

Catalytic N-Sulfonyliminium Ion-Mediated Cyclizations to α -Vinyl-Substituted Isoquinolines and β -Carbolines and Applications in Metathesis

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Catalytic $Sn(OTf)_2$ -induced cyclization of linear, aryl-containing allylic *N*,*O*-acetals produced vinylsubstituted tetrahydroisoquinolines and tetrahydro-1*H*- β -carbolines. The usefulness of the vinyl moiety in the resulting products was demonstrated via the synthesis of various key building blocks for alkaloid structures. The α -vinyl moiety was utilized in a [2,3] signatropic rearrangement, in ring-closing metathesis and a cross-metathesis-based synthesis of vincantril, an antianoxia agent, and a synthetic member of the vincamine type natural products.

Introduction

Isoquinolines and β -carbolines are two classes of important biologically active structural moieties and are substructures of many alkaloids present in different plants.¹ α -Substituted tetrahydroisoquinolines and tetrahydro-1*H*- β -carbolines are of prime importance for the construction of isoquinoline- and β -carboline-containing compounds.² The Pictet–Spengler³ and Bischler–Napieralski⁴ condensations have been used to synthesize the majority of α -substituted tetrahydroisoquinolines and tetrahydro-1*H*- β -carbolines. For α -vinyl-substituted building blocks such as **1** and **2**, however, both of these condensation-based approaches are not suitable (Chart

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CHART 1. α -Vinyl-Substituted Isoquinolines and Carbolines



1). It has been demonstrated that only substituted vinyl moieties can be introduced through the Pictet–Spengler condensation⁵ or the Bischler–Napieralski condensation/ reduction sequence.⁶ Alternative methods to introduce a vinyl substituent are the addition of vinyllithium, vinyl Grignards, or vinyl cuprates to 3,4-dihydroisoquinolines

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(3),⁷ or a Pd-catalyzed hydrostannylation-cyclization sequence⁸ with allenamides such as 4. Nevertheless, a general entry into α -vinyl-substituted tetrahydroiso-quinolines 1 and tetrahydro-1*H*- β -carbolines 2 would be highly useful. Due to the poor accessibility of this structural motif, few applications of α -vinyl-substituted tetrahydroisoquinolines and tetrahydro-1*H*- β -carbolines have been reported.^{7a,b}

Considering the growing applications of metathesis reactions, α -vinyl-substituted tetrahydroisoquinolines and tetrahydro-1*H*- β -carbolines, in particular, would be highly useful as versatile building blocks and precursors in metathesis-based construction of isoquinoline- and β -carboline-containing biologically active products. This paper describes our efforts on *intra*molecular aromatic additions onto linear, allylic *N*-sulfonyliminium ions.⁹⁻¹¹ Thus, cyclization of the allylic iminium ion **9** derived from the allylic *N*,*O*-acetals **10** would lead to the efficient construction of α -vinyl-substituted tetrahydroisoquinolines of type **8** and the analogous tetrahydro-1*H*- β carbolines (Scheme 1). The required *N*,*O*-acetals **10** are

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TABLE 1. Precursor Synthesis

H ₂ ľ	R^{Ar}	$\begin{array}{c} \text{-1}\text{SO}_2\text{Cl} \\ \text{Et}_3\text{N} \\ \text{CH}_2\text{Cl}_2 \\ 0 \ ^\circ\text{C} \end{array} \begin{array}{c} \text{Ar} \\ \text{HN} \\ \text{PG} \\ \text{R}^1 \end{array}$	BnO Pd(OAc) ₂ , Et ₃ N, Meo	dppp BnO	Ar R ¹ PG			
		12-23		24-35				
entry	\mathbb{R}^1	Ar	PG	sulfonamide (% yield) ^a	acetal (% yield) ^a			
1	Н	$m-MeOC_6H_4$	Ts	12 (94)	24 (91)			
2	Н	Ph	Ts	13 (91)	25 (89)			
3	Н	$m-{ m MeC_6H_4}$	Ns	14 (58)	26 (98)			
4	Η	m-ClC ₆ H ₄	Ns	15 (79)	27(100)			
5	Η	$p-MeOC_6H_4$	Ns	16 (87)	28 (96)			
6	Me^b	m-MeOC ₆ H ₄	Ns	$17 (70)^b$	29 $(65)^b$			
7	Η	3,4-(MeO) ₂ C ₆ H ₃	Ns	18a (96)	30a (94)			
8	Η	3,4-(MeO) ₂ C ₆ H ₃	2,4-dNs	18b (55)	30b (42)			
9	Me^b	3,4-(MeO) ₂ C ₆ H ₃	Ns	$19 (55)^b$	31 $(58)^b$			
10	CO_2Me	3,4-(MeO) ₂ C ₆ H ₃	Ns	20 (69)	32(51)			
11	Η	2-furanyl	Ns	21 (54)	33 (85)			
12	Η	3-indolyl	Ts	22 (98)	34 (74)			
13	$\mathrm{CO}_2\mathrm{Me}$	3-indolyl	Ts	23 (86)	35(64)			
^a Isolated yields. ^b Racemic material was used.								

readily accessible via Pd-catalyzed condensation of the corresponding sulfonamides 11 with alkoxyallenes.^{11,12}

Results and Discussion

The required phenethylamines were either commercially available or synthesized through condensation of the desired aryl aldehyde with nitromethane or nitroethane, followed by LiAlH₄ reduction of the resulting nitrostyrene following literature procedures.¹³ Sulfonylation of the amines with either *p*-toluenesulfonyl chloride or *p*-nitrobenzenesulfonyl chloride afforded the desired sulfonamides **12–23** (Table 1).

The allylic *N*,*O*-acetal cyclization precursors (24–35) were synthesized through a Pd-catalyzed amidation of the sulfonamides 12-23 with benzyloxyallene, a reaction that was previously discovered in our group.^{11,12} The yields of the amidopalladation with benzyl propadienyl ether ranged from reasonable (42-65%) in the case of the α -substituted amides 17, 18b, 19, 20, and 23 (Table 1, entries 6, 8–10, and 13) to good or excellent (74–100%) for the other sulfonamides (12-16, 18a, 21, and 22, entries 1-5, 7, 11, and 12). The linear allylic *N*,*O*-acetal 24 was chosen as a test substrate for the determination of optimal reaction conditions for the cyclization onto the allylic iminium ion. Because cationic cyclizations of aromatic nucleophiles are essentially cycloisomerizations, a catalytic amount of acid would in principle be sufficient to effect cyclization.^{9d} Therefore, it is remarkable that even today the use of stoichiometric acid to induce aromatic cyclizations is common practice, while catalytic methods may well be used. To establish a good (catalytic) protocol, both stoichiometric and catalytic amounts of protic and Lewis acids were tested (Table 2). A useful

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⁽¹⁰⁾ For aromatic N-sulfonylamidoalkylations, see: (a) Weinreb, S.
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⁽¹³⁾ For aryl aldehydes, see: (a) Dowd, C. S.; Herrick-Davis, K.; Egan, C.; DuPre, A.; Smith, C.; Teitler, M.; Glennon, R. A. J. Med. Chem. **2000**, 43, 3074. For indole aldehydes, see: (b) Güngör, T.; Malabre, P.; Teulon, J.-M.; Camborde, F.; Meignen, J.; Hertz, F.; Virone-Oddos, A.; Caussade, F.; Cloarec, A. J. Med. Chem. **1994**, 37, 4307.



