Vincamine by synthesis and semi-synthesis

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ABSTRACT: This review summarizes the main strategies aimed at the total synthesis of vincamine and congeners. Then, our contribution in this field is presented: we describe (+)-vincamine semi-synthesis using tabersonine as starting material. Characterization and quantification of the main impurities are discussed, and HPLC conditions, structural elucidation and NMR data of four of them are reported.

Vincamine [(3α, 14β, 16α)-14,15-Dihydro-14-hydroxyeburnamenine-14-carboxylic acid methyl ester] is an indole alkaloid obtained from the leaves of *Vinca minor L.*, exhibiting various biological benefits including vasodilating, blood thinning, memory enhancing and nootropic effects (Chattopadhyay et al. 1991; Chattopadhyay 1999; Van der Heijden et al. 2004, Archna, et al. 2016). These properties make vincamine of particular interest for the treatment of severe neurodegenerative conditions, such as Parkinson's and Alzheimer diseases. (Karpati et al. 2002; Vas and Gulyas 2005; Vereczkey 1985; Han et al. 2018). In addition, the interest toward vincamine is increased by its use to produce the vinpocetine, another well-known vasodilating agent (Zhang et al. 2018).

For these reasons, in the period between 1985 and 2000, the total synthesis of vincamine and structurally related compounds, such as eburnamine, eburnamonine and apovincamine, became a hot topic in the scientific community. From a structural point of view, vincamine and other *Vinca* alkaloids share a common fused pentacyclic scaffold, containing and indole framework (Figure 1).

Figure 1. Should go here

The majority of the reported studies dealing with the total synthesis of these compounds involved as key step the formation of the ABCD tetracyclic system, starting from a differently substituted indole, while the E ring is often introduced at the end of the synthesis.

Here, we are going to report the most representative approaches, distinguishing them on the basis of the strategy exploited for the construction of the main scaffold:

1. Bischler-Napieralski or Pictet-Spengler cyclisation.
2. Pericyclic cyclisation.
3. Rearrangements/annulation reactions.
4. Michael-like alkylation.

Then, our contribute will be presented, consisting into the semi-synthesis of (+)-vincamine, exploiting the natural product tabersonine as starting material.

1. Bischler-Napieralski or Pictet-Spengler cyclization.

The most over-represented strategy towards the synthesis of vincamine and congeners is based on the cyclization between indole C2 position and an iminium salt, to generate the C ring. This cyclization could be accessed exploiting a Bischler-Napieralski or a Pictet-Spengler reaction.

These approaches usually required a key intermediate **1** (Scheme 1 and Scheme 2), that could be easily accessed from commercially available reagents, such as tryptamine. **1** contains the A, B and D rings typical of vincamine, and is the substrate on which the cyclization should occur. The D ring in **1** could be eventually decorated on the lactam α-position, usually with an ethyl group and an ester, attached on α-carbon directly or through an ethyl chain. These motives are fundamental to build the E ring and could also be inserted after C ring formation.

One of the first examples taking advantage of this strategy was developed by Hermann and co-workers (Hermann et al. 1974, Hermann et al. 1979), that successfully completed the total synthesis of vincamine (Scheme 1).

Scheme 1. Should go here.

There, tryptamine was alkylated by a bromo ester, giving after nucleophilic cyclization a **1**-like intermediate, bearing an ethyl group on lactam α-position. That position was subsequently alkylated with 2-thiomethylacrylate, exploiting dianions chemistry. $POCl_3$-mediated Bischler-Napieralski cyclization, followed by stereospecific reduction of the iminium salt in the presence of lithium tri-tert-butoxyaluminum hydride, gave the required tetracyclic scaffold, with the proper *cis*-junction, as main product. The next step was an oxidation of the methyl sulphide to sulfoxide, followed by the formation of an heptacyclic lactam sulfoxide, promoted by sodium hydride. This compound was directly converted into racemic vincamine, upon treatment with acetyl chloride and sodium methoxide in methanol. In detail, acetyl chloride should form an α-acetoxy sulphide that, in the presence of sodium methoxide, should yield the α-keto lactam. Methoxide attack on the lactam would lead to the ring opening in a methyl pyruvate derivative, that undergoes a spontaneous cyclization to (±)-vincamine.

A different approach, still exploiting a **1**-like scaffold as fundamental building block, envisaged the conversion of the ABCD-tetracyclic system, accessed through the Bischler-Napieralski reaction, into the so-called Oppolzer's aldehyde **4**. This efficient strategy has been exploited to a great extent by several research groups, including Langlois and Lounasmaa ones (Langlois et al., 1983; Lounasmaa and Tolvanen, 1990), and is exemplified in Scheme 2.

Scheme 2 should go here.

In both of the cases a tetracyclic compound **2,** substituted in lactam α-position with an ethyl group and a methyl ester, was afforded through the Bischler-Napieralski cyclization of **1**. After the stereospecific reduction of the iminium salt **2**, the methyl ester was reduced to alcohol, that was oxidized to give the required Oppolzer's aldehyde **4** (Scheme 2A). This key intermediate could be converted into vincamine in different ways. Langlois exploited the "Oppolzer's protocol" (Oppolzer et al., 1977), that foresaw a Horner-Wadsworth-Emmons reaction on **4**, to access an α,β-unsaturated methyl ester that, after hydrogenation of the double bond, was cyclized with indole, giving again an heptacyclic lactam **5**. Its α-isonitrosation gave oxime **6**, that could be cleaved leading to oxo-lactam **7**, convertible into vincamine upon methanolysis (Scheme 2B).

On the other hand, Lounasmaa reacted **4** with the enolate obtained from *N*,*N*-dimethylglycine methyl ester, affording an heptacyclic lactam that, upon dehydration, led to heptacyclic enamine **8.** The latter compound was hydrolyzed to the same oxo-lactam (**7**), used in the previous example (Scheme 2C).

A modified version to this strategy was reported by Pfäffli and co-workers (Pfäffli et al., 1975). In that case, starting from a **1**-like intermediate bearing an ethyl and an aldehyde groups on the lactam α-position, the olefination anticipated the Bischler-Napieralski reaction. Therefore, after the reduction of the iminium salt deriving from the cyclization, an intermediate bearing an O-methoxy substituted α,β-unsaturated methyl ester was accessed and converted into (+)-apovincamine, a well-known precursor of (+)-vincamine. Notably, a good control over stereoselectivity was secured through the exploitation of pseudoephedrine as chiral auxiliary for the synthesis of an enantiopure intermediate **1**, that was processed into (+)-vincamine.

Furthermore, the use of the ring contraction protocol, exploited by Oppolzer and Langlois to build vincamine E-cycle, was reported also by Desmaele and collaborators (Desmaele et al., 1997). There, the D ring of the key intermediate **1** was decorated with a CH_2CH_2COOMe chain, instead of the methyl ester used in the previous methods. This difference avoided the olefination reaction after the formation of the ABCD scaffold, because the required C3 carbon chain was already present in the compound. This side chain was exploited to build the heptacyclic lactam **5**-like with the indole nitrogen, that was converted into (+)-vincamine after α-isonitrosation, formation of the oxo-lactam and methanolysis. In Desmaele work, the enantiopurity of the final compound was secured using an enantiopure version of intermediate **1** and was enhanced by the enantioenrichment of compound **3**-like, through recrystallization of its (+)-dibenzoyl-D-tartarate salt.

A similar strategy was also exploited by Alves and co-workers, that took advantage of chiral auxiliaries to access an enantiopure form of **1**, that was then converted into (+)-vincamine (Alves et al. 1997; Alves et al. 1999), and by Gmeiner and collaborators (Gmeiner et al. 1990).

A Bischler-Napieralski cyclization was the key step also in the work by Takano (Takano et al. 1985), aimed at the stereoselective total synthesis of some *Eburna alkaloids*. This protocol took advantage of the (*S*)-trityl-lactone, often called "Takano's lactone", as key chiral synthon (Scheme 3). This reactant can be easily prepared from L-glutamic acid or D-mannitol. Its treatment with propane-1,3-dithiol, in the presence of catalytic *p*-toluenesulfonic acid, afforded a dithiane lactone that, in turn, reacted with tryptamine. The obtained intermediate underwent the Bischler-Napieralski reaction, followed by the reduction of the iminium salt.

Cleavage of the dithiane moiety gave an aldehyde that spontaneously cyclized to (+)-eburnamine, a known precursor of vincamine. Notably, few years later Myers reported an alternative stereoselective strategy toward the synthesis of Takano's lactone (Meyers et al. 1990).

Scheme 3. Should go here

Furthermore, different approaches based on a Pictect-Spengler cyclization, rather than a Bischler-Napieralski reaction, were developed by Hakam and Node, as reported in Scheme 4.

In the first case (Hakam et al. 1987), the key step was a Pictect-Spengler reaction between and enantiopure cyclopropanecarboxyaldehyde and tryptamine, generating in a highly stereoselective fashion a tetracyclic intermediate **10**. Cyanide-mediated nucleophilic ring opening, followed by decarboxymethylation, generated lactam **11**. Hydrolysis of the nitrile gave a carboxylic acid that reacted with indole nitrogen, to afford an hexacyclic lactam **12**. The use of Meerwein reagent and subsequent methanolysis allowed the opening of the pentacyclic lactam, leading to an amino ether that was alkylated with ethyl bromoacetate (**14**). A Dieckmann cyclization guaranteed the formation of the required pentacyclic ABCDE scaffold (**15**), that was converted first into (-)-eburnamonine and then into (+)-apovincamine **16**, through a novel protocol involving a radical bromination. This strategy could be easily adapted toward the obtainment of both vincamine enantiomers (scheme 4a).

