRMS were performed on an Agilent 6210 TOF mass spectrometer. GC/CI analyses were performed on a Thermo Trace GC DSQ–Single Quadrupole. The ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz with a Varian Mercury 300 and are reported in ppm from internal TMS on the δ scale. The ^{13}C NMR spectra were recorded in $CDCl_3$ at 75.4 MHz with a Varian Mercury 300 instrument. The IR spectra were recorded with a Bruker Vector 22 instrument as films on a NaCl disk. Thin layer chromatography analyses (TLC) were performed with 0.20 mm Silica Gel 60, F-254 precoated plates (Selecto Scientific). Chromatographies were performed on silica gel columns (Fisher, Silica Gel Sorbent, 230–400 Mesh) using the flash technique or on alumina (Aluminoxid 90, Activity II–III, EMD).

(±)-1-Methyl-2-(3-pyridyl)-3-piperideine: (±)-N-methyl-isoanatabine, 3a. 3-Bromopyridine (598 μL, 981 mg, 6.22 mmol) was added to *i*-PrMgCl (2*M*/THF, 3.11 mL, 6.22 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at −10°C, then a solution of **1a** (152 mg, 1.24 mmol) in THF (2 mL) was added. The resulting reaction mixture was allowed to stir for 1 h at −10°C then left overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with CH_2Cl_2 (3 × 10 mL), drying over magnesium sulfate and column chromatography using CH_2Cl_2/CH_3OH/NH_3 (95:5:1) as eluent afforded (±)-*N*-methyl-isoanatabine, **3a** (167 mg, 0.96 mmol, 77%). IR (NaCl): 3031, 2945, 2785, 1650, 1577, 1425, 1362, 1281, 1057, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, 1H, J = 2.4 Hz, ArH), 8.50 (dd, 1H, J = 1.8, 4.8 Hz, ArH), 7.68 (dt, 1H, J = 1.8, 7.8 Hz, ArH), 7.25 (ddd, 1H, J = 0.6, 4.8, 7.8 Hz, ArH), 5.86 (m, 1H, C*H*=CH), 5.45 (dq, 1H, J = 1.5, 9.9 Hz, CH=C*H*), 3.66 (app quintet, 1H, J = 1.2 Hz, NC*H*Ar), 2.93 (m, 1H, NCH_2), 2.50 (m, 2 H, NCH_2 + CH_2—CH=CH), 2.12 (m, 1H, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 150.3 (CH), 149.0 (CH), 138.7 (C), 136.3 (CH), 129.3 (CH), 125.5 (CH), 123.8 (CH), 65.9 (CH), 51.9 (CH_2), 44.0 (CH_3), 26.2 (CH_2). ESI-HRMS: m/z = 175.1244 (calculated for $[M + H]^+$: 175.1230); 197.1064 (calculated for $[M + Na]^+$: 197.1049); 371.2228 (calculated for $[2M + Na]^+$: 371.2206).

(±)-1-Benzyl-2-(3-pyridyl)-3-piperideine: (±)-N-Benzyl-isoanatabine, 3b. 3-Bromopyridine (130 μL, 213 mg, 1.35 mmol) was added to *i*-PrMgCl (2*M*/THF, 675 μL, 1.35 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at 0°C, then a solution of **1b** (51 mg, 0.26 mmol) in THF (1 mL) was added. The resulting reaction mixture was stirred overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with CH_2Cl_2 (3 × 10 mL), drying over magnesium sulfate and column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (97:3:1) as eluent afforded **3b** (43 mg, 0.17 mmol, 67%). IR (NaCl): 3029, 2918, 2707, 1655, 1576, 1424, 1027, 849 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, 1H, J = 2.1 Hz, ArH), 8.49 (dd, 1H, J = 1.8, 4.8 Hz, ArH), 7.80 (dt, 1H, J = 2.1, 7.8 Hz, ArH), 7.26 (ddd, 1H, J = 0.6, 4.8, 7.8 Hz, ArH), 5.85 (m, 1H, C*H*=CH), 5.49 (dq, 1H, J = 1.5, 9.9 Hz, CH=C*H*), 4.00 (app quintet, 1H, J = 2.4 Hz, NC*H*Ar), 3.52 (d, J = 13.5 Hz, 1H, CH_2 (Bn)), 3.43 (d, J = 13.5 Hz, 1H, CH_2 (Bn)), 2.93 (m, 1H, NCH_2), 2.41–2.25 (m, 2H, NCH_2 + CH_2—CH=CH), 2.06 (bd, 1H, J = 14.1 Hz, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 150.4, 148.9, 139.4, 139.2, 136.3, 129.6, 128.8, 128.4, 127.1, 125.7, 123.8, 63.8, 59.0, 47.3, 25.9. ESI-HRMS: m/z = 251.1567 (calculated for $[M + H]^+$: 251.1543); 273.1372 (calculated for $[M + Na]^+$: 273.1362).