Lewis acid was found in the form of $Sc(OTf)_3^{14}$ (entry 1), which is well-known to activate acetals in a catalytic fashion. Indeed, the use of 10 mol % induced a smooth cyclization to the α -vinylisoquinoline **36** in 74% isolated yield. A catalytic amount of $Sn(OTf)_2^{15}$ showed an even better conversion and afforded the product in 87% yield in 1 h (entry 2).

While the use of this tin-based Lewis acid is not preferred from an environmental point of view, it has some advantages over Sc(OTf)₃. It is difficult to keep the hygroscopic $Sc(OTf)_3$ free of water, and besides $Sc(OTf)_3$ has to be freed from triflic acid by removal with water. Therefore, it is more convenient to keep $Sn(OTf)_2$ at a satisfactory quality level than $Sc(OTf)_3$. To reduce the environmental impact of the use of tin, we showed that the initial amount of 10 mol % could even be reduced to 2 mol % without loss of conversion. Trifluoroacetic acid (containing 5% of trifluoroacetic anhydride (TFAA)) as a protic acid gave a high conversion as well, to yield 36 in 83% (entry 3). To prove the catalytic action of a protic acid, 5 mol % of triflic acid was also used.¹⁶ This gave a good conversion and led to the product in 76% vield after 4 h (entry 4). A potentially useful novel medium for these types of cyclizations is the Lewis acidic chloroaluminate ionic liquids.¹⁷ By adding 1.5 equiv of a 2 M solution of the trimethylammonium-based chloroaluminate, [TMAH]-[Al₂Cl₇], ionic liquid to a solution of the precursor in dichloromethane at -50 °C, a fast disappearance of the starting material was observed. Although these conditions also led to considerable decomposition of the acetal and possible cleavage of the methyl ether,^{17b} the desired product could be isolated in a somewhat disappointing 42% yield (entry 5). Considering these results, it was concluded that the use of catalytic $Sn(OTf)_2$ in dichloromethane at 0 °C formed the most promising and attractive reaction conditions for this type of cyclization.

Next, a wider range of linear, allylic acetals (25-35) were subjected to these reaction conditions (Table 3). The





^{*a*} All cyclizations were carried out with Sn(OTf)₂ (2 mol %) or TFA (4 equiv) in CH₂Cl₂ (0.05 M) from 0 °C to room temperature with reaction times ranging from 1 to 6 h as indicated by TLC except for entry 3. ^{*b*} Yields after column chromatography; diastereoisomeric ratios were determined from the spectral data of the crude reaction mixture. ^{*c*} In [BMIm][NTf₂] ionic liquid at 50 °C for 1 h. ^{*d*} Determined by ¹H NMR. ^{*e*} Racemic material was used.

first entry shows the cyclization experiments with the unsubstituted aryl precursor **25**. All attempts to cyclize this precursor failed, as was also observed for the slightly deactivated, chloro-substituted aryl precursor **27**, shown in entry 4. In general, when cyclization does not occur, one typically isolates a mixture of free sulfonamide and enamide (through rearrangement, vide infra) for short reaction times. After longer periods, both the N,O-acetal

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⁽¹⁵⁾ Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. Tetrahedron **1984**, 40, 1381.

⁽¹⁶⁾ For a review on triflic acid: Howells, R. D.; McCown, J. D. Chem. Rev. 1977, 77, 69.

⁽¹⁷⁾ For a review on ionic liquids, see: (a) Wasserscheid, P.; Keim,
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Kemperman, G. J.; Roeters, T. A.; Hilberink, P. W. Eur. J. Org. Chem.
2003, 1681 and references cited.

and enamide are hydrolyzed to the amide. To study the minimum nucleophilicity needed, a slight increase in nucleophilicity of the aryl-part compared to an unsubstituted benzene moiety was required. Therefore, the m-methyl-substituted precursor 26 was prepared, containing an aryl moiety with electronic properties between those of a *m*-methoxy and an unsubstituted aryl (entries 2 and 3). Entry 2 shows that with various regular methods no cyclization was observed and that only cleavage of the acetal occurred. Some product formation could be observed and measured with $^1\!\mathrm{H}\,\mathrm{NMR}$ when the precursor was treated with $Sc(OTf)_3$ in the polar, nonnucleophilic butylmethylimidazolium-based ionic liquid [BMIm][N(Tf)₂] at 50 °C (entry 3). The importance of an electron-donating substituent at the meta-position was again underlined by the failed attempts to cyclize precursor **28** with a *p*-methoxy-substituted benzene ring (entry 5). It was clear from these pioneering experiments that an electron-rich aromatic system was a minimum requirement for cyclization. Cyclization of the α -methylsubstituted *m*-methoxyphenethylamide **29** afforded the product 38 in 79% yield as a mixture of diastereoisomers in a ratio of 86:14 with $Sn(OTf)_2$ (entry 6). The major diastereoisomer was identified as the cis-isomer from ¹H NOE NMR experiments (10% enhancement of the internal vinylic proton upon irradiation of the α -methyl and 3% enhancement vice versa).

The use of 4 equiv of TFA led to an almost quantitative yield of the product 38, but in a diastereoisomeric ratio of about 1:1 (entry 7). An additional methoxy substituent at the para-position gave an excellent cyclization with 2 mol % of $Sn(OTf)_2$ to afford **39a** in an isolated yield of 92% (entry 8) and gave **39b** in 74% yield when a 2,4dinitrobenzenesulfonyl protecting group was used (entry 9). Introduction of an α -methyl or an α -methyl ester substituent in these precursors led to high yields of both 40 (88%, entry 10) and 41 (99%, entry 11). Rather surprisingly, both cyclizations proceeded without any diastereomeric preference and led to approximately 1:1 mixtures of isomers. Changing to for example TFA for the cyclization did not make much difference (entry 12). Finally, alternative electron-rich aryl nucleophiles were tested. The 2-furanyl moiety (33) did not cyclize with different conditions (entry 13), thus again showing the narrow, delicate balance between allylic iminium ion reactivity and nucleophilicity of the aryl moiety. As anticipated, the strongly nucleophilic indolvl moiety cyclized smoothly in the case of the unsubstituted tryptamine system to give 42 in 65% yield (entry 14) and provided 43, derived from tryptophan in 80% yield as a 57:43 mixture of diastereoisomers (entry 15). The reluctance of the nonactivated aromatics to cyclize onto the allylic iminium ions prompted us to investigate such systems in more detail. In particular the result observed in entry 3 of Table 3 showed the need for higher temperatures, while cleavage of the acetal should be avoided. As a stabilizing, nonnucleophilic (thus nonacetal cleaving) medium Ac₂O was chosen, containing up to 20 equiv of HOAc as the acid. In this way an absolute waterfree solvent was created, hopefully allowing for higher temperatures. The results of these experiments are depicted in Scheme 2.