On the other hand, Node reported a formal total synthesis of vincamine (Node et al., 1990), taking advantage of the chiral salt **20**, that could be rearranged into into the required alkaloid (Danieli et al., 1981, see paragraph 3). **20** was efficiently accessed in few steps from tryptamine. Tryptamine and the chiral lactone **17** underwent the Pictect-Spengler cyclization, affording a separable 1:l epimeric mixture at C21. Reduction with $LiAlH_4$ gave a primary alcohol **19**, that after mesylation, was alkylated by the nitrogen on C21, generating the required chiral salt **20**, a precursor of vincamine (scheme 4b).

Scheme 4. Should go here

A worth mentioning approach, involving the use of an analogue of **1**, in which the lactam was replaced by an hexacyclic enamide, was developed by Lavilla and co-workers. There, the formation of the *vinca* ABCD system was promoted by a radical mechanism (Lavilla et al. 2001).

Finally, an interesting approach was reported by Shultz and collaborators (Schultz et al. 1997). Analogously to the previously illustrated methodologies, tryptamine was reacted with chiral butyrolactone **21**, to give the corresponding amide. After the protection of the indole nitrogen as *t*-butylamide, the lactone was reduced to diol (**23**) and then oxidized under Swern's conditions to aminoketoaldehyde **24**. Notably, treatment of this intermediate with trifluoroacetic acid promoted a tri-cyclization that, upon base-induced methanol elimination, secured the desired *cis*-fused diene lactam **25** as main product.

Reduction of the diene lactam led to piperidine **26** that, after electrophilic bromination of the enamine-like double bond, was treated with $AgBF_4$ to give (+)-apovincaminal **28**. This compound can be easily converted into (+)-apovincamine and (+)-vincamine (Scheme 5).

Scheme 5. Should go here

2. Pericyclic cyclisation.

Another strategy to build *Vinca*- ABCD tetracyclic scaffold involves the exploitation of pericyclic reactions, such as Diels-Alder or intramolecular [3+2]-cyclizations. These approaches could be envisaged in particular for the formation of the D ring. The works published by Langlois and Genin are really similar each other and were based exactly on this principle (Langlois et al., 1983; Genin et al., 1987).

Both of them employed the tricyclic 3,4-dihydro-*β*-carboline **30** as starting material, and they reacted its imine with an activated diene, in an imino-Diels-Alder reaction. Langlois exploited l-cyano-l,3-butadiene, while Genin used methyl pentadienoate. In both of the cases a mixture of regioisomers (**31**) was accessed and then treated with LDA-HMPA and ethyl iodide, to alkylate the position bearing the electron withdrawing group. This alkylation was completely stereoselective, but led to opposite configurations: in Langlois case, H-21 and the ethyl group were *trans*, while in Genin's work were *cis*. The double bond was hydrogenated and the EWG group was reduced to Oppolzer's aldehyde. Of course, an epimerisation at C20 was required in Langlois protocol. The aldehyde was then converted in (±)-vincamine as reported in the previous paragraph (Scheme 6a).

Scheme 6. Should go here

A similar strategy was exploited few years later by Kaufman and Grieco (Kaufman and Grieco 1994). Their intramolecular imino-Diels-Alder cycloaddition was performed on the key intermediate **34**, synthesized in few steps from the commercially available indole-3-carboxaldehyde. Notably, in this case both the C and E rings were built one-pot. Olefin isomerization led to racemic eburnamonine, that can be then converted into (±)-vincamine (Scheme 6b).

Finally, a Rh(II)-catalyzed intramolecular [3+2]-cycloaddition was the fundamental step in the synthesis of racemic 21-epivincamine (England and Padwa 2007). In detail, α-diazo indolo amide **37** was heated in the presence of $Rh_2(OAc)_4$, generating a rhodium carbenoid, that underwent cyclization with the amido carbonyl group. In this way, a carbonyl ylide was generated and reacted through the expected [3+2]-cycloaddition with the side chain attached on C ring. The cycloadduct **38** was converted into a thiolactam, then reduced with Raney-Nichel. Treatment with Zn/AcOH promoted the ring-opening giving compound **40**, with the *trans* D/E fusion typical of 21-epivincamine. Reaction with MgI_2, followed by oxidation in the presence of Dess Martin Periodinane, afforded the oxo-lactam **41**, convertible into 21-epivincamine through methanolysis (Scheme 6c).

3. Annulation / rearrangements reactions

An alternative strategy to access vincamine and congeners involves annulation reactions and rearrangements, to build the key tetracyclic system. A common approach is the semi-synthesis starting from vincadifformine or its derivatives. This natural alkaloid possesses a peculiar pentacyclic scaffold that could be rearranged to *Vinca*- ABCDE system. For example, Hugel and Levy realized that pyrolysis of vincadifformine derivative **42** led to vincamine, through the mechanism depicted in scheme 7a, involving or the cleavage of the *gem*-hydroxy, methoxycarbonyl function to a carbonyl group, or a radical mechanism (Hugel and Lévy 1984).

Scheme 7. Should go here

Key intermediate **42** could be accessed through vincadifformine ozonisation, as demonstrated by Danieli and collaborators. Then, **42** spontaneously undergoes the same rearrangement, globally leading to the one-pot conversion of (-)-vincadifformine into vincamine upon ozonisation (Danieli et al. 1981) (Scheme 7b).

Also the work published by Magnus and co-workers exploited a similar rearrangement on a synthetic vincadifformine analogue (Scheme 7c). In this case, intermediate **43** reacted with cyanogen chloride, giving an atypical gem-dichloroimine **44**. This compound rapidly rearranged to eburnamonine lactam, through the mechanism depicted in Scheme 7c, when treated with HCl in methanol. Reduction in the presence of $LiAlH_4$, gave (±)-eburnamonine, a known vincamine precursor (Magnus et al 1986).

Finally, an annulation reaction was exploited by Oppolzer et al. to prepare the aforementioned Oppolzer's aldehyde (Scheme 7d). This result was accessed reacting dihydro-*β*-carboline **30** with a silyl ether **49**, synthesized in few steps. In this way, an iminium salt **50** was generated and underwent an intramolecular Mannich reaction, involving cleavage of the Si-O bond and the formation of the required C-C bond. Therefore, a 1:1 mixture of the racemic *cis*- and *trans*-isomers of Oppolzer's aldehyde **4** was afforded, as starting point for the syntheses of vincamine and 21-epivincamine reported in the previous paragraphs. Notably, some efforts were oriented to the obtainment of the enantiopure *cis*-aldehyde required to access (+)-vincamine. To this extent, the undesired stereoisomers were recycled through a reversible Mannich reaction, followed by the crystallization of the required aldehyde salt with (+)-malic acid.

4. Michael-like alkylation for E ring formation.

Finally, two works reporting the formation of vincamine E ring, taking advantage of a Michael-like alkylation of building block **51,** will be presented in this section. **51** was accessed back in 1965 by Wenkert and Wickberg through a Pictect-Spengler-based approach, as an intermediate in the synthesis of eburnamonine and congeners (Wenker and Wickberg 1965).

In the strategy published by Rossey and co-workers (Rossey et al., 1982), Michael-type alkylation of **51** with hydrazine **52** resulted into an iminium salt **53** that, upon reduction with sodium borohydride, gave the correct *cis*-junction between rings C and D (**54**). Hydrolytic cleavage of hydrazine moiety, to favor the formation of E ring, proved to be challenging. However, the obtained iminium salt **55** could be accessed directly from **53**, upon treatment with sodium perborate. **55** was then converted into (±)-vincamine, through reduction with

Zn/AcOH or into (±)-21-epivincamine with sodium borohydride (Scheme 8a). Notably, the protocol was then adapted in a stereoselective fashion, in order to access (+)-vincamine.

A similar methodology was exploited one year later by Szabò and collaborators (Szabò et al., 1983): enamine **51** was alkylated with diethyl methylene malonate, giving an iminium salt that was selectively hydrogenated to the *cis*-ester **57**. The selectivity during the hydrogenation step was guaranteed by steric factors.

Selective hydrolysis of the diester gave an hemiester **58** that, upon treatment with sodium nitrite in aqueous acetic acid, afforded oxime ester **59**. After transesterification to methyl ester **60**, (+)-apovincamine was accessed upon acid treatment. As already mentioned, this natural product could be then easily transformed into (+)-vincamine (Scheme 8b).

Scheme 8. Should go here

Furthermore, Wenkert and collaborators reported that pyrolysis of an indole derivative, substituted in its C3 position with an alkyl chain bearing a masked hexacyclic enamide, afforded (±)-eburnamonine in a one-pot fashion (Wenkert et al 1978).