Assays of *N*-demethylation of (±)-*N*-methyl-isoanatabine 3a and *N*-debenzylation of (±)-*N*-benzyl-isoanatabine 3b with 1-chloroethyl chloroformate.

Attempted N-demethylation of (±)-N-methyl-isoanatabine 3a. 1-Chloroethyl chloroformate (80 μL, 106 mg, 0.74 mmol) was added at 0°C to a stirred solution of **3a** (107 mg, 0.61 mmol) in dry 1,2-dichloroethane (6 mL) under argon. The resulting mixture was heated to reflux for 16 h. The solvent was removed under reduced pressure to give the *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-

methyl-carbamic acid 1-chloro-ethyl ester (**7**). **7** was dissolved in 40 mL of 2.5% sodium hydroxide in aqueous ethanol (1:9) at 0°C; after 1 h at 0°C, the mixture was stirred at room temperature during 24 h. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to yield **3a** as yellow oil (80.3 mg, 0.46 mmol, 75%). *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-methyl-carbamic acid 1-chloro-ethyl ester (**7**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (m, 1H, ArH), 8.83 (d, 1H, J = 4.5 Hz, ArH), 8.54 (d, 1H, J = 8.4 Hz, ArH), 8.05 (m, 1H, ArH), 6.89 (m, 1H, CH=CH), 6.74 (m, 1H, CH=CH), 6.57 (m, 1H, *CH*ClCH$_3$), 4.66 (app quint., 1H, NC*H*Ar), 3.49 (m, 2H, NC*H*$_2$), 2.99 (s, 3H, NCH$_3$), 2.21 (m, 2H, C*H*$_2$—CH=CH), 1.83 (d, 3H, J = 5.7 Hz, CHCl*CH*$_3$). - ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 153.5 (CO), 153.3 (CO), 142.5 (CH), 139.4 (CH), 139.0 (CH), 137.0 (CH), 136.9 (CH), 136.2 (C), 127.3 (CH), 125.0 (CH), 124.8 (CH), 124.7 (CH), 124.1 (CH), 83.3 (CH), 58.4 (CH), 46.7 (CH_2), 45.9 (CH_2), 36.2 (CH_2), 35.6 (CH_2), 35.4 (CH_2), 34.7 (CH_2), 25.4 (CH_3), 25.1 (CH_3).

Attempted N-debenzylation of (±)-N-benzyl-isoanatabine 3b. 1-Chloroethyl chloroformate (9 μL, 12 mg, 0.08 mmol) was added at 0°C to a stirred solution of **3b** (21 mg, 0.08 mmol) in dry dichloromethane (3 mL) under argon. The resulting mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure to give the 1-chloro-1-(3-pyridyl)-5-benzylamino-pent-2-en (**9**). Compound **9** was then stirred with 5 mL of 2.5% sodium hydroxide in aqueous ethanol (1:9) at 0°C; after 1 h at 0°C, the mixture was stirred at room temperature during 5 h. The mixture was extracted with dichloromethane (3 × 7 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to yield **3b** as a yellow oil (15.6 mg, 0.06 mmol, 78%). 1-Chloro-1-(3-pyridyl)-5-benzylamino-pent-2-en (**9**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (bs, 1H, ArH), 9.32 (bs, 1H, ArH), 8.73 (bs, 1H, ArH), 8.03 (bs, 1 H, ArH), 7.74 (bs, 2 H, ArH), 7.35 (s, 3 H, Bn-H), 6.32 (bs, 1 H), 6.03 (bs, 1 H), 5.72 (bs, 1 H), 4.64 (bs, 2 H), 3.40 (bs, 1 H), 3.23 (bs, 1 H), 3.05 (m, 1 H), 2.42 (m, 1 H). The ESI-MS of **9** indicated polymeric material; this probably arised in the MS apparatus by the intermolecular substitution in **9** of the chlorine by the amino group. On the other hand, the GC-MS of **9** gave the MS spectrum of **3b**; at the temperature of the GC column oven (Rxi-5ms column, program: injector 200°C, detector 280°C, program: 40°C (1 min), 30°C/min to 280°C, 280°C (15 min); RT:12.08 min), **9** spontaneously cyclized into **3b** by the intramolecular substitution of the chlorine by the amino group.