Precursor 26, bearing a *m*-methyl substituent, was gradually heated in this solvent mixture. No reaction

SCHEME 2. Cyclization vs Enamide Formation



SCHEME 3. Pathways for the Allylic Iminium Ion



occurred up to 110 °C, but above this temperature (120-130 °C), all starting material disappeared to form a new single spot on TLC overnight. The isolated product turned out to be enamide 45, which was formed as a single (E)isomer in almost quantitative yield. To force cyclization, the temperature was also raised to 150 °C. Unfortunately, at this temperature both the N,O-acetal and the enamide decomposed mainly into the amide. Also precursor 28, bearing a *p*-methoxy substituent, was stable up to 110 °C and above that temperature gave clean formation of the enamide **46** in 94% yield. Applying the same conditions, precursor 29 cyclized into the desired isoquinoline 38 in 66% isolated yield as a 70:30 mixture of diastereoisomers. Under these conditions, a directing α -methyl substituent (44) also only showed formation of enamide 47 in 97% yield. A number of observations from the previous results can be translated into some important mechanistic implications. The different pathways that are possible from the allylic iminium ion are outlined in Scheme 3.

The first step in the cyclization is $Sn(OTf)_2$ -mediated formation of the *N*-sulfonyliminium ion **49**.¹⁸ An undesired pathway would be the formation of the oxycarbenium ion **50** (the sulfonamide moiety acts as the leaving group), which theoretically can go back to the *N*,*O*-acetal, but most probably will react further to give decomposition. In the case of activated (electron rich) aryl moieties, the iminium ion **49** gives instant cyclization to the desired product (**51**). For less reactive aryls, the iminium ion chooses a route that leads to the thermodynamically most stable product. This is the pathway to the enamide **52**, which proceeds via rearrangement of the *N*,*O*-acetal **48**, or via attack of a nucleophile present in the solvent (e.g.

⁽¹⁸⁾ A related, oxygen-substituted allylic *N*-acyliminium ion has been used in [4+3] cycloadditions, see: Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. J. Am. Chem. Soc. **2001**, *123*, 7174.



^a Reagents and conditions: (a) PhSK, MeCN, rt (75% for **39a** and 83% for **39b**); (b) (CH₂O)_n, HCO₂H, reflux (67%); (c) BrCH₂-CO₂Et (98%); (d) DBU, THF, rt (70%, (E)/(Z) 96:4).

alkoxide, TfO⁻, CF₃CO₂⁻) on the 3-position of the iminium ion. Upon long reaction times, the enamide eventually will decompose under the influence of acid. In conclusion, the system gives either cyclization or slow, but complete decomposition to the amide. The enamide can be isolated quantitatively when the reaction is performed in Ac₂O/ HOAc. In this system, the enamide is only decomposed by applying high temperatures.

Applications of α-Vinyl Tetrahydroisoquinolines and Tetrahydro-1*H-β*-carbolines. With the novel availability of α-vinyltetrahydroisoquinolines and tetrahydro-1H- β -carbolines we set out to explore the usefulness of the α -vinyl substituent as a handle for further transformations. An example describing a useful application of an α -vinyl substituent is the [2,3] sigmatropic rearrangement of an α -vinyltetrahydroisoquinoline, leading to a nine-membered-ring heterocycle.7b,19 To effect the rearrangement, the isoquinoline 39a was deprotected by using thiophenolate in acetonitrile at room temperature, which afforded the free secondary amine 53 in 75%(Scheme 4). This yield could be improved to 83% by switching to the 2,4-dinitrobenzenesulfonyl-substituted compound **39b**. Unfortunately, this latter sulfone group gave significantly lower yields in the amidopalladation and subsequent cyclization. On large scale, the nosyl moiety is therefore preferred over the dinitro-substituted one.

Clark–Eschweiler methylation with paraformaldehyde in refluxing formic acid²⁰ afforded the *N*-methyltetrahydroisoquinoline **54** in 67% yield. From this point, the literature procedure was followed.^{7b} Alkylation with ethyl bromoacetate afforded the reported ammonium salt in high yield. Subjecting this compound to DBU in THF at room temperature gave the [2,3] sigmatropic rearrangement product **55** in an isolated yield of 70%. The product consisted of a mixture of double bond isomers in an (*E*)/ (*Z*) ratio of 96:4 (lit. 90% yield, (*E*)/(*Z*) 95:5).^{7b}

The α -vinyl moiety was also recognized as an interesting substituent for the construction of heterocycles via cross- or ring-closing metathesis. Both processes are not commonly applied to the vinyl moiety.²¹ This is mainly due to the better accessibility of, for example, the α -allyl-



			OMe	OMe
	OMe	MeO	MeC	
MeO				
		а) c	Ť Ì
~	[]	or b	N -	N N
	× N	/	MnX	↓ √n ×
	53	56-6	0 X = H ₂ , O	61-63
			diolefin	RCM
entry	n	Х	(% yield)	(% yield)
1	0	H_2	56 (52)	
2	1	H_2	57 (60)	
3	0	0	58 (100)	61 (dec)
4	1	0	59 (91)	62 (65)
5	2	0	60 (88)	63 (98)

 a Reagents and conditions: (a) alkenyl bromide, $K_2CO_3,\,MeCN,$ reflux, 16 h; (b) alkenyl acid chloride, 2,6-lutidine, dichloromethane, 0 °C, 1 h; (c) 2nd generation Grubbs catalyst, CH_2Cl_2 , reflux, 6 h.

substituted nitrogen heterocycles.²² Besides, the characteristics of a vinyl moiety (sterically more hindered, higher rigidity) compared to the flexible allyl moiety make this functionality less attractive for the metathesis reaction.

To study the usefulness of this moiety, we set out to explore ring-closing metathesis reactions on the tetrahydroisoquinoline system. The desired metathesis precursors 56–60 were synthesized via alkylation of 53 with either the alkenyl bromide $(X = H_2)$ or the olefinic acid chloride (X = O) as outlined in Table 4. The alkylation gave moderate yields (52 and 60%) for 56 and 57, but the acylation went in excellent yields with 2,6-lutidine as a bulky base to prevent side reactions such as double bond isomerization. In this way, the amides 58-60 were obtained in approximately 90-100% yield. The ringclosing experiments were performed with the dihydroimidazolidene-based 2nd generation Grubbs catalyst in dichloromethane at reflux temperature. Quite unexpectedly, both the tertiary amines 56 and 57 failed to undergo the metathesis reaction. Although the presence of a tertiary amine has been reported to be troublesome for the ruthenium-based catalysts, there are examples known which give good results.²³ As expected, the amides 58-**60** all showed conversion to the metathesis products. The 5,6-bicyclic system **61** was formed in a rather good yield, but isolation of the product was impossible due to fast decomposition of the product (blue color) through air oxidation. The metathesis products 62 and 63 suffered less from decomposition and could be nicely isolated in 65% and 98% yield, respectively. With these experiments it was shown that the vinyl moiety can be constructively used in the ring-closing metathesis, even in the conformationally rigid tetrahydroisoquinoline systems. The best result was obtained with the longest alkenyl chain on