5. Our approach: semi-synthesis of (+)-vincamine from tabersonine.

In the frame of our interest in the chemistry of indole alkaloids (Danieli et al. 1994; Danieli et al. 2000; Passarella et al. 2003; Sagui et al. 2009; Christodoulou et al. 2013), here we report our efforts toward the synthesis of (+)-vincamine. A semi-synthetic approach, starting from tabersonine (a natural alkaloid extracted from *Voacanga africana* seeds) appeared to be an appealing strategy, because it would overcome the problem of introducing *ex-novo* the stereogenicity in the molecule backbone, and would result convenient from an industrial point of view (US Patent, 3.892.755, 1975).

Furthermore, we determined HPLC conditions for the evaluation of the purity of the final compound. Four impurities (1-3% range) were isolated and their structures elucidated.

As first synthetic step, (-)-tabersonine (**61**) was converted into vincadifformine (**62**) through catalytic hydrogenation (Scheme 9). Treatment of compound **62** in the presence of m-CPBA and HCl, induced the transient formation of hydroxyl derivative **63**, accompanied by the corresponding *N*-oxide **63a** in minor amount.

In basic environment, the former compound **63** rearranged with a formal migration of C-21 from C-7 to C-2, generating the *eburnea* skeleton (Nemes et al. 2007) and accessing (+)-vincamine (**64**) and 16-*epi*-vincamine (**65**) in 8:2 *ratio*. The use of sodium methoxide in methanol guaranteed the epimerization of **65** to **64**. In summary, the complete conversion of tabersonine (**61**) into **64** took place with a total yield of about 50%.

Scheme 9. Should go here

(+)-Vincamine (**64**) was obtained as white solid and its purity was evaluated by HPLC analysis (Figure 2a). The HPLC trace revealed the presence of six impurities (peaks *a-c, e-g*) together with vincamine (90%, peak *d*). Semi-preparative HPLC allowed the isolation of the four major impurities (*b, c, e, g*), that were fully characterized. Peak *c* was identified as 16-epivincamine (**65**) while peaks *b, e* and *g* were recognized as compounds **66**, **67** and **68** respectively (Figure 2b).

Figure 2. Should go here

The structures of all the isolated compounds **64-68** were fixed by spectroscopic analysis (EIMS and NMR). ^{1}H and ^{13}C NMR assignments for compounds **64-68** are reported in Tables 1 and 2, respectively.

Compound **66** presents in the EIMS analysis a molecular peak at 384 m/z. Other characteristic fragments, such as m/z 354, 325 (M-CO_2Me), 297 (M-CO_2Me –CO) and 282 were observed. The last one corresponds to the characteristic vincamine fragment 252 m/z, in which the difference of 30 units is due to the presence of the OMe group on the indole nucleus. ^{1}H-NMR spectrum shows three signals in the aromatic region for the presence of a substituent on the indole portion. Multiplicity of those signals (d, d and dd) and the coupling constants (2 and 9 Hz) confirm the presence of the substituent at position 10 or 11. COSY spectrum evidences two relevant correlations: the signal at 6.94 (d, J = 2 Hz, H-9) presents a cross peak with the signal at δ 6.73 ppm (dd, J = 2 and 9 Hz, H-11) and a second cross peak with the signal at δ 3.90 ppm (s, H-21). NOESY spectrum shows a contact between the signal at 7.07 ppm (H-12) and the singlet at δ 3.77 ppm (CO_2CH_3). A further interaction between signals at δ 6.94 (H-9, d) and δ 2.50–2.55 (H-6) unambiguously confirms the presence of a methoxy residue at C-10 position of compound **66**.

EIMS analysis of **67** and **68** showed the loss of two hydrogens and H_2O respectively from the molecular formula of vincamine. For compound **67**, the presence of C14-C15 double bond is confirmed by the unambiguous signals at δ 5.82 (d, *J*=10.3 Hz, H-15) and δ 5.5 (dd, *J*= 10.3, 1.8 Hz, H-14) in the ^{1}H-NMR spectrum, together with the corresponding signals in the ^{13}C-NMR spectrum at δ 125.6 (C14) and 128.1 (C15). Compound **68** is characterized by a signal at δ 6.16 (s, H-17) and by the signal at δ 7.20 (d, H-12). The downfield effect over the H-12 signal confirms a change in the orientation of the carboxymethyl group deriving from the introduction of the double bond, as appreciable from the 3D structures represented in Figure 3. The corresponding C17 signal appears at δ 128.2 (Table 2).

Figure 3. Should go here.

Table 1 and **Table 2** Should go here

As aforementioned, the HPLC analysis of (+)-vincamine revealed also two further impurities, identified by peaks *a* and *f* in Figure 2a, that being present in very low amount (0.053%) weren't isolated by semi-preparative HPLC. Considering the exploited synthetic pathway, we wondered if they could not be possible by-products deriving from the over-hydrogenation of (**61**), leading to the reduction of the C2-C16 double bond. Once formed as by-product, 2,16-dihydrovincadifformine (**69**) could generate other minor and unexpected compounds, when submitted to the following peroxyacid oxidation, NaOH treatment and methoxide induced epimerization. To confirm if this sort of compounds could have been responsible for peaks *a* and *f* of the HPLC chromatogram, we planned to force the prolonged hydrogenation of tabersonine (**61**), to reduce both the double bonds, and to proceed with the following reactions of the synthetic route, to isolate and characterize the obtained products (Scheme 10).

Scheme 10. Should go here

After 24h under hydrogen atmosphere, vincadifformine disappeared from the reaction mixture and the expected compound **69** was obtained in 87% yield. EIMS analysis showed the molecular ion at m/z 340,

consistent with the complete hydrogenation of vincadifformine on both the double bonds C14-C15 and C2-C16. This result was supported by the ^{13}C-NMR spectrum of **69**, showing 7 CH_2, 4 aromatic CH, 2 CH_3 and 3 aliphatic CH signals (Table 3) (Zsandon et al. 1994). The relative configuration of C2 was confirmed by a NOESY cross-peak between the signal at δ 3.98 (d, H-2) and the signal at δ 1.92–1.81 (m, H-6). The small coupling constant (around 2 Hz) was in agreement with an amplitude of the dihedral angle (H-2-C2-C16-H-16) in the range of 45-55 degrees, compatible with an H-2 and H-3 *syn* configuration.

Compound **69** was then submitted to the same synthetic pathway used to convert vincadifformine **2** into vincamine **64**. Reaction of **69** with m-CPBA in the presence of HCl and the subsequent treatment with NaOH led to the cleavage of the C7-C21 ring junction, according to the literature on a similar compound (Eles et al, 2002), affording the stable derivative **70** (53%, Scheme 10). Its formation was accompanied by compound **71** (26%), deriving from the base-induced epimerization at C16 of compound **69**. **71** is characterized by a molecular ion (EIMS) at m/z 340. The relative configuration of C2 was confirmed by NOESY spectrum, that evidenced a cross-peak between the signals at 3.67 (H-2) and 2.35-2.39 (H-6), suggesting that C2 configuration remained unchanged. Therefore **69** and **71** should be epimers at C16. The relative configuration of C16 was confirmed by the multiplicity of the signal due to H-2 that appears at δ 3.67 as a doublet with a coupling constant of 10 Hz (Table 3). This agrees with the expected *anti*- configuration with H-2. The orientation of the cited hydrogen atoms could be appreciated in the 3D structures of **69** and **71**, in Figure 4.

Figure 4. Should go here

For what concern the main product **70**, the NMR spectra (^{1}H, ^{13}C, Table 3) showed 2 CH_3, 8 CH_2, 5 CH (1 aliphatic and 4 aromatics) and 6 C (one of which at up-field) signals. In particular, the presence of 8 signals (4 C and 4 CH) between δ 111 and 136 indicated the presence of the indole ring. In agreement with our hypothesis, in the HMBC spectrum a CH_2 signal (2.92 – 2.89, H-6) had a correlation with the signal at δ 112.3 ppm (C7), while the quaternary C atom at δ 36.4 ppm (C20) correlated with other 4 CH_2 signals (H-15, H-17, H-19, H-21). Regarding the stereochemistry of **70**, the CH proton H-16 (5.67) seemed to be in axial position (dd, *J* = 12 and 2 Hz). In addition, H-16 presented NOESY cross-peaks with H-6 (2.92 – 2.89), that in turn, was correlated to H-9 (7.53). With compounds **69**, **70** and **71** in our hands, we proceeded with the HPLC analysis.

However, none of them matched with any of the unknown peaks in the chromatogram of Figure 2a, confirming that tabersonine over-hydrogenation was not crucial for the purity of the final compound.

Table 3. Should go here

In summary, the main strategies aimed at the total synthesis of vincamine or its well-known precursors were illustrated in the first part of this review. Then, our contribute, consisting into the development of a rapid and efficient protocol for the semi-synthesis of (+)-vincamine starting from tabersonine, was reported. In particular, the determination of (+)-vincamine purity, as well as the detection of six impurities were achieved through an effective HPLC analytical method. Four impurities, present in 1-3% amount, were isolated and their structures completely elucidated by NMR and MS analysis. The reported results shed new light on the preparation of a relevant natural product that is widely used in human medicine and highlight the importance of the use of plant natural products as advanced building blocks.