Assay for the *N*-debenzylation of (±)-*N*-benzyl-isoanatabine 3b with CAN (ammonium cerium (IV) nitrate). To compound **3b** (37 mg, 0.15 mmol), dissolved in a 5:1 mixture of CH_3CN-H_2O (2.4 mL), CAN (329 mg, 0.60 mmol) was added portionwise. After stirring 24 h at room temperature, the mixture was basified with an aqueous saturated solution of $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered, and concentrated *under vacuo* to obtain the starting compound **3b** (33 mg, 0.13 mmol, 88%).

(±)-N-methyl-isoanatabine-N-oxide, 10. To a solution of **3a** (206 mg, 1.18 mmol) in CH_2Cl_2 (6 mL) at 0°C was added a solution of 70–75% aq. *m*-CPBA (320 mg, 1.3 mmol) in CH_2Cl_2 (11 mL). After stirring 1.5 h at 0°C under argon, the reaction mixture was concentrated *in vacuo* to a volume of 7 mL and then poured over alumina and chromatographed using CH_2Cl_2/CH_3OH (95:5) as eluent to afford the *N*-oxide **10** as a mixture of two diastereomers in a 6:4 ratio (204 mg, 1.07 mmol, 91%). The diastereomers were not separated and were used in the next step as a mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, 0.6 H, J = 1.8 Hz, ArH), 8.68 (dd, 0.6 H, J = 1.8, 4.8 Hz, ArH), 8.64 (d, 0.4 H, J = 1.5 Hz, ArH), 8.63 (dd, 0.4 H, J = 1.5, 4.8 Hz, ArH), 8.10 (dt, 0.4 H, J = 2.1, 7.8 Hz, ArH), 7.97 (dt, 0.6 H, J = 1.8, 7.8 Hz, ArH), 7.40 (ddd, 0.6 H, J = 0.6, 4.8, 7.8 Hz, ArH), 7.36 (ddd, 0.4 H, J = 0.6, 4.8, 7.8 Hz, ArH), 6.18 (m, 1H, C*H*=CH), 5.84 (dq, 0.6 H, J = 1.8, 10.2 Hz, CH=C*H*), 5.66 (dq, 0.4 H, J = 2.1, 10.5 Hz, CH=C*H*), 5.07 (app quintet, 0.6 H, J = 2.7 Hz, NC*H*Ar), 4.90 (app quintet, 0.4 H, J = 2.4 Hz, NC*H*Ar), 3.60 (m, 1.2 H, NC*H*$_2$), 3.43 (m, 0.8 H, NC*H*$_2$), 3.19 (s, 1.2 H, NC*H*$_3$), 2.92 (m, 0.6 H, C*H*$_2$CH=CH), 2.75 (s, 1.8 H, NC*H*$_3$), 2.58 (m, 1H, C*H*$_2$CH=CH), 2.41 (m, 0.4 H, C*H*$_2$CH=CH). ^{13}C NMR ($CDCl_3$): Major diastereomer, δ 151.5 (CH), 150.5 (CH), 139.0 (CH), 129.1 (C), 126.4 (CH), 123.8 (CH), 123.1 (CH), 76.4 (CH), 64.2 (CH_2), 51.1 (CH_3), 24.1 (CH_2). ^{13}C NMR ($CDCl_3$): Minor diastereomer, δ 152.0 (CH), 150.1 (CH), 139.8 (CH), 129.3 (C), 126.3 (CH), 123.6 (CH), 122.9 (CH), 73.2 (CH), 61.9 (CH_2), 56.9 (CH_3), 23.2 (CH_2). ESI-HRMS: m/z = 191.1192 (calculated for $[M + H]^+$: 191.1179); 213.1006 (calculated for $[M + Na]^+$: 213.0998); 381.2312 (calculated for $[2M + H]^+$: 381.2285); 403.2114 (calculated for $[2M + Na]^+$: 403.2104).