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SCHEME 5. A Metathesis-Based Synthetic Route to Vincantril $(74)^a$



^a Reagents and conditions: (a) MeNO₂, NH₄OAc, reflux, 2 h (100%); (b) LiAlH₄, THF, reflux, 2 h (99%); (c) NsCl, Et₃N, CH₂Cl₂, 6 h (76%); (d) benzyl propadienyl ether, Et₃N, Pd(OAc)₂, dppp, MeCN, rt, 2 h (83%); (e) Sn(OTf)₂ (2 mol %), CH₂Cl₂, 0 °C, 2 h (94%); (f) KHMDS, acryloyl chloride, THF, rt, 1 h (41%); (g) PhSK, MeCN, rt, 48 h (80%); (h) BOC₂O, CH₂Cl₂, reflux, 6 h (100%); (i) methyl acrylate, Hoveyda-Grubbs 2nd generation catalyst (2 mol %), toluene, 60 °C, 24 h (82%); (j) PtO₂, 1 atm of H₂, MeOH, 1 h (99%); (k) NaHMDS, toluene, rt, 2 h (39%); (l) TFA, CH₂Cl₂, 16 h (88%).

the nitrogen, probably because the two double bonds are more able to reach each other.

A third application was directed toward the use of the α -vinyl moiety in a tetrahydro-1*H*- β -carboline system. This time we planned the construction of vincantril (**74**, Scheme 5) through either a ring-closing metathesis approach or a cross-metathesis based synthesis. Vincantril is a synthetic antianoxia agent, but never marketed as such. Nevertheless, as a member it represents a very important class of biologically active compounds.²⁴ The only known synthesis is short and described in a patent by Synthelabo.²⁵ Our purpose was not to improve the synthesis, but to provide an alternative route to this compound class, open for easy derivatization. The synthesis commenced with the required sulfonamide starting material **65** that was readily available through the earlier

mentioned condensation/reduction and protection sequence in an overall yield of 75% from the commercially available aldehyde **64**.

Amidopalladation with benzyl propadienyl ether and $Pd(OAc)_2$ afforded the corresponding allylic *N*,*O*-acetal in 84% yield, which spontaneously started to cyclize in for example CHCl₃. Controlled, catalytic Sn(OTf)₂induced cyclization afforded the α -vinyltetrahydro-1H- β -carboline **66** in 94% yield as the key intermediate. For the ring-closing metathesis approach, acylation of 66 was performed with acryloyl chloride and KHMDS as a base. Because this type of acylation is known to be difficult, it explained the rather low yield of the product 67 (41%). More importantly, subjection of this diolefin to the 2nd generation Grubbs catalyst in toluene did give some metathesis although the temperature had to be raised to 80 °C. Unfortunately, but not completely unexpected, the product was very susceptible to air oxidation and could not be isolated. Therefore, we turned to the alternative approach starting with the cross-metathesis of **66** with methyl acrylate.²⁶ The commercially available and phosphine free Hoveyda-Grubbs catalyst turned out to give the best performance and afforded the metathesis product 68 in an isolated yield of 58%. Further elaboration of this system to vincantril required hydrogenation of the double bond. Therefore, the hydrogenationincompatible *p*-nitrobenzenesulfonyl protecting group had to be replaced by a Boc group. This was performed on 66 via a straightforward deprotection/protection sequence to give 70 in a combined yield of 80%. Crossmetathesis with methyl acrylate proceeded in 82% yield to give 71 and subsequent double bond hydrogenation afforded the methyl ester 72 in 99% yield. Ring-closure of this ester to form the lactam appeared troublesome; the use of NaHMDS as a base in this process was crucial to effect cyclization.²⁷ In this way, the lactam **73** could be isolated in 39% yield. Finally, deprotection of the Boc moiety under standard conditions afforded the desired vincantril (74) in 88% yield. Starting from the commercially available aldehyde, the total sequence consisted of 11 steps with an overall yield of 13%.

Conclusions

The palladium-catalyzed allylic N,O-acetal formation/ aromatic cyclization sequence forms a powerful combination to access α -vinyltetrahydroisoquinolines and tetrahydro-1H- β -carbolines. The method is catalytic and high yielding, and therefore a valuable method for the synthesis of such systems. It was shown that the aromatic cyclization onto allylic N-sulfonyliminium ions is a delicate process, which proceeds well only for electronrich aromatics. By taking advantage of the low reactivity of regular aromatics, a series of linear enamides were synthesized, possessing a surprising stability at high temperatures. The usefulness of α -vinyltetrahydroisoquinolines and tetrahydro-1H- β -carbolines was outlined

^{(24) (}a) Taborsky, R. G.; McIsaac, W. M. J. Med. Chem. 1964, 7, 135.

⁽²⁵⁾ Koletar, G. I.; Najer, H.; Lefevre, J. P. G.; Dupont, R.; Giudicelli, P. R. L.; Morel, C. C. H. Patent US4190657; *Chem. Abstr.* **1978**, *88*, 50831j.

⁽²⁶⁾ For an example of cross-metathesis with methyl acrylate and the Hoveyda-Grubbs 2nd generation catalyst: Lazarova, T.; Chen, J. S.; Hamann, B.; Kang, J. M.; Homuth-Trombino, D.; Han, F.; Hoffmann, E.; McClure, C.; Eckstein, J.; Sun Or, Y. J. Med. Chem. **2003**, 46, 674.

⁽²⁷⁾ A comparable lactam formation has been reported with NaH-MDS: Desmaële, D.; Mekouar, K.; d'Angelo, J. J. Org. Chem. **1997**, 62, 3890.

by the synthesis of a nine-membered nitrogen heterocycle via a known [2,3] sigmatropic ring expansion. Besides, the usefulness of the α -vinyl moiety for metathesis-based transformations was demonstrated for both the tetrahydroisoquinoline and the tetrahydro-1*H*- β -carboline system. This resulted in the construction of interesting tricyclic nitrogen heterocycles and a metathesis based route to the antianoxia compound vincantril.

Experimental Section

General details are described in the Supporting Information. All NMR spectra were measured in CDCl_3 , unless stated otherwise.