EXPERIMENTAL PART

Materials and methods

All available chemicals and solvents were purchased from commercial sources and were used without any further purification. Thin layer chromatography (TLC) was performed using 0.25 mm silica gel precoated plates Si 60-F254 (Merck) visualized by UV-254 light and CAM staining. Purification by flash column chromatography (FCC) was conducted by using silica gel Si 60, 230-400 mesh, 0.040-0.063 mm (Merck). Melting points were determined on a Büchi B450 apparatus and are corrected. HPLC analyses were performed using a 15 cm X 4.6 mm ASCENTIS® C-18 column. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at 589 nm, using a 10 cm x 5 ml cell and c is in g/100 ml. FTIR spectra were recorded on an Agilent Cary 630 infrared spectrophotometer and are reported in frequency of absorption (cm–1). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier 300 (recorded at: 300.13 MHz for ^{1}H; 75.00 MHz for ^{13}C) or Bruker Avance Spectrometer (recorded at: 400.13 MHz for ^{1}H; 100.62 MHz for ^{13}C); chemical shifts are indicated in ppm downfield from TMS, using the residual proton ($CHCl_3$ = 7.28 ppm; acetone = 2.05 ppm; DMSO = 2.45 ppm) and carbon ($CDCl_3$ = 77.0 ppm; acetone = 207.1 and 30.9 ppm) solvent resonances as internal reference. Coupling constants values *J* are given in Hz. All 1D and 2D NMR spectra were collected using the standard pulse sequences available with Bruker Topspin 1.3. High resolution mass spectra were obtained with an electrospray ion-trap mass spectrometer ICR-FTMS APEX II (Bruker Daltonics) by Unitech COSPECT (University of Milano).

Preparation of vincadifformine 62: In a round bottle flask, tabersonine **61** (6.0 mmol, 2.0 g) was added to a mixture of 5% Palladium on charcoal catalyst in EtOH [0.06 M]. The mixture was charged with H_2 and stirred until the theoretical volume of hydrogen was absorbed, at atmospheric pressure. After the completion of the reaction, the catalyst was filtered off through a celite pad. The solvent was then evaporated under reduced pressure and the residue was purified by crystallization from heptane to afford vincadifformine **62** (1.82 g, 89%) as a white solid, mp 101 –102 °C; $[\alpha]_D^{20}$= -646.1 ° (*c*1, $CHCl_3$); ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.23 (s, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 3.71 (s, 3H), 3.14 – 3.11 (m, 1H), 2.91 (t, *J* = 7.6 Hz, 1H), 2.76 (d, *J* = 15.0 Hz, 1H), 2.64 –2.58 (m, 1H), 2.49

(s, 1H), 2.44 (td, *J* = 10.7, 2.9 Hz, 1H), 2.29 (dd, *J* = 15.2, 1.6 Hz, 1H), 1.99 (td, *J* = 11.3, 6.5 Hz, 1H), 1.85 – 1.81 (m, 2H), 1.63 (dd, *J* = 11.2, 4.5 Hz, 1H), 1.58 – 1.53 (m, 1H), 1.28 (td, J = 13.8, 13.3, 4.7 Hz, 1H), 1.04 – 0.97 (m, 1H), 0.68 – 0.57 (m, 4H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 168.7, 167.8, 144.4, 138.6, 128.0, 121.5, 120.9, 110.3, 92.8, 73.2, 56.2, 51.9, 50.9, 50.7, 46.2, 38.8, 33.5, 29.8, 26.2, 22.9, 7.2. Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.58; H, 7.77; N, 8.32.

Preparation of Vincamine 64: HCl 37% (0.4 mL) was slowly added to a stirred solution of vincadifformine **62** (1.50 g, 4.50 mmol) and *m*-chloro-perbenzoic acid (863 mg, 5.00 mmol) in MeOH (9 mL) at room temperature. After the completion of the reaction (6 hours), the pH of the reaction mixture was adjusted at 7.0 by the addition of NaOH [1 M]. The obtained mixture was then diluted with 10% aqueous sodium hydroxide and stirred for additional 4 hours. Then, a solution of sat. $NaHCO_3$ was added and the organic phase was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by FCC - AcOEt/hexane (1:1) - on silica gel. Yields and physical, spectroscopic, and analytical data of vincamine **64**, 16-epivincamine **65**, and impurities **66–68** are reported below.

Vincamine **64**: (989 mg, 62%); white solid, mp 212 –217 °C; $[\alpha]_D^{20}$= +43.5 (*c* 1, pyridine);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 1H), 7.18 – 7.08 (m, 3H), 4.65 (bs, 1H), 3.95 (s, 1H), 3.85 (s, 3H), 3.40 – 3.27 (m, 2H), 3.06 – 2.97 (m, 1H), 2.66 – 2.51 (m, 3H), 2.33 –2.20 (m, 1H), 2.25 (d, *J* = 14.1 Hz, 1H), 2.15 (d, *J* = 14.3 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.55 – 1.39 (m, 3H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 134.8, 132.0, 129.6, 122.4, 120.9, 119.2, 111.0, 106.6, 82.6, 59.9, 55.0, 51.7, 45.3, 45.1, 35.8, 29.6, 25.8, 21.5, 17.5, 8.3. ESI-HRMS *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{26}N_2O_3Na$: 377.1841. Found: 377.1838

Epivincamine **65**: (22.1 mg, 1.3 %); white solid, mp 181–183 °C; $[\alpha]_D^{20}$= -38.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.48 – 7.45 (m, 1H), 7.42 – 7.40 (m, 1H), 7.09 – 7.03 (m, 2H), 3.86 (s, 1H), 3.68 (s, 3H), 3.27 (dd, *J* = 13.5, 6.2 Hz, 1H), 3.18 (td, *J* = 13.6, 12.6, 5.6 Hz, 1H), 3.01 –2.92 (m, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.59 – 2.53 (m, 3H), 2.12 – 2.07 (m, 1H), 2.02 (d, *J* = 14.6 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.48 – 1.41 (m, 1H), 1.36 (dt, *J* = 13.4, 2.8 Hz, 1H), 1.29 – 1.26 (m, 1H), 1.17 (td, *J* = 13.2, 3.6 Hz, 1H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.6, 137.0, 131.6, 129.0, 121.3, 120.0, 117.9, 113.8, 106.2, 84.1,

59.5, 52.4, 51.4, 46.8, 44.9, 36.9 , 29.0, 24.7, 20.9, 16.7, 7.0. ESI-HRMS *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{26}N_2O_3Na$: 377.1841. Found: 377.1845.

10-Metoxy Vincamine **66**: (5 mg, 2.9%); white solid, mp 158–160 °C; $[\alpha]_D^{20}$= +15.7 (*c* 1,$CHCl_3$); ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.07 (d, *J* = 8.9 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.90 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.30 –3.20 (m, 2H), 3.00 –2.91 (m, 1H), 2.60 –2.50 (m, 3H), 2.23 – 2.14 (m, 3H), 1.80 – 1.65 (m, 2H), 1.51 – 1.35 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 173.9, 155.1, 131.7, 130.1, 129.82 , 112.0, 110.9, 105.3, 101.0, 82.8, 59.7, 55.5, 53.1, 51.2, 44.7, 44.5, 35.6, 29.0, 25.6, 20.9, 16.9, 7.1. ESI-HRMS *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{28}N_2O_4Na$: 407.1947. Found: 407.1945.

Δ^{14}- Vincamine **67:** (4 mg, 2.6%); white solid, mp 187–188 °C; $[\alpha]_D^{20}$= +121.9 (*c* 1, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 1H), 7.15-7.10 (m, 3H), 5.82 (d, *J* = 10.3 Hz, 1H), 5.55 (dd, *J* = 10.3 Hz, *J*= 1.8 Hz, 1H), 4.24 (s, 1H), 4.03 (bs, 1H), 3.87 (s, 3H), 3.62-3.51 (m, 1H), 3.50-3.39 (m, 1H), 3.37-3.25 (m, 1H), 3.21-3.06 (m, 2H), 2.85 – 2.65 (m, 1H), 2.38 (d, *J* = 2.9 Hz, 1H), 2.18-2.02 (m, 1H), 1.70 (td, *J* = 14.6, 7.4 Hz, 1H), 1.02 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 134.7, 131.6, 129.7, 128.7, 125.6, 122.4, 120.8, 118.7, 110.7, 106.6, 82.1, 57.6, 54.3, 50.0, 43.5 (2 CH_2), 36.9, 34.8, 16.8, 8.5. ESI-HRMS *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{24}N_2O_3Na$: 375.1685. Found: 375.1689.

Apovincamine **68:** (6 mg, 4.0%); white solid, mp 163–164 °C; $[\alpha]_D^{20}$= +129.9 (*c* 1, pyridine); ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (d, *J* = 7.1 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.16 (s, 1H), 4.18 (s, 1H), 3.95 (s, 3H), 3.30 (d, *J* = 6.1 Hz, 1H), 3.24 (td, *J* = 13.6, 12.5, 5.1 Hz, 1H), 3.07 – 2.99 (m, 1H), 2.61 (d, *J* = 6.8 Hz, 2H), 2.54 (dd, *J* = 16.3, 3.5 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.91 –1.82 (m, 1H), 1.79 – 1.62 (m, 1H), 1.54 (d, *J* = 13.7 Hz, 1H), 1.43 (d, *J* = 13.4 Hz, 1H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.94 (td, *J* = 13.6, 3.3 Hz, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 165.9, 135.2, 130.8, 129.5, 128.8, 128.2, 122.3, 120.6, 118.4, 112.6, 109.0, 55.9, 52.3, 51.5, 45.0, 38.4, 29.2, 27.4, 20.4, 16.4, 8.2. Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.09; H, 7.27; N, 8.24.

