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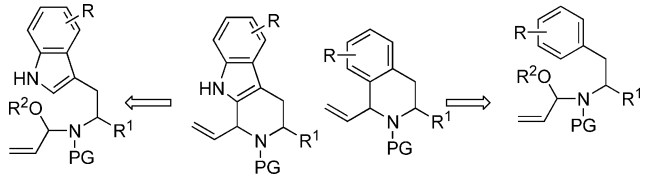
Catalytic *N*-Sulfonyliminium Ion-Mediated Cyclizations to α-Vinyl-Substituted Isoquinolines and *β*-Carbolines and Applications in Metathesis

Sape S. Kinderman, Monique M. T. Wekking, Jan H. van Maarseveen, Hans E. Schoemaker,[†] Henk Hiemstra,* and Floris P. J. T. Rutjes*,[‡]

J. H. van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 129, NL-1018 WS Amsterdam, The Netherlands

hiemstra@science.uva.nl; f.rutjes@science.ru.nl

Received March 13, 2005

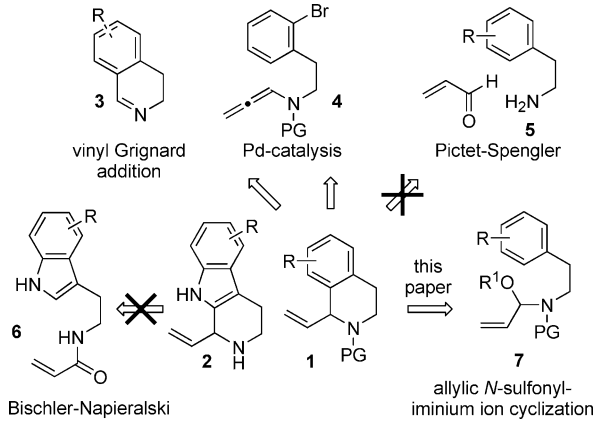


Catalytic $Sn(OTf)_2$-induced cyclization of linear, aryl-containing allylic *N*,*O*-acetals produced vinyl-substituted tetrahydroisoquinolines and tetrahydro-1*H*-*β*-carbolines. The usefulness of the vinyl moiety in the resulting products was demonstrated via the synthesis of various key building blocks for alkaloid structures. The α-vinyl moiety was utilized in a [2,3] sigmatropic 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−Spengler[3] and Bischler−Napieralski[4] 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 1). It has been demonstrated that only substituted vinyl moieties can be introduced through the Pictet−Spengler condensation[5] 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

CHART 1. α-Vinyl-Substituted Isoquinolines and Carbolines



[†] Present address: DSM Research, Life Science Products, P.O. Box 18, NL-6160 MD Geleen, The Netherlands.

[‡] Present address: Radboud University Nijmegen, Institute for Molecules and Materials, Toernooiveld 1, NL-6525 ED Nijmegen, The Netherlands, Fax: +31 24 365 3393.

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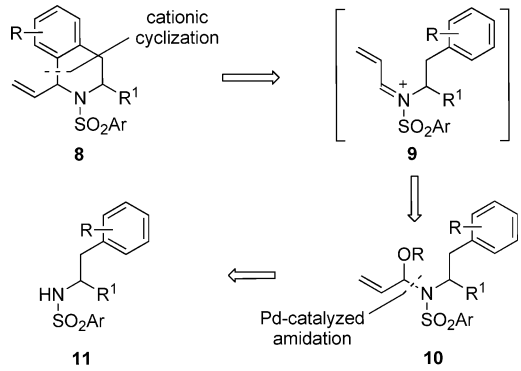
10.1021/jo050503t CCC: $30.25
Published on Web 05/26/2005

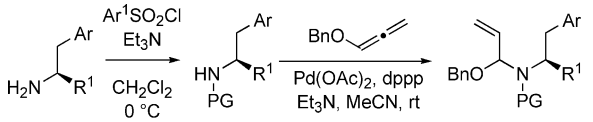
SCHEME 1. Retrosynthetic outline



(**3**),[7] or a Pd-catalyzed hydrostannylation−cyclization sequence[8] with allenamides such as **4**. Nevertheless, a general entry into α-vinyl-substituted tetrahydroisoquinolines **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 readily accessible via Pd-catalyzed condensation of the corresponding sulfonamides **11** with alkoxyallenes.[11,12]