6,7-Dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (54). A solution of 53 (0.5 g, 2.28 mmol) and formaldehyde (37% solution, 0.25 mL, 2.74 mmol, 1.2 equiv) in formic acid (1 mL, 5.7 mmol, 2.5 equiv) was refluxed for 16 h until the evolution of CO₂ ceased. The mixture was concentrated and coevaporated two times with ethyl acetate. Column chromatography (CH₂Cl₂/MeOH/25% NH₃ 98:2:¹/₂ to 90:10: $1/_2$) afforded the product as an oil. Yield 0.354 g (1.52 mmol, 67%). Rf 0.58 (CH₂Cl₂/MeOH/25% NH₃ 90:10:¹/₂). IR (CHCl₃) ν 1256, 1514, 2937 cm⁻¹. ¹H NMR (400 MHz) δ 6.60 (s, 1H), 6.59 (s, 1H), 5.78-5.69 (m, 1H), 5.35-5.27 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.66 (d, J = 8.4 Hz, 1H), 3.07-2.95 (m, 2H), 2.71–2.66 (m, 1H), 2.56–2.51 (m, 1H), 2.43 (s, 3H). $^{\rm 13}{\rm C}$ NMR $(100~{\rm MHz})~\delta$ 147.4, 146.9, 139.7, 126.1, 118.2, 110.9, 110.5, 69.3, 55.7, 55.6, 51.1, 43.8, 28.5. HRMS (FAB) calcd for C₁₄H₂₀-NO₂ (MH⁺) 234.1494, found 234.1490.

2-Allyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline (56). A solution of 6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline (53) (100 mg, 0.456 mmol), allyl bromide (43 μL, 0.50 mmol, 1.1 equiv), and K₂CO₃ (0.125 g, 0.912 mmol, 2 equiv) in MeCN (10 mL) was refluxed for 48 h. H₂O (20 mL) was added and the product extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. Column chromatography (pentane/ethyl acetate 1:1 to 1:2) was used to separate the mono- and dialkylated product. Yield of dialkylated product 16 mg (0.053 mmol, 12%), yield of monoalkylated product 61 mg (0.235 mmol, 52%). $R_{f(di)}$ 0.64, $R_{f(mono)}$ 0.28 (EtOAc). IR $(CHCl_3) \nu$ 925, 994, 1120, 1225, 1465, 1515, 2836, 2938 cm⁻¹. ¹H NMR (400 MHz) δ 6.57 (s, 2H), 5.96-5.86 (m, 1H), 5.84- $5.75~({\rm m},\,1{\rm H}),\,5.30-5.14~({\rm m},\,4{\rm H}),\,3.96~({\rm d},\,J=8.4~{\rm Hz},\,1{\rm H}),\,3.83$ (s, 3H), 3.79 (s, 3H), 3.45 (dd, J = 5.4, 13.9 Hz, 1H), 3.11-2.99 (m, 2H), 2.86-2.78 (m, 1H), 2.75-2.68 (m, 1H), 2.56-2.50 (m, 1H). $^{13}\mathrm{C}$ NMR (100 MHz) δ 147.4, 146.8, 139.4, 135.4, 127.8, 126.5, 117.9, 117.4, 111.0, 110.9, 66.1, 57.4, 55.7, 55.6, 46.1, 28.1. HRMS (FAB) calcd for C₁₆H₂₂NO₂ (MH⁺) 260.1651, found 260.1649.

2-Butenyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline (57). Amine **53** (100 mg, 0.456 mmol) was alkylated with 4-bromobutene in the same way as for **56**. Column chromatography (pentane/ethyl acetate 1:1 to 0:1) afforded the product as an oil. Yield 74 mg (0.27 mmol, 60%). R_f 0.47 (EtOAc). IR (CHCl₃) ν 1100, 1375, 1469, 3150 cm⁻¹. ¹H NMR (400 MHz) δ 6.58 (s, 2H), 5.86–5.79 (m, 2H), 5.25 (dd, J = 10.1, 17.1 Hz, 2H), 5.04 (dd, J = 10.1, 17.1 Hz, 2H), 3.99 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.11–3.08 (m, 1H), 2.86–2.76 (m, 3H), 2.63–2.54 (m, 2H), 2.33–2.25 (m, 2H). ¹³C NMR (100 MHz) δ 146.9, 139.7, 118.2, 115.0, 111.0, 110.9, 99.9, 66.0, 55.7, 55.6, 53.5, 46.9, 46.4, 32.3, 27.5. HRMS (FAB) calcd for C₁₇H₂₄NO₂ (MH⁺) 274.1807, found 274.1803.

1-(6,7-Dimethoxy-1-vinyl-3,4-dihydro-1*H*-isoquinolin-2-yl)propenone (58). To an ice-cold solution of 53 (100 mg, 0.456 mmol) and 2,6-lutidine (47 μ L, 0.405 mmol, 1.05 equiv) in dichloromethane (10 mL) was added acryloyl chloride (37 μ L, 0.456 mmol, 1.0 equiv). After being stirred for 1 h at 0 °C, the crude mixture was concentrated in vacuo. Column chromatography (pentane/ethyl acetate 1:1 to 0:1) afforded the product as a colorless oil. Yield 124 mg (0.454 mmol, 100%). R_{f} 0.35 (EtOAc). ¹H NMR (400 MHz) both confomers: δ 6.62–6.56 (m, 3H), 6.28 (d, J = 16.8 Hz, 1H), 6.05 (br s, $^{1}\!_{2}$ H), 5.97–5.91 (m, 1H), 5.66 (d, J = 10.3 Hz, 1H), 5.34 (br s, $^{1}\!_{2}$ H), 5.17–4.97 (m, 2H), 4.50 (br d, J = 11.6 Hz, $^{1}\!_{2}$ H), 3.89 (br d, J = 11.9 Hz, $^{1}\!_{2}$ H), 3.80 (s, 3H), 3.88 (s, 3H), 3.49–3.40 (m, $^{1}\!_{2}$ H), 3.10–3.00 (m, $^{1}\!_{2}$ H), 2.87–2.79 (m, 1H), 2.69–2.61 (m, 1H). 13 C NMR (100 MHz) both confomers: δ 148.0, 147.7, 137.0, 128.0, 127.6, 126.3, 125.8, 116.7, 115.9, 111.2, 111.0, 110.7, 109.9, 58.0, 55.8, 55.7, 54.2, 40.1, 36.8, 28.6, 27.6. HRMS (FAB) calcd for $C_{16}H_{20}NO_3$ (MH⁺) 274.1443, found 274.1454.