Prolonged catalytic hydrogenation: synthesis of 69. Following the procedure for preparation of vincadifformine **62**, the catalytic hydrogenation of **61** was continued for 24 hours. After the standard work up, the crude was purified by FCC on silica gel (PE/AcOEt 10:1), affording pure compound **69** (87 %) as a white solid. mp 79–81°C; $[\alpha]_D^{20}$= + 52 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 4.36 (bs, 1H), 3.98 (d, *J* = 2.1 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.75 (s, 3H), 3.05 (t, *J* = 8.8 Hz, 1H), 3.03 – 2.99 (m, 1H), 2.33 (ddd, *J* = 13.1, 8.7, 1.2 Hz, 1H), 2.20 (q, *J* = 8.8 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.80 – 1.68 (m, 4H), 1.57 – 1.53 (m, 1H), 1.51 – 1.47 (m, 1H), 1.18 – 1.09 (m, 1H), 1.05 (dd, *J* = 13.3, 4.3 Hz, 1H), 0.95 – 0.86 (m, 1H), 0.52 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 150.6, 136.0, 127.7, 123.4, 118.3, 108.9, 75.4, 67.4, 53.6 (2 CH_2), 52.6, 51.6, 43.3, 39.3, 36.4, 34.0, 33.8, 28.5, 22.2, 7.8. Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.20; H, 8.39; N, 8.12

Treatment of 69 according to vincamine production. According to the general procedure for the preparation of vincamine **64**, compounds **70** and **71** were obtained from **69** after purification by flash column chromatography (Hex/EtOAc 98:2) and evaporation of the solvent. Yields and physical, spectroscopic, and analytical data of **70** and **71** are reported below.

70 (53 %); white wax; $[\alpha]_D^{20}$ = + 69.8 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (bs, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.67 (dd, *J* = 11.7 Hz, *J*= 2.1 Hz, 1H), 3.72 (s, 3H), 3.04 – 3.01 (m, 1H), 2.92 – 2.89 (m, 2H), 2.66 (d, *J* = 13.5 Hz, 1H), 2.48 (td, *J* = 10.1, 3.0 Hz, 1H), 2.34 – 2.28 (m, 1H), 2.23 – 2.15 (m, 2H), 1.95 – 1.82 (m, 3H), 1.70 –1.55 (m, 2H), 1.15 – 0.97 (m, 3H), 0.70 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 136.9, 134.6, 130.9, 122.1, 119.7, 118.7, 112.4, 111.3, 61.4, 54.7, 54.5, 52.4, 43.8, 41.5, 37.7, 36.4, 36.0, 26.9, 24.1, 7.8. Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.21; H, 8.34; N, 8.16

71: (26 %); white solid; mp 65 – 66°C; $[\alpha]_D^{20}$= - 155 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.01 (m, 2H), 6.74 (td, *J* = 7.4, 0.8 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.39 (bs, 1H), 3.74 (s, 3H), 3.67 (d, *J* = 10.1 Hz, 1H), 3.14 (td, *J* = 8.7, 2.7 Hz, 1H), 3.06 (d, *J* = 10.9 Hz, 1H), 2.47 – 2.34 (m, 2H), 2.31 – 2.28 (m, 2H), 2.16 (t, *J* = 13.4 Hz, 1H), 2.05 – 1.92 (m, 1H), 1.81 – 1.68 (m, 2H), 1.56 – 1.39 (m, 4H), 1.17 (td, *J* = 13.5, 4.4

Hz, 1H), 1.05 –0.91 (m, 1H), 0.71 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 148.6, 135.1, 127.4, 122.6, 118.9, 110.3, 70.3, 66.8, 54.1, 53.6, 52.6, 51.9, 43.7, 38.6, 36.0, 34.2, 30.1, 26.3, 21.7, 6.8. ESI-MS *m/z* 341.2 $[M + 1]^+$. Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.95; H, 8.20; N, 8.31

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LEGENDS

Figure 1. Structures of (+)-vincamine and structurally related alkaloids.

Scheme 1. Total synthesis of vincamine by Hermann and collaborators, based on a Bischler-Napieralski reaction on the key intermediate **1**.

Scheme 2. A) General scheme for the preparation of Oppolzer's aldehyde **4**, involving a Bischler-Napieralski reaction on the key intermediate **1**. B) Langlois and Oppolzer's protocol for the conversion of **4** into vincamine. C) Elaboration of **4** into racemic vincamine and 16-epivincamine, by Lounasmaa and Tolvanen.

Scheme 3. Takano's approach toward the synthesis of eburnamine-like alkaloids.

Scheme 4. Synthetic approaches based on a Pictect-Spengler cyclisation as key step, developed by Hakam (a) and Node (b).

Scheme 5. Shultz's approach toward the synthesis of (+)-apovincamine and (+)-vincamine.

Scheme 6. Main examples of vincamine total synthesis through pericyclic mechanisms.

Scheme 7. Schematic representation of the approaches based on an annulation reaction or rearrangements.

Scheme 8. Synthesis of vincamine from key enamine **51**.

Scheme 9. Synthesis of (+)-vincamine (**64**) from tabersonine (**61**).

Figure 2. a) HPLC profile of crude (+)-vincamine (**64)**. HPLC conditions: isocratic with 1mL/min flow. Eluent: 65% water, 18% ACN, 17% THF with 1% of ammonium acetate. Column: Polaris C18 250 x 4.6mm (particle size: 5µm). Column oven: 30°C. Wavelength: 272 nm. b) Structures of compounds **66** – **68**.

Figure 3. 3D structures of compounds **64** and **68**.

Scheme 10. Prolonged catalytic hydrogenation of tabersonine (**61**) and subsequent treatment as done for vincadifformine.

Figure 4. 3D structures of compounds **69** and **71**, displaying with the blue arrows the observed NOESY correlations. In compound **71** no H-2 – H-16 cross-peak could be observed (red arrow), accordingly to the hypothesized *anti*-relationship.

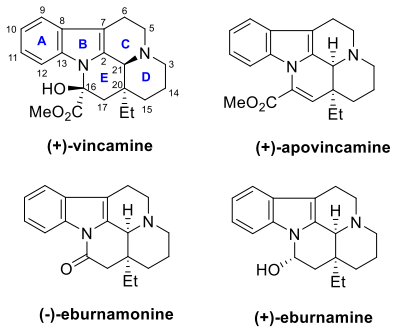
Table 1. ^{1}H-NMR (ppm) assignment for compounds **64** – **68.**

Table 2. ^{13}C-NMR (ppm) assignment for compounds **64 – 68**.

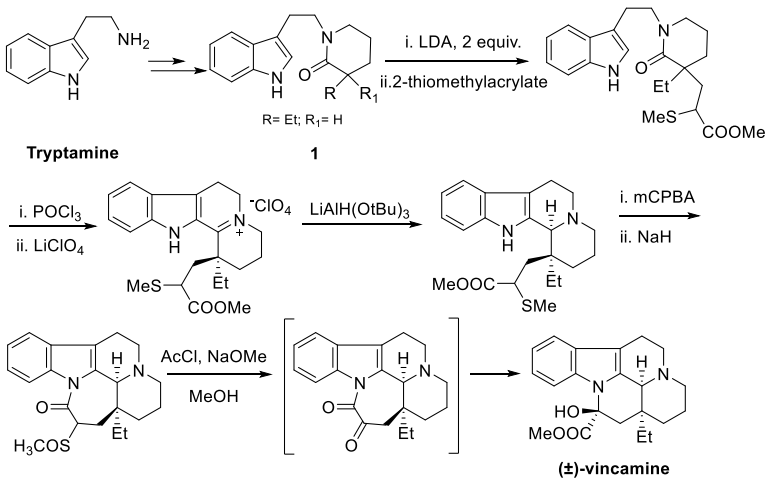
Table 3. ^{1}H- and ^{13}C-NMR of compounds **69**, **71** and **70.**

FIGURES AND TABLES

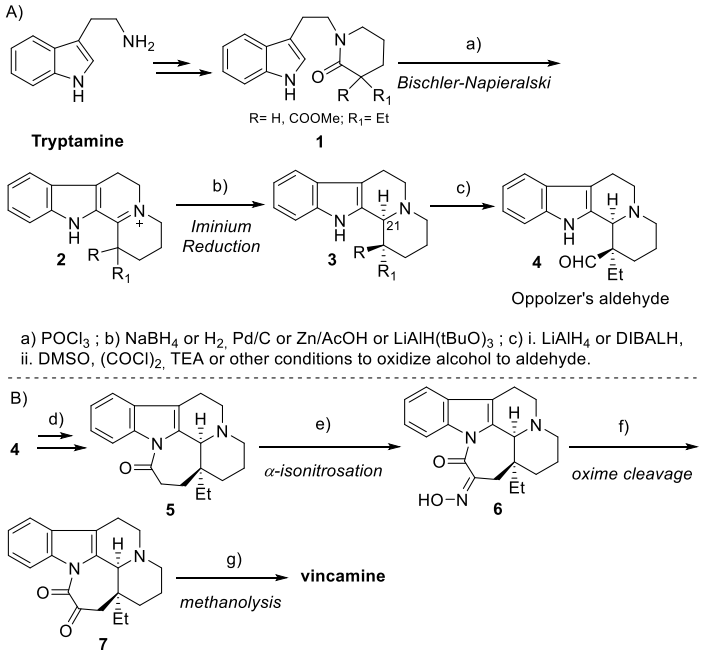
Figure 1.