TABLE 1. Precursor Synthesis



entry	R^1	Ar	PG	sulfonamide (% yield)[a]	acetal (% yield)[a]
1	H	*m*-$MeOC_6H_4$	Ts	**12** (94)	**24** (91)
2	H	Ph	Ts	**13** (91)	**25** (89)
3	H	*m*-MeC_6H_4	Ns	**14** (58)	**26** (98)
4	H	*m*-ClC_6H_4	Ns	**15** (79)	**27** (100)
5	H	*p*-$MeOC_6H_4$	Ns	**16** (87)	**28** (96)
6	Me[b]	*m*-$MeOC_6H_4$	Ns	**17** (70)[b]	**29** (65)[b]
7	H	3,4-$(MeO)_2C_6H_3$	Ns	**18a** (96)	**30a** (94)
8	H	3,4-$(MeO)_2C_6H_3$	2,4-dNs	**18b** (55)	**30b** (42)
9	Me[b]	3,4-$(MeO)_2C_6H_3$	Ns	**19** (55)[b]	**31** (58)[b]
10	CO_2Me	3,4-$(MeO)_2C_6H_3$	Ns	**20** (69)	**32** (51)
11	H	2-furanyl	Ns	**21** (54)	**33** (85)
12	H	3-indolyl	Ts	**22** (98)	**34** (74)
13	CO_2Me	3-indolyl	Ts	**23** (86)	**35** (64)

[a] Isolated yields. [b] Racemic material was used.

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 $LiAlH_4$ 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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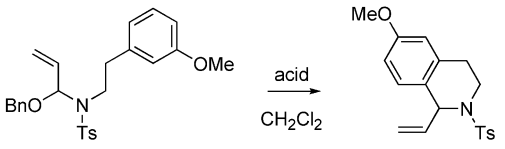
TABLE 2. Evaluation of Different Acids



24 **36**

entry	acid (equiv)	*T* (°C)	*t* (h)	**36** (%)[a]
1	$Sc(OTf)_3$ (0.1)	0	3	74
2	$Sc(OTf)_2$ (0.1)	0	1	87
3	TFA/TFAA (2/0.1)	0	1	83
4	CF_3SO_3H (0.05)	0	4	76
5	[TMAH][Al_2Cl_7] (1.5)	−50 to rt	1	42

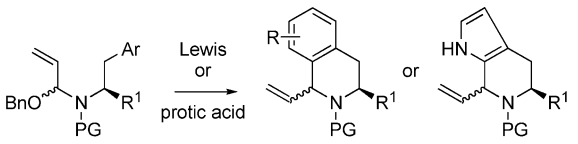
[a] Isolated yields.

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% yield 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]-[Al_2Cl_7], 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

TABLE 3. Scope of the Aromatic Cyclizations



25-35 **37-43**

entry	acetal (Ar)	cyclization conditions[a]	cyclization product (yield, ratio)[b]
1	**25**: Ar = Ph, R^1 = H, PG = Ts	multiple	-
2	**26**: R = *m*-Me	TFA or $Sn(OTf)_2$	**37** (0%)
3	**26**: R = *m*-Me	$Sc(OTf)_3$[c]	**37** (4%)[d]
4	**27**: R = *m*-Cl	multiple	-
5	**28**: R = *p*-MeO	multiple	-
6	**29**	$Sn(OTf)_2$	**38** (79%, 86:14)
7	**29**	TFA	**38** (96%, 50:50)
8	**30a**: PG = Ns	$Sn(OTf)_2$	**39a**: PG = Ns (92%)
9	**30b**: PG = 2,4-dNs	$Sn(OTf)_2$	**39b**: PG = 2,4-dNs (74%)
10	**31**: R^1 = Me[e]	$Sn(OTf)_2$	**40**: R^1 = Me (88%, 50:50)[e]
11	**32**: R^1 = CO_2Me	$Sn(OTf)_2$	**41**: R^1 = CO_2Me (99%, 50:50)
12	**32**: R^1 = CO_2Me	TFA	**41**: R^1 = CO_2Me (76%, 75:25)
13	**33**: Ar = 2-furanyl R^1 = H, PG = Ns	multiple	-
14	**34**: R^1 = H	$Sn(OTf)_2$	**42**: R^1 = H (65%)
15	**35**: R^1 = CO_2Me	$Sn(OTf)_2$	**43**: R^1 = CO^2Me (80%, 57:43)