Attempted *N*-demethylation of (±)-*N*-methyl-isoanatabine-*N*-oxide 10. ***With selenium dioxide.*** To a stirred mixture of **10** (193 mg, 1.02 mmol) in 95% ethanol (10 mL) was added portionwise selenium dioxide (169 mg, 1.52 mmol) for 10 min. The mixture was heated to reflux for 4 h under an atmosphere of argon. The reaction was monitored by TLC. After 4 h, the starting material was still present. The mixture was

refluxed for 4 h more. The residue obtained by evaporation of the reaction mixture was purified by column chromatography through silica gel column, using $CH_2Cl_2/CH_3OH/NH_3$ (90:10:1) as eluent to give 115 mg (0.66 mmol, 65%) of **3a** and 19 mg (0.1 mmol, 10%) of **10**.

With $FeSO_4 \cdot 7H_2O$. *N*-oxide **10** (95 mg, 0.50 mmol) was dissolved in MeOH (10 mL) and cooled at 10°C. $FeSO_4 \cdot 7H_2O$ (278 mg, 1 mmol) was added then the reaction mixture was stirred at 10°C for 1.5 h. Evaporation of the solvent afforded an orange solid, which was dissolved in 0.1*M* EDTA. Then, the pH was raised to 10 by addition of concentrated NH_4OH. The solution was extracted with $CHCl_3$ (3 × 20 mL), and the dried organic extracts over $MgSO_4$ were filtered and evaporated to yield a mixture of **4** and **3a** (2.3:1). These were separated by column chromatography on silica gel using $CH_2Cl_2/CH_3OH/NH_3$ (90:10:1) as an eluent. Pure (±)-isoanatabine (**4**) was obtained with a yield of 55% (44 mg, 0.28 mmol); pure (±)-*N*-methyl-isoanatabine (**3a**) was obtained with a yield of 23% (20 mg, 0.12 mmol). (±)-Isoanatabine (**4**): IR (NaCl): 3285, 3029, 2914, 2832, 1650, 1578, 1477, 1102, 1028, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, 1H, J = 1.8 Hz, ArH), 8.51 (dd, 1H, J = 1.5, 4.8 Hz, ArH), 7.70 (dt, 1H, J = 1.5, 7.5 Hz, ArH), 7.25 (ddd, 1H, J = 0.9, 5.1, 7.8 Hz, ArH), 6.01 (m, 1H, C*H*=CH), 5.71 (dq, 1H, J = 1.8, 9.3 Hz, CH=C*H*), 4.52 (app quintet, 1H, J = 2.7 Hz, NHC*H*Ar), 3.0 (m, 2 H, $NHCH_2$), 2.2 (m, 3 H, CH_2CH=CH + N*H*). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 149.7 (CH), 149.0 (CH), 139.3 (C), 135.6 (CH), 128.9 (CH), 127.6 (CH), 123.7 (CH), 56.2 (CH), 41.9 (CH_2), 25.7 (CH_2). ESI-HRMS: m/z = 161.1087 (calculated for $[M + H]^+$: 161.1073); 183.0893 (calculated for $[M + Na]^+$: 183.0893).