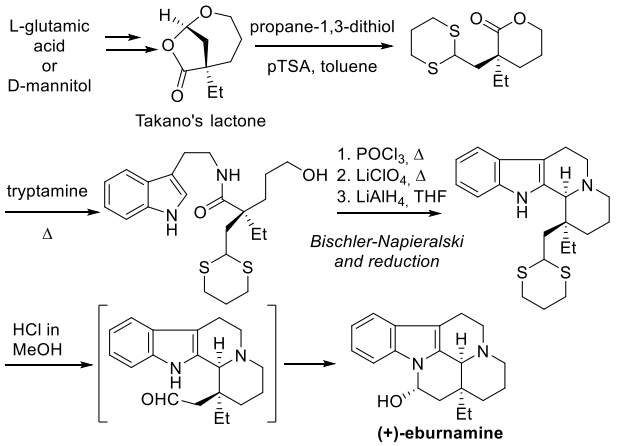
Scheme 1



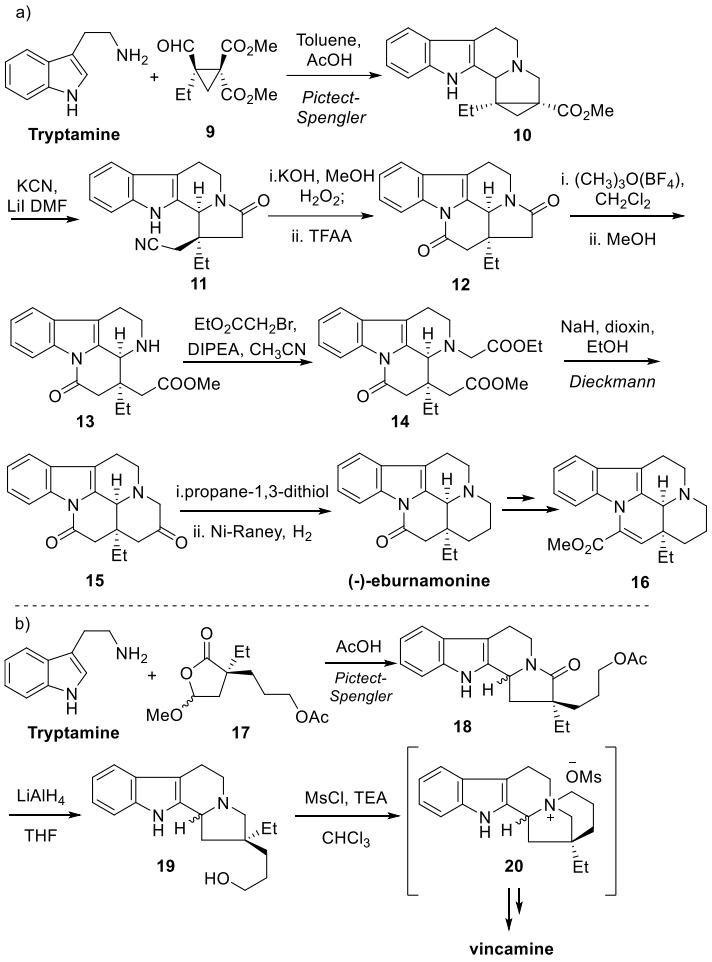
Scheme 2.



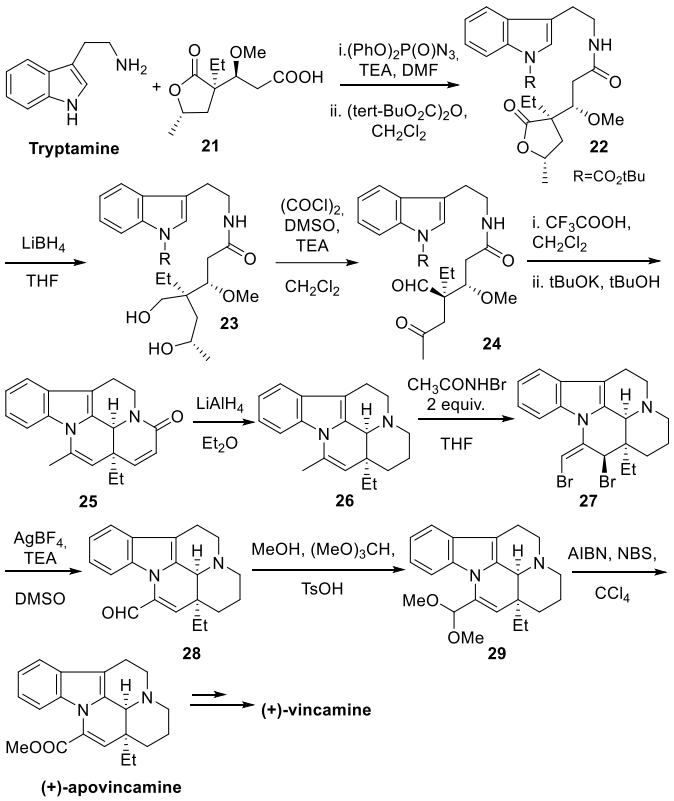
Scheme 3.



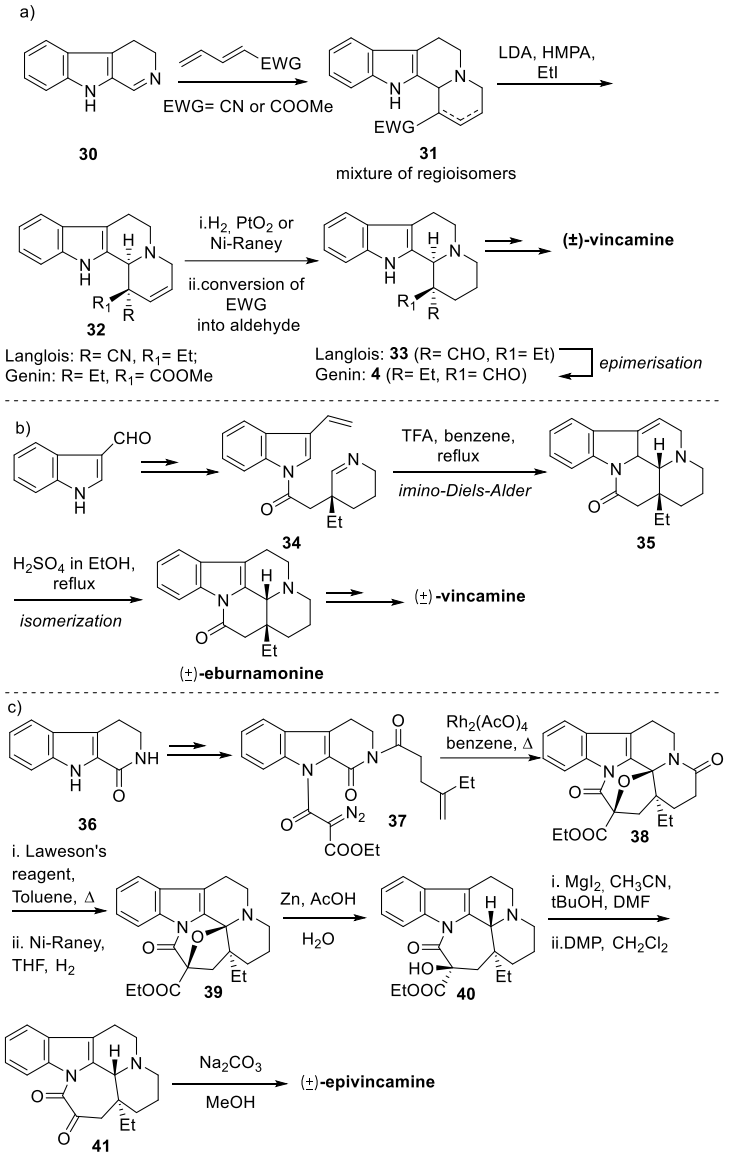
Scheme 4.


a)
Tryptamine
9
Toluene, AcOH
Pictect-Spengler
10
KCN, LiI DMF
11
i.KOH, MeOH
H2O2;
ii. TFAA
12
i. (CH3)3O(BF4), CH2Cl2
ii. MeOH
13
EtO2CCH2Br, DIPEA, CH3CN
14
NaH, dioxin, EtOH
Dieckmann
15
i.propane-1,3-dithiol
ii. Ni-Raney, H2
(-)-eburnamonine
16
b)
Tryptamine
17
AcOH
Pictect-Spengler
18
LiAlH4
THF
19
MsCl, TEA
CHCl3
20
vincamine