1-(6,7-Dimethoxy-1-vinyl-3,4-dihydro-1H-isoquinolin-2-yl)but-3-en-1-one (59). In the same way as for 58, 6,7 $dimethoxy \text{-}1\text{-}vinyl\text{-}1\text{,}2\text{,}3\text{,}4\text{-}tetrahydroisoquinoline} \left(53 \right) \left(160 \text{ mg}, \right.$ 0.729 mmol) was treated with freshly prepared 3-butenoyl chloride. Column chromatography (pentane/ethyl acetate 1:1 to 1:3) afforded the product as a colorless oil. Yield 190 mg (0.66 mmol, 91%). Rf 0.62 (CH₂Cl₂/MeOH/25% NH₃ 90:10:¹/₂). IR (CHCl₃) v 1126, 1253, 1442, 1517, 1630, 2937 cm⁻¹. ¹H NMR (400 MHz) both conformers: δ 6.63 (s, 3H), 6.60 (s, 3H), 6.07-5.91 (m, 2H), 5.27–5.10 (m, 4H), 5.02 (d, J = 17.0 Hz, 0.7H), 4.59 (dd, J = 3.2, 11.2 Hz, 0.3H), 3.86 (s, 3H), 3.84 (s, 3H), $3.86{-}3.79\ (m,\ 1H),\ 3.51{-}3.44\ (m,\ 0.7H),\ 3.27{-}3.18\ (m,\ 2H),$ 3.09-3.02 (m, 0.3H), 2.92-2.82 (m, 1H), 2.74-2.67 (m, 1H). ¹³C NMR (100 MHz) both conformers: δ 170.0, 169.3, 147.9, 147.6, 137.2, 137.1, 131.7, 131.5, 127.2, 126.5, 125.9, 125.7, 117.9, 117.7, 116.8, 116.1, 111.5, 111.0, 110.9, 110.1, 58.3, 56.0, 55.9, 54.1, 40.3, 39.1, 38.7, 36.5, 28.7, 27.9. HRMS (FAB) calcd for C₁₇H₂₂NO₃ (MH⁺) 288.1600, found 288.1597.

1-(6,7-Dimethoxy-1-vinyl-3,4-dihydro-1H-isoquinolin-2-yl)pent-4-en-1-one (60). Similar to 58, amine 53 (75 mg, 0.34 mmol) was treated with 4-pentenoyl chloride. Column chromatography (pentane/ethyl acetate 1:1 to 0:1) afforded the product as a colorless oil. Yield 90 mg (0.30 mmol, 88%). R_f 0.76 (CH₂Cl₂/MeOH/25% NH₃ 90:10:¹/₂). IR (CHCl₃) v 1126, 1253, 1440, 1518, 1629, 2938 cm⁻¹. ¹H NMR (400 MHz) both conformers: δ 6.58 (s, 1H), 6.57 (s, 1H), 6.03 (d, J = 4.9 Hz, $^{1}/_{2}$ H), 5.94–5.81 (m, 1 $^{1}/_{2}$ H), 5.25–4.92 (m, 4 $^{1}/_{2}$ H), 4.60–4.50 (m, ¹/₂H), 3.81 (s, 3H), 3.79 (s, 3H), 3.81–3.76 (m, 1H), 3.46– 3.41 (m, ¹/₂H), 3.05-2.96 (m, ¹/₂H), 2.83-2.79 (m, 1H), 2.71-2.62 (m, 1H), 2.51-2.38 (m, 4H). ¹³C NMR (100 MHz) both conformers: δ 171.0, 170.4, 148.0, 147.7, 147.4, 137.4, 137.3, 137.2, 137.0, 127.0, 126.5, 125.8, 125.6, 116.4, 115.8, 115.0,114.9, 111.3, 110.9, 110.7, 110.0, 58.0, 55.8, 55.7, 53.9, 39.9, 36.2, 32.6, 32.4, 29.0, 28.5, 27.7. HRMS (FAB) calcd for C₁₈H₂₄-NO₃ (MH⁺) 302.1756, found 302.1762.

9,10-Dimethoxy-3,6,7,11b-tetrahydropyrido[2,1-a]isoquinolin-4-one (62). A solution of 59 (95 mg, 0.33 mmol) in dichloromethane (20 mL) was degassed with argon and refluxed for 30 min. Second generation Grubbs catalyst (14 mg, 0.016 mmol, 5 mol %) was added and the solution was refluxed for 1 h. The mixture was concentrated and purified by column chromatography (pentane/ethyl acetate 2:1 to 0:1) to yield the product as a yellowish, solidifying oil. Yield 55.2 mg (0.213 mmol, 65%). Rf 0.12 (pentane/ethyl acetate). Mp 29.5-29.6 °C. IR (CHCl₃) v 1014, 1118, 1224, 1256, 1466, 1515, 1632, 2938 cm^-1. ¹H NMR (500 MHz) δ 6.72 (s, 1H), 6.64 (s, 1H), 6.20 (dd, J = 2.4, 10.3 Hz, 1H), 5.90 (dd, J = 2.4, 10.3 Hz, 1H), 5.25 (br s, 1H), 4.80-4.78 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.06-2.92 (m, 4H), 2.69-2.66 (m, 1H). ¹³C NMR (125 MHz) δ 166.3, 147.9, 147.5, 128.2, 127.0, 123.7, 122.9, 111.7, 107.9, 56.6, 56.0, 55.8, 40.5, 31.8, 27.8. HRMS (FAB) calcd for $\rm C_{15}H_{18}\textsc{-}$ NO₃ (MH⁺) 260.1287, found 260.1293. Anal. Calcd for C₁₅H₁₇-NO₃: C, 69.48; H, 6.61; N, 5.40. Found: C, 66.19; H, 6.21; N, 4.93.

10,11-Dimethoxy-3,7,8,12b-tetrahydro-4H-azepino[2,1*a*]isoquinolin-5-one (63). A solution of 60 (76.5 mg, 0.254 mmol) in dichloromethane (10 mL) was degassed with argon and refluxed for 30 min. Second generation Grubbs catalyst (25 mg, 0.0296 mmol, 10 mol %) was added and the solution was refluxed for 2 h. The mixture was concentrated and purified by column chromatography (pentane/ethyl acetate 1:1 to 0:1) to yield the product as a yellowish oil. Yield 68 mg (0.249 mmol, 98%). R_f 0.13 (EtOAc). IR (CHCl₃) ν 1121, 1229, 1254, 1435, 1464, 1518, 1633, 2938 cm⁻¹. ¹H NMR (500 MHz) δ 6.65 (s, 1H), 6.63 (s, 1H), 5.78–5.69 (m, 3H), 4.06–4.02 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.52–3.47 (m, 1H), 3.40–3.37 (m, 1H), 2.76–2.74 (m, 2H), 2.54–2.50 (m, 3H). ¹³C NMR (125 MHz) δ 173.6, 147.9, 147.8, 133.0, 131.5, 128.0, 127.3, 110.9, 109.4, 56.0, 55.8, 52.4, 38.3, 33.4, 28.5, 25.4. HRMS (FAB) calcd for C₁₆H₂₀NO₃ (MH⁺) 274.1443, found 274.1443.