(±)-2-Cyano-1-methyl-4-piperideine, 12. To a stirred solution of potassium cyanide (5.45 g, 83.6 mmol) in water (11 mL) layered with ether (16 mL) was added a solution of 5*N* HCl (6.5 mL, 32.5 mmol). The mixture was stirred at 0°C, then 1-methylpyridinium iodide (5 g, 22.6 mmol) was added portionwise followed by $NaBH_4$ (1.03 g, 27.1 mmol). The stirring was continued for 5 h at room temperature. Water was added and the mixture was extracted with ether. The organic phases were combined, dried and evaporated to dryness. The resulting yellow oil was flash chromatographed on silica gel (CH_2Cl_2/CH_3OH 95:5 + 1% conc. NH_4OH). This yielded **12** (2.62 g, 21.5 mmol, 95%) as a colorless oil. IR (NaCl): 3043, 2945, 2789, 2223, 1658, 1452, 1260, 1141, 1002, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (m, 2H, C*H*=C*H*), 3.81 (dd, 1H, J = 1.5, 6 Hz, NC*H*CN), 3.24 (bd, 1H, J = 16.5 Hz, NCH_2), 2.96 (bd, 1H, J = 16.5 Hz, NCH_2), 2.69 (m, 1H, CH_2—CH=CH), 2.44 (s, 3H, NCH_3), 2.33 (m, 1H, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 125.5 (CH), 120.9 (CH), 116.3 (CN), 51.2 (CH), 50.0 (CH_2), 43.6 (CH_3), 29.5 (CH_2). ESI-HRMS: m/z = 123.0925 (calculated for $[M + H]^+$: 123.0917); 145.0745 (calculated for $[M + Na]^+$: 145.0736).

Attempt of isomerization of 12 into 1a. The amino nitrile **12** (52 mg, 0.43 mmol) in 1 mL of 6*N* HCl was heated at 80°C. After refluxing for 4 h, the mixture was cooled and enough aqueous sodium cyanide was added until the final solution was alkaline (pH 10). After stirring for 2 h, the mixture was extracted by CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$ and concentrated to yield the starting amino nitrile **12** (48 mg, 0.39 mmol, 92%).

(±)-1-Methyl-2-(3-pyridyl)-4-piperideine: (±)-*N*-methyl-anatabine, 13. 3-Bromopyridine (210 μL, 346 mg, 2.19 mmol) was added to *i*-PrMgCl (2*M*/THF, 1.1 mL, 2.19 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at −10°C, then a solution of **12** (89 mg, 0.73 mmol) in THF (2 mL) was added. The resulting reaction mixture was allowed to stir for 1 h at −10°C then left overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with CH_2Cl_2 (3 × 10 mL), drying over magnesium sulfate and column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (95:5:1) as eluent afforded (±)-*N*-methyl-anatabine **13** (106 mg, 0.61 mmol, 83%). IR (NaCl): 3034, 2985, 2910, 2773, 1666, 1577, 1427, 1321, 1258, 1051, 718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, J = 2.1 Hz, 1H, ArH), 8.52 (dd, J = 1.8, 5.1 Hz, 1H, ArH), 7.70 (dt, J = 2.1, 7.8 Hz, ArH), 7.29 (ddd, 1H, J = 0.6, 4.8, 7.8 Hz, ArH), 5.80 (m, 2H, C*H*=C*H*), 3.35 (m, 2H, NCH_2 + NC*H*Ar), 2.95 (m, 1H, NCH_2), 2.32 (m, 2H, CH_2—CH=CH), 2.07 (s, 3H, NCH_3). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 149.8 (CH), 149.0 (CH), 138.6 (C), 135.6 (CH), 125.5 (CH), 124.9 (CH), 123.9 (CH), 63.1 (CH), 55.2 (CH_2), 44.6 (CH_3), 35.3 (CH_2). ESI-HRMS: m/z = 175.1223 (calculated for $[M + H]^+$: 175.1230).

(±)-1-Methyl-2-(3-pyridyl)-4-piperideine-*N*-oxide: (±)-*N*-methyl-anatabine-*N*-oxide, 14. To a solution of **13** (210 mg, 1.2 mmol) in CH_2Cl_2 (17 mL) at 0°C was added, in several portions, 70–75% aq. *m*-CPBA (327 mg, 1.33 mmol). After stirring 1.5 h at 0°C under argon, the reaction mixture was concentrated *in vacuo* to a volume of 3 mL and then poured over alumina and chromatographed using CH_2Cl_2/CH_3OH (95:5) as eluent to afford the *N*-oxide **14** as a mixture of two diastereomers in a 7:3 ratio. The major diastereomer was isolated as a white solid and the minor diastereomer as an oil (combined 200 mg, 1.06 mmol, 88%). Major diastereomer, ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, J = 1.8 Hz, 1H, ArH), 8.64 (dd, J = 1.5, 4.8 Hz, 1H, ArH), 8.40