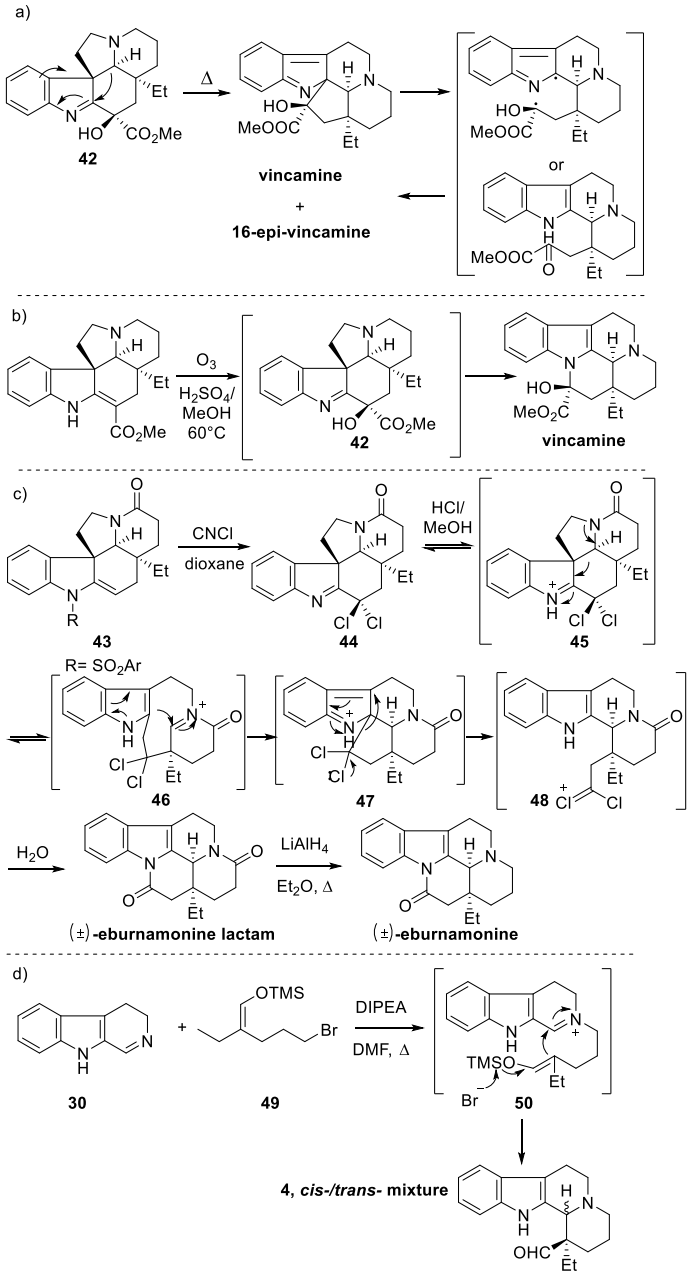
Scheme 5.


Tryptamine
21
i.(PhO)2P(O)N3, TEA, DMF
ii. (tert-BuO2C)2O, CH2Cl2
22
R=CO2tBu
LiBH4
THF
23
(COCl)2, DMSO, TEA
CH2Cl2
24
i. CF3COOH, CH2Cl2
ii. tBuOK, tBuOH
25
LiAlH4
Et2O
26
CH3CONHBr 2 equiv.
THF
27
AgBF4, TEA
DMSO
28
MeOH, (MeO)3CH,
TsOH
29
AIBN, NBS,
CCl4
(+)-vincamine
(+)-apovincamine

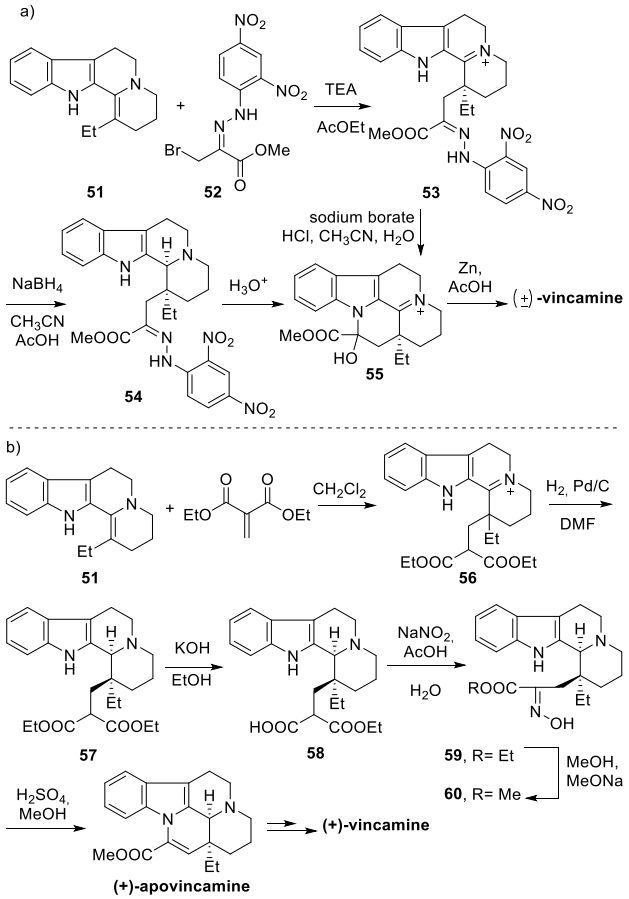
Scheme 6.


a)
EWG
EWG= CN or COOMe
LDA, HMPA,
EtI
30
31
mixture of regioisomers
i.H2, PtO2 or
Ni-Raney
ii.conversion of
EWG
into aldehyde
(±)-vincamine
32
Langlois: R= CN, R1= Et;
Genin: R= Et, R1= COOMe
Langlois: 33 (R= CHO, R1= Et)
Genin: 4 (R= Et, R1= CHO)
epimerisation
b)
CHO
TFA, benzene,
reflux
imino-Diels-Alder
34
35
H2SO4 in EtOH,
reflux
isomerization
(±)-vincamine
(±)-eburnamonine
c)
Rh2(AcO)4
benzene, Δ
36
37
38
i. Laweson's
reagent,
Toluene, Δ
ii. Ni-Raney,
THF, H2
Zn, AcOH
H2O
i. MgI2, CH3CN,
tBuOH, DMF
ii.DMP, CH2Cl2
39
40
Na2CO3
MeOH
(±)-epivincamine
41

Scheme 7.


a)
Δ
HO
CO2Me
42
HO
MeOOC
Et
vincamine
+
16-epi-vincamine
or
MeOOC
O
b)
O3
H2SO4/
MeOH
60°C
CO2Me
HO
MeO2C
vincamine
c)
CNCl
dioxane
HCl/
MeOH
R
43
Cl
44
45
R= SO2Ar
46
47
48
H2O
LiAlH4
Et2O, Δ
(±)-eburnamonine lactam
(±)-eburnamonine
d)
OTMS
Br
DIPEA
DMF, Δ
30
49
TMSO
50
4, cis-/trans- mixture
OHC

Scheme 8.



Scheme 9

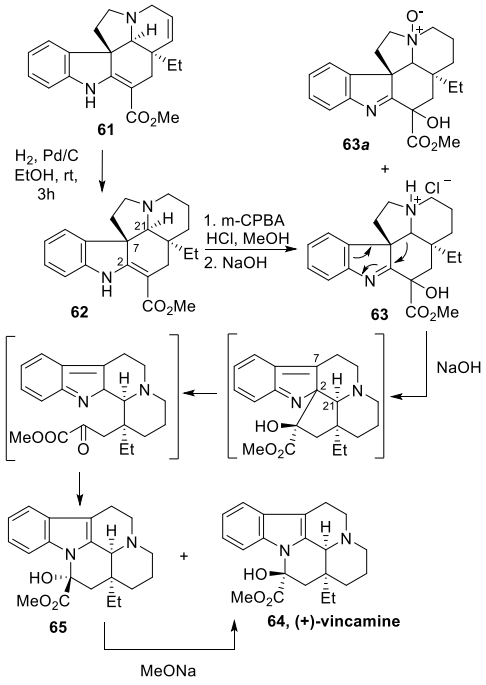
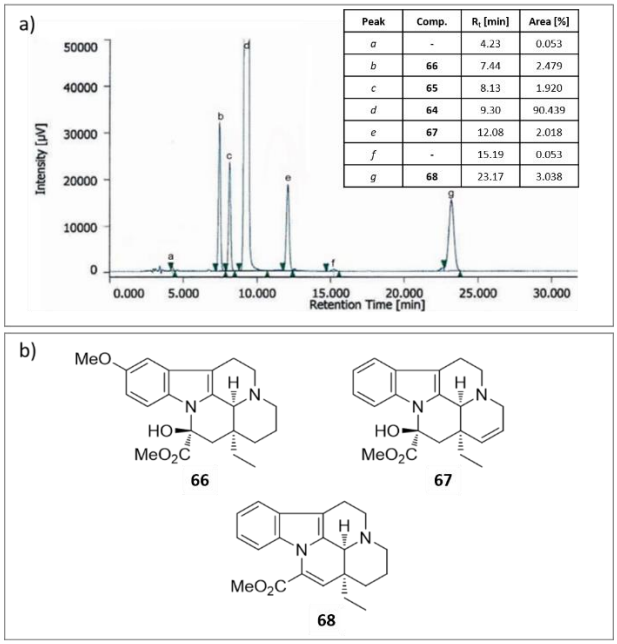
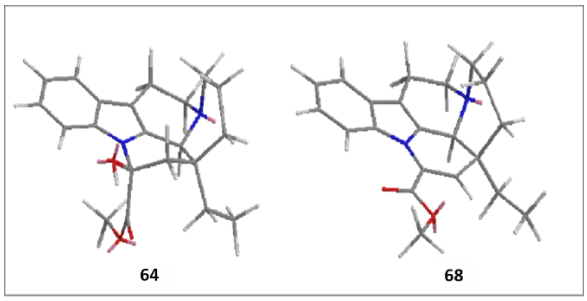