6-Chloro-2-(4-nitrobenzenesulfonyl)-1-vinyl-2,3,4,9-tetrahydro-1*H*- β -carboline (66). To a solution of *N*-[2-(5-chloro-1H-indol-3-yl)ethyl]-4-nitrobenzenesulfonamide (65, 2.99 g, 7.87 mmol) in acetonitrile (40 mL) was added Et₃N (1.64 mL, 11.8 mmol), Pd(OAc)₂ (88 mg, 0.39 mmol), dppp (160 mg, 0.39 mmol), and benzyl propadienyl ether (1.14 g, 8.66 mmol). After being stirred for 6 h at room temperature the solution was concentrated and purified by column chromatography with silica gel with some Et_3N in the eluent. Yield 3.40 g (6.50 mmol, 83%). R_f 0.49 (pentane/ethyl acetate 1:1). ¹H NMR (400 MHz) δ 8.22 (d, J = 8.8 Hz, 2H), 8.12 (br s, NH), 7.97 (d, J =8.8 Hz, 2H), 7.55 (d, J = 1.8 Hz, 1H), 7.38–7.30 (m, 5H), 7.23 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 2.0, 8.6 Hz, 1H), 7.00 (d, R + 1.0), 7.00 (d, R + 1.J = 2.2 Hz, 1H), 5.75 (d, J = 2.7 Hz, 1H), 5.60–5.55 (m, 2H), 5.40-5.37 (m, 1H), 4.73 (d, J = 13.1 Hz, 1H), 4.65 (d, J = 11.9Hz, 1H), 3.51–3.43 (m, 1H), 3.39–3.32 (m, 1H), 3.15–3.11 (m, 2H). ¹³C NMR (100 MHz) δ 145.8, 140.6, 136.8, 134.4, 132.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 126.8, 125.0, 124.1, 124.0, 122.2, 119.9, 118.1, 112.2, 112.1, 86.6, 69.6, 44.5, 26.8. To an ice-cold solution of the crude N,O-acetal (3.19 g, 6.06 mmol) in CH₂Cl₂ (100 mL) was added Sn(OTf)₂ (50 mg, 0.12 mmol). The mixture was stirred for 1-2 h at 0 °C and quenched with a few drops of Et₃N. The solution was concentrated in vacuo and purified by column chromatography as indicated. The crude reaction mixture was diluted with EtOAc and washed with H₂O (30 mL) and brine (30 mL), dried over Na₂SO₄, and concentrated. Column chromatography (pentane/ ethyl acetate 2:1) afforded the product as a yellow solid. Yield 2.37 g (5.7 mmol, 94%). R_f 0.26 (pentane/ethyl acetate 2:1). Mp 225.6–226.0 °C. IR (CHCl₃) ν 1030, 1248, 1708, 3387 cm⁻¹. ¹H NMR (400 MHz, CDCl₃ + acetone- d_6) δ 9.52 (br s, NH), 7.98 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.79 (dd, J = 2.0, 8.5 Hz, 1H)1H), 5.73-5.67 (m, 1H), 5.46 (d, J = 5.9 Hz, 1H), 5.01 (d, J =10.0 Hz, 1H), 4.95 (d, J = 17.1 Hz, 1H), 3.93-3.89 (m, 1H), 3.17-3.11 (m, 1H), 2.39-2.35 (m, 2H). ¹³C NMR (125 MHz, $CDCl_3 + acetone-d_6) \delta 149.3, 146.2, 134.2, 134.0, 131.2, 127.6,$ 127.0, 124.3, 123.6, 121.6, 118.2, 117.0, 111.7, 107.1, 54.7, 39.4, 20.1. HRMS (FAB) calcd for C₁₉H₁₇N₃O₄SCl (MH⁺) 418.0628, found 418.0628. Anal. Calcd for C₁₉H₁₆N₃O₄SCl: C, 54.61; H, 3.86; N, 10.06. Found: C, 54.74; H, 3.92; N, 9.94.

6-Chloro-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline (69). To an ice-cold solution of sulfonamide **66** (0.40 g, 0.96 mmol) in MeCN (10 mL) was added potassium thiophenolate (1.38 g, 1.48 mmol) and the mixture was stirred at room temperature for 48 h. Water (10 mL) was added and the product was extracted with EtOAc (3 \times 20 mL). The organic layers were washed with brine, dried over Na₂SO₄, and concentrated. Column chromatography (CH_2Cl_2/MeOH/25% NH_3 90:10:1/_2) afforded the product as an off-white solid. Yield 177 mg (0.76 mmol, 80%). Rf 0.12 (CH₂Cl₂/MeOH/25% NH₃ 90:10:¹/₂). IR (CHCl₃) v 1064, 1294, 1441, 2205, 2360, 2918, 3466 cm⁻¹. ¹H NMR (400 MHz) δ 7.88 (br s, NH), 7.45 (d, J = 1.9 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 2.0, 8.6 Hz, 1H), 6.00– 5.92 (m, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.31 (d, J = 10.0 Hz,1H), 4.58 (d, J = 7.8 Hz, 1H), 3.36–3.31 (m, 1H), 3.11–3.05 (m, 1H), 2.80–2.65 (m, 2H), 1.91 (br s, NH). $^{13}\mathrm{C}$ NMR (100 MHz) & 137.9, 134.9, 133.9, 128.6, 124.9, 121.6, 118.2, 117.6, 111.5, 108.8, 56.4, 42.0, 22.0. HRMS (FAB) calcd for C₁₃H₁₄N₂-Cl (MH⁺) 233.0846, found 233.0835. Anal. Calcd for C₁₃H₁₃N₂-Cl: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.02; H, 5.54; N, 12.15.

6-Chloro-2-tert-butyloxycarbonyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline (70). To a solution of 6-chloro-1vinyl-2,3,4,9-tetrahydro-1*H*- β -carboline (69) (0.218 g, 0.937 mmol) in dichloromethane (20 mL) was added Boc₂O (0.205 g, 0.937 mmol, 1 equiv). The solution was refluxed for 6 h, then H_2O (50 mL) was added, followed by layer separation. The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were washed with 1% aqueous HCl (30 mL), saturated aqueous NaHCO₃ (30 mL), and brine (30 mL) and concentrated in vacuo. Column chromatography (pentane/ethyl acetate 4:1 to 2:1) afforded the product as an off-white solid. Yield 0.312 g (0.937 mmol, 100%). R_f 0.42 (pentane/ethyl acetate 2:1). IR (CHCl₃) v 1167, 1413, 1679, 2981, 3466 cm $^{-1}$. ¹H NMR (500 MHz) δ 7.47 (s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 2.0, 8.8 Hz, 1H), 6.04–5.97 (m, 1H), 5.90–5.50 (br m, 1H), 5.27 (d, J = 10.0 Hz, 1H), 5.18 (br d, J = 15.6 Hz, 1H), 4.60–4.20 (br m, 1H), 3.13 (br s, 1H), 2.85-2.79 (m, 1H), 2.72-2.67 (m, 1H), 1.54 (s, 9H). ¹³C NMR $(125~\mathrm{MHz})~\delta$ 154.7, 135.0, 134.5, 133.1, 129.0, 128.0, 127.5, 125.2, 122.0, 117.8, 117.5, 111.8, 80.31, 29.7, 28.5, 21.3. HRMS (FAB) calcd for $C_{18}H_{22}N_2O_2Cl(MH^+)$ 333.1370, found 333.1388.