(bd, J = 7.8 Hz, 1H, ArH), 7.37 (dd, J = 4.5, 8.1 Hz, 1H, ArH), 6.07 (m, 1H, CH=C*H*), 5.72 (m, 1H, CH=C*H*), 4.27 (dd, J = 4.2, 10.8 Hz, 1H, NC*H*Ar), 4.16 (m, 1H, NCH_2), 3.92 (m, 1H, NCH_2), 3.24 (m, 1H, CH_2—CH=CH), 2.93 (s, 3H, NCH_3), 2.32 (m, 1H, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 150.9 (CH), 150.8 (CH), 137.8 (CH), 131.0 (C), 125.9 (CH), 123.7 (CH), 120.2 (CH), 71.4 (CH), 68.8 (CH_2), 58.6 (CH_3), 30.1 (CH_2). Minor diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, J = 2.1 Hz, 1H, ArH), 8.66 (dd, J = 1.2, 4.8 Hz, 1H, ArH), 7.97 (dt, J = 2.1, 8.1 Hz, 1H, ArH), 7.36 (dd, J = 4.8, 8.1 Hz, 1H, ArH), 6.08 (m, 1H, CH=C*H*), 5.83 (m, 1H, CH=C*H*), 4.47 (m, 1H, NC*H*Ar), 4.15 (m, 1H, NCH_2), 3.97 (m, 1H, NCH_2), 2.98 (s, 3H, NCH_3), 2.31 (m, 2H, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 151.1 (CH), 150.8 (CH), 138.3 (CH), 129.7 (C), 124.9 (CH), 123.3 (CH), 121.9 (CH), 73.7 (CH), 68.5 (CH_2), 51.7 (CH_3), 29.1 (CH_2). ESI-HRMS (diastereomers): m/z = 191.1176 (calculated for $[M + H]^+$: 191.1179); 213.0998 (calculated for $[M + Na]^+$: 213.0998); 381.2304 (calculated for $[2M + H]^+$: 381.2285); 403.2134 (calculated for $[2M + Na]^+$: 403.2104).

(±)-2-(3-Pyridyl)-4-piperideine: (±)-Anatabine, 15. A mixture of diastereomeric *N*-oxide **14** (171 mg, 0.9 mmol) was dissolved in MeOH (15 mL) and cooled at 10°C. $FeSO_4 \cdot 7H_2O$ (500 mg, 1.8 mmol) was added and the reaction mixture was stirred at 10°C for 3 h. Evaporation of the solvent afforded an orange solid which was dissolved in 0.1*M* EDTA (30 mL), then the pH was raised to 10 by addition of concentrated NH_4OH. The solution was extracted with $CHCl_3$ (3 × 30 mL), and the dried organic extracts over $MgSO_4$ were filtered and evaporated to yield a mixture of anatabine **15** and (±)-*N*-methyl-anatabine **13** (1:1). These were separated by flash column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (95:5:1) as eluent. Pure (±)-anatabine (**15**) was obtained in 44% yield (60 mg, 0.4 mmol); pure (±)-*N*-methyl-anatabine (**13**) was obtained with a yield of 44% (70 mg, 0.4 mmol). (±)-Anatabine **15**: IR (NaCl): 3280, 3031, 2916, 2830, 1655, 1578, 1427, 1311, 1100, 807 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, J = 2.1 Hz, 1H, ArH), 8.52 (dd, J = 1.8, 4.8 Hz, 1H, ArH), 7.73 (dt, J = 2.1, 7.8 Hz, ArH), 7.27 (ddd, 1H, J = 0.6, 5.1, 8.1 Hz, ArH), 5.84 (m, 2H, C*H*=C*H*), 3.90 (t, 1H, J = 7.2 Hz, NC*H*Ar), 3.64 (bd, J = 15.0 Hz, 1H, NCH_2), 3.49 (bd, J = 15.0 Hz, 1H, NCH_2), 2.27 (m, 2H, CH_2—CH=CH). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 148.9 (CH), 148.8 (CH), 140.1 (C), 134.3 (CH), 126.5 (CH), 125.3 (CH), 123.7 (CH), 55.5 (CH), 46.2 (CH_2), 34.1 (CH_2). ESI-HRMS: m/z = 161.1084 (calculated for $[M + H]^+$: 161.1078).

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