Figure 2



Peak	Comp.	R_t [min]	Area [%]
a	-	4.23	0.053
b	**66**	7.44	2.479
c	**65**	8.13	1.920
d	**64**	9.30	90.439
e	**67**	12.08	2.018
f	-	15.19	0.053
g	**68**	23.17	3.038

Figure 3



Scheme 10

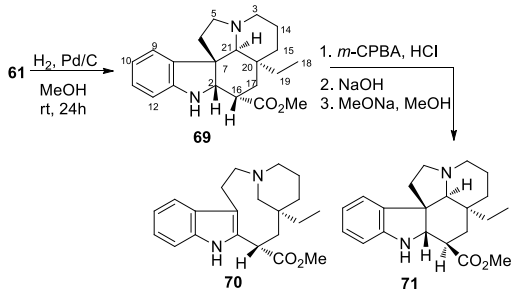


Figure 4

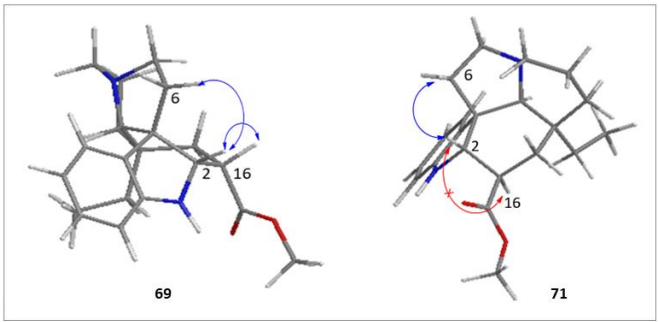
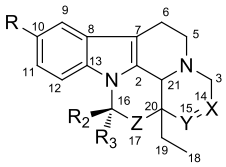


Table 1

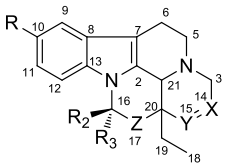


64: R=H, R_2= OH, R_3= CO_2Me, X= CH_2, Y= CH_2, Z= CH_2
65: R=H, R_2=CO_2Me, R_3= OH, X= CH_2, Y= CH_2, Z= CH_2
66: R= OMe, R_2= OH, R_3= CO_2Me, X= CH_2, Y= CH_2, Z= CH_2
67: R=H, R_2= OH, R_3= CO_2Me, X= CH, Y= CH, Z= CH_2
68: R=H, R_2= CO_2Me, X= CH_2, Y= CH_2, Z= CH, Δ_{16}

Compound	**64**	**65**	**66**	**67**	**68**
HPLC peak / **Signal**	***d***	***c***	***b***	***e***	***g***
3	2.50–2.66	2.53–2.59	2.50–2.60	3.25-3.37 3.06-3.21	2.61
5	3.27–3.40	3.18 3.27	3.20–3.30	3.51-3.62 3.39-3.50	3.24 3.30
6	2.51–2.60 2.97–3.06	2.92–3.01 2.50–2.55	2.50–2.55 2.91–3.00	2.65–2.85 3.06-3.21	2.54 2.99–3.07
9	7.50-7.53	7.40–7.42	6.94	7.52-7.41	7.44
10	7.08–7.18	7.03–7.09	-	7.10–7.15	7.07–7.14
11	7.08–7.18	7.03–7.09	6.73	7.10–7.15	7.07–7.14
12	7.08–7.18	7.45–7.48	7.07	7.10–7.15	7.20
14	1.39–1.53 1.67–1.81	1.36 1.65–1.76	1.35–1.43 1.65–1.78	5.55	1.43 1.62–1.79
15	1.45–1.55 1.67–1.75	1.17 1.26–1.29	1.45–1.51 1.65–1.80	5.82	0.94 1.54
17	2.15 (AB) 2.25 (AB)	2.02 (AB) 2.73 (AB)	2.23–2.14	2.38	6.16
18	0.94	0.93	0.93	1.02	1.03
19	1.35–1.50 2.20–2.33	1.40–1.48 2.07–2.12	1.41–1.48 2.23–2.14	1.70 2.02–2.18	1.82-1.91 1.91-2.01

21	3.95	3.86	3.90	4.24	4.18
OCH_3	3.85	3.68	3.77	3.87	3.95
Ar-OCH_3	--	--	3.81	--	--

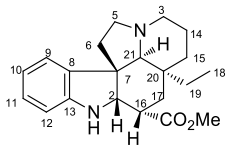
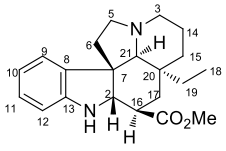
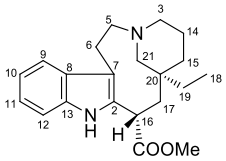
Table 2



64: R=H, R_2= OH, R_3= CO_2Me, X= CH_2, Y= CH_2, Z= CH_2
65: R=H, R_2=CO_2Me, R_3= OH, X= CH_2, Y= CH_2, Z= CH_2
66: R= OMe, R_2= OH, R_3= CO_2Me, X= CH_2, Y= CH_2, Z= CH_2
67: R=H, R_2= OH, R_3= CO_2Me, X= CH, Y= CH, Z= CH_2
68: R=H, R_2= CO_2Me, X= CH_2, Y= CH_2, Z= CH, Δ_{16}

Compound	**64**	**65**	**66**	**67**	**68**
HPLC peak / **Signal**	***d***	***c***	***b***	***e***	***g***
2	129.6	129.0	129.8	131.6	130.8
3	45.3	44.9	44.7	43.5	45.0
5	51.7	51.4	51.2	50.0	51.5
6	17.50	16.7	16.9	16.6	16.4
7	106.6	106.2	105.3	106.3	109.0
8	132.0	131.6	130.1	129.7	135.2
9	119.2	117.9	101.0	118.7	118.4
10	120.9	120.0	155.1	120.8	120.6
11	122.4	121.3	112.0	122.4	122.3
12	111.0	113.8	110.9	110.7	112.6
13	134.8	137.0	131.7	134.7	129.5
14	21.5	20.9	20.9	125.6	20.4
15	25.8	24.7	25.6	128.7	29.2
16	82.6	84.1	82.8	82.1	128.8
17	45.1	46.8	44.5	43.5	128.2
18	8.3	7.0	7.1	8.5	8.2
19	29.6	29.0	29.0	34.8	27.4
20	35.8	36.9	35.6	36.9	38.4
21	59.9	59.5	59.7	57.6	55.9
CO	175.2	172.6	173.9	173.1	165.9
OCH_3	55.0	52.4	55.5	54.3	52.3
Ar-OCH_3	--	--	53.1	--	--

Table 3

	 **69**		 **71**		 **70**	
	69		**71**		**70**	
Signal	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
2	67.4	3.98	66.8	3.67	134.6	--
3	52.6	2.99 - 3.03 1.81 – 1.85	53.6	3.06 1.92-2.05	54.5	3.01 – 3.04 2.48
5	53.6	3.05 2.20	52.6	3.14 2.28 – 2.31	54.7	2.66 2.28– 2.34
6	43.3	2.33 1.81 – 1.92	38.6	2.35 – 2.39 1.55 – 1.50	26.9	2.89– 2.92
7	53.6		54.1		112.4	--
8	136.0		148.6		130.9	--
9	123.4	7.07	122.6	7.07	118.7	7.53
10	118.3	6.71	118.9	6.74	119.7	7.11
11	127.7	7.03	127.4	7.04	122.1	7.17
12	108.9	6.55	110.3	6.66	111.3	7.37
13	150.6	-	135.1		136.9	--
14	22.2	1.69 – 1.67 1.53 – 1.57	21.7	1.73 – 1.81 1.56 – 1.50	24.1	1.96– 1.88 1.65– 1.56
15	36.4	1.47 – 1.51 1.05	34.2	1.72 – 1.68 1.17	37.7	1.70– 1.55 1.12– 1.05
16	39.3	3.96 – 3.90	43.7	2.44 – 2.47	41.5	5.67
17	28.5	1.80– 1.71	26.3	2.16 1.44 – 1.39	43.8	2.23 1.93
18	7.8	0.52	6.8	0.71	7.8	0.70
19	34.0	1.03 – 1.18 0.86 – 0.95	30.1	1.50 – 1.45 0.91-1.05	36.0	1.15– 0.97
20	33.8		36.0		36.4	--
21	75.4	1.69	70.3	2.28	61.4	2.16 1.83
OCH_3	51.6	3.75	51.9	3.74	52.4	3.72
CO	176.8		175.8		177.0	--

NH		4.36		4.39		8.65