[a] All cyclizations were carried out with $Sn(OTf)_2$ (2 mol %) or TFA (4 equiv) in CH_2Cl_2 (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][NTf_2] 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

(14) For a review, see: (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev*. **2002**, *102*, 2227. For a typical application: (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem*. **2001**, *66*, 809.

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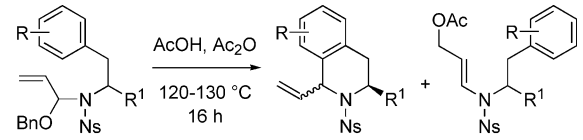
(17) For a review on ionic liquids, see: (a) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. For recent use, see: (b) Kemperman, G. J.; Roeters, T. A.; Hilberink, P. W. *Eur. J. Org. Chem*. **2003**, 1681 and references cited.

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}H 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-methyl-substituted *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 ^{1}H 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 2,4-dinitrobenzenesulfonyl 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 indolyl 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 Ac_2O was chosen, containing up to 20 equiv of HOAc as the acid. In this way an absolute water-free solvent was created, hopefully allowing for higher temperatures. The results of these experiments are depicted in Scheme 2.

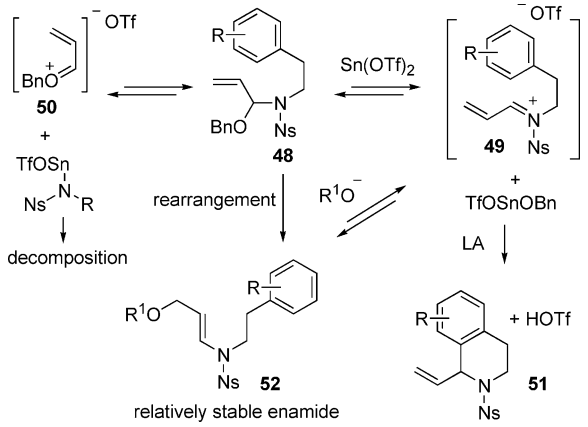
Precursor **26**, bearing a *m*-methyl substituent, was gradually heated in this solvent mixture. No reaction occurred up to 110 °C, but above this temperature (120−130 °C), all starting material disappeared to form a new single spot on TLC overnight. The isolated product turned out to be enamide **45**, 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.

SCHEME 2. Cyclization vs Enamide Formation



26: R = *m*-Me, R^1 = H	-	**45** (97%)
28: R = *p*-OMe, R^1 = H	-	**46** (94%)
29: R = *m*-OMe, R^1 = Me	**38** (66%,70:30)	-
44: R = H, R^1 = Me	-	**47** (97%)

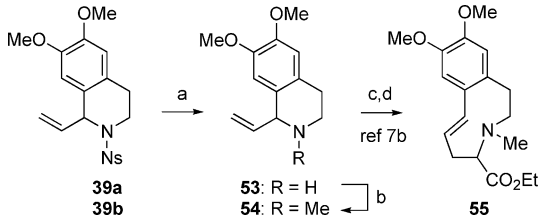
SCHEME 3. Pathways for the Allylic Iminium Ion



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.

SCHEME 4. [2,3] Sigmatropic Rearrangement[a]



[a] Reagents and conditions: (a) PhSK, MeCN, rt (75% for **39a** and 83% for **39b**); (b) $(CH_2O)_n$, HCO_2H, reflux (67%); (c) $BrCH_2CO_2Et$ (98%); (d) DBU, THF, rt (70%, (*E*)/(*Z*) 96:4).