6-Chloro-1-(2-methoxycarbonylvinyl)-1,3,4,9-tetrahydro- β -carboline-2-carboxylic Acid *tert*-Butyl Ester (71). To a degassed solution of 70 (0.365 g, 1.1 mmol) in toluene (20 mL) was added methyl acrylate (1.0 mL, 11 mmol, 10 equiv) and Hoveyda-Grubbs catalyst (15 mg, 0.022 mmol, 2 mol %). The solution was heated at 60 °C for 48 h. After concentration in vacuo, column chromatography (pentane/ diethyl ether 2:1 to 1:1) afforded the product as a colorless oil. Yield 0.353 g (0.902 mmol, 82%). R_f 0.13 (pentane/diethyl ether 1:1). IR (CHCl₃) v 1166, 1284, 1414, 1678, 2981, 3327, 3463 cm⁻¹. 1H NMR (400 MHz) δ 9.27 and 8.72 (br s, NH), 7.42 (s, 1H), 7.20 (br d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.99 (br d, J = 12.8 Hz, 1H), 6.00–5.73 (m, 2H), 4.45 and 4.32 (br s, 1H), 3.75 and 3.67 (br s, 3H), 3.09-3.01 (m, 1H), 2.84-2.76 (m, 1H), 2.66-2.63 (m, 1H), 1.56 and 1.47 (br s, 9H). HRMS $(FAB) \ calcd \ for \ C_{20}H_{24}N_2O_4Cl \ (MH^+) \ 391.1425, \ found \ 391.1420.$

6-Chloro-1-(2-methoxycarbonylethyl)-1,3,4,9-tetrahydro-β-carboline-2-carboxylic Acid *tert*-Butyl Ester (72). The olefin 71 (0.29 g, 0.742 mmol) was dissolved in dry methanol (15 mL) together with a catalytic amount of PtO₂. The stirred solution was exposed to 1 atm of H₂ pressure for 1 h. Filtration of the suspension over Hyflo and concentration in vacuo afforded the product as a yellowish foam. Yield 0.29 g (0.74 mmol, 99%). R_f 0.55 (pentane/ethyl acetate 1:1). IR $(CHCl_3) \nu 1167, 1232, 1367, 1417, 1671, 1725, 2932, 2980,$ 3327, 3463 cm⁻¹. ¹H NMR (400 MHz) δ 9.17 and 8.77 (br s, NH), 7.44 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.5Hz, 1H), 5.41 and 5.30 (br s, 1H), 4.50 and 4.31 (br s, 1H), 3.76 and 3.65 (br s, 3H), 3.18-3.08 (m, 1H), 2.83-2.79 (m, 1H), 2.65 (d, J = 15.4 Hz, 1H), 2.51-2.46 (m, 1H), 2.25-2.19 (m, 1H)1H), 2.13-2.05 (m, 1H), 1.55 and 1.51 (br s, 9H). ¹³C NMR (125 MHz) both conformers: δ 173.9, 155.4, 154.6, 135.6, 135.2, 134.4, 127.8, 124.8, 121.7, 117.5, 111.9, 108.5, 107.9, 80.2, 51.6, 50.7, 50.2, 38.6, 37.3, 30.6, 29.6, 29.4, 28.3, 21.2, 20.9. HRMS $(FAB)\ calcd\ for\ C_{20}H_{26}N_2O_4Cl\ (MH^+)\ 393.1581,\ found\ 393.1578.$

10-Chloro-6-oxo-1,2,3a,4,5,6-hexahydroindolo[3,2,1-de]-[1,5]naphthyridine-3-carboxylic Acid tert-Butyl Ester (73). To an ice-cold solution of the ester 72 (0.213 g, 0.542 mmol) in dry toluene (10 mL) was added NaHMDS (1 M in toluene, 1.88 mL, 1.88 mmol) and stirring was continued for 2 h at room temperature. The solution was cooled to 0 °C and ice-cold saturated aqueous NaHCO₃ (15 mL) was added. The product was extracted with CH_2Cl_2 (2 × 15 mL) after layer separation. The organic layers were washed with brine (15 mL), dried over Na₂SO₄, and concentrated. Column chromatography (pentane/ethyl acetate 3:1 to 1:1) afforded the product as a colorless oil. Yield 76 mg (0.211 mmol, 39%). R_f 0.49 (pentane/ethyl acetate 1:1). IR (CHCl₃) v 1216, 1402, 1692, 3020 cm⁻¹. ¹H NMR (500 MHz) δ 8.31 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 4.98 (d, J = 9.5 Hz, 1H), 4.48 (d, J = 12.4 Hz, 1H), 2.96–2.88 and 2.73–2.68 (m, 5H),

2.58–2.54 (m, 1H), 1.94–1.90 (m, 1H), 1.56 (s, 9H). $^{13}\mathrm{C}$ NMR (125 MHz) δ 167.8, 154.8, 135.3, 133.3, 130.3, 129.8, 124.7, 118.1, 117.2, 114.1, 80.8, 49.3, 40.5, 33.2, 28.5, 27.8, 21.7.

Vincantril (74).²⁴ To an ice-cold solution of the carbamate $\textbf{73}~(50~\text{mg},\,0.139~\text{mmol})~\text{in}~CH_2Cl_2~(4~\text{mL})$ was added TFA (0.32 mL, 4.15 mmol, 30 equiv). The solution was stirred at room temperature for 6 h and then ice-cold saturated aqueous $Na\dot{H}CO_3$ (10 mL) was added. The product was extracted with CH_2Cl_2 (3 \times 10 mL) after layer separation. The combined organic layers were washed with brine (10 mL), dried over Na₂-SO₄, and concentrated. Column chromatography (CH₂Cl₂/ MeOH/25% NH₃ 95:5:1/2) afforded vincantril as a slightly greenish solid. Yield 32 mg (0.123 mmol, 88%). Rf 0.37 (CH2-Cl₂/MeOH/25% NH₃ 90:10:¹/₂). Mp 171.5-172.6 °C (lit.²⁸ mp 161-163 °C). IR (CHCl₃) v 1382, 1448, 1602, 1706, 2360, 2928, 3606, 3691 cm⁻¹. ¹H NMR (500 MHz) δ 8.28 (d, J = 8.5 Hz, 1H), 7.39 (s, 1H), 7.28 (d, J = 3.9 Hz, 1H), 4.02–3.99 (m, 1H), 3.55–3.51 (m, 1H), 2.89–2.60 (m, 4H), 2.34–2.29 (m, 1H), 1.87–1.78 (m, 1H), 1.69 (br s, NH). $^{13}\mathrm{C}$ NMR (125 MHz) δ 168.0, 137.5, 132.9, 131.2, 129.5, 124.4, 118.0, 117.0, 112.3, 50.6, 43.7, 33.1, 29.0, 21.5. HRMS (FAB) calcd for $C_{14}H_{14}N_2\text{-}OCl\,(MH^+)\,261.0795$, found 261.0805. Anal. Calcd for $C_{14}H_{13}N_2\text{-}OCl:\ C,\,64.49;\,H,\,5.03;\,N,\,10.74.$ Found: C, 64.56; H, 4.95; N, 10.66.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data of all the compounds both mentioned and not mentioned in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²⁸⁾ According to: Combined Chemical Dictionary, on CD-ROM; Chapmann & Hall/CRC: London, UK, 2001; compound number NCV30-I.