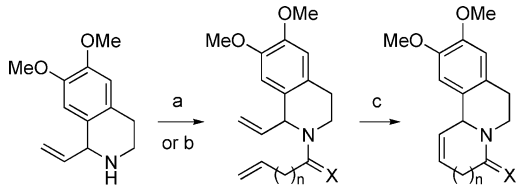
alkoxide, TfO^-, $CF_3CO_2^-$) on the 3-position of the iminium ion. Upon long reaction times, the enamide eventually will decompose under the influence of acid. In conclusion, the system gives either cyclization or slow, but complete decomposition to the amide. The enamide can be isolated quantitatively when the reaction is performed in Ac_2O/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-1*H*-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 acid[20] 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-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.

TABLE 4. RCM on the Tetrahydroisoquinoline System[a]



entry	*n*	X	diolefin (% yield)	RCM (% yield)
1	0	H_2	**56** (52)	
2	1	H_2	**57** (60)	
3	0	O	**58** (100)	**61** (dec)
4	1	O	**59** (91)	**62** (65)
5	2	O	**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.

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 ring-closing 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

(19) (a) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem*. **1978**, *43*, 1185. (b) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem*. **1979**, *44*, 3230. (c) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem*. **1978**, *43*, 4831. (d) Sato, Y.; Shirai, N.; Machida, Y.; Ito, E.; Yasui, T.; Kurono, Y.; Hatano, K. *J. Org. Chem*. **1992**, *57*, 6711.

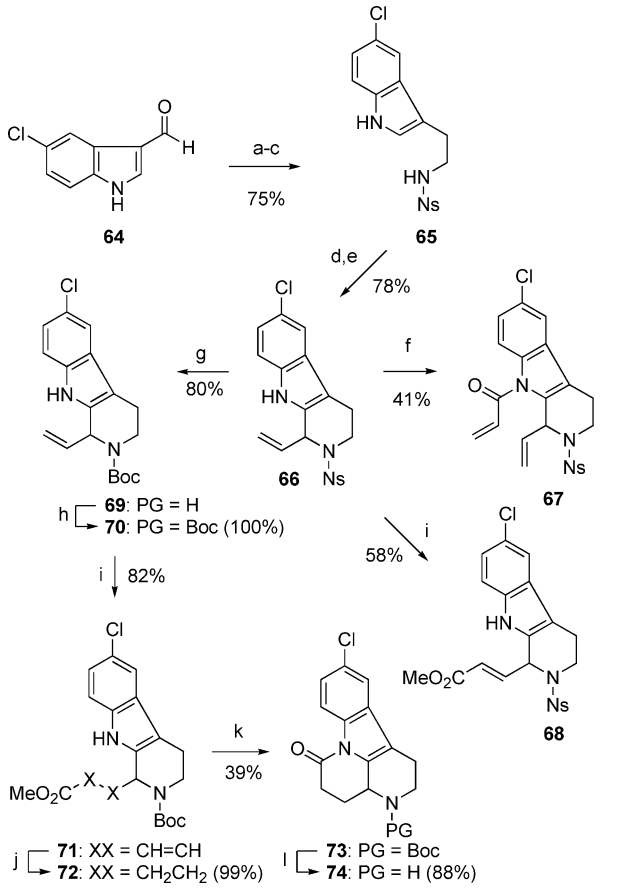
(20) Newman, M. S.; Lloyd, H. A. *J. Am. Chem. Soc*. **1952**, *74*, 2672.

(21) For a recent example: Neipp, C. E.; Martin, S. F. *Tetrahedron Lett*. **2002**, *43*, 1779.

(22) For approaches see: (a) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett*. **2000**, *2*, 3679 and references cited.

(23) For example in quinolizidine formation: Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal*. **2002**, *344*, 736.

SCHEME 5. A Metathesis-Based Synthetic Route to Vincantril (74)[a]



[a] Reagents and conditions: (a) $MeNO_2$, NH_4OAc, reflux, 2 h (100%); (b) $LiAlH_4$, THF, reflux, 2 h (99%); (c) NsCl, Et_3N, CH_2Cl_2, 6 h (76%); (d) benzyl propadienyl ether, Et_3N, $Pd(OAc)_2$, dppp, MeCN, rt, 2 h (83%); (e) $Sn(OTf)_2$ (2 mol %), CH_2Cl_2, 0 °C, 2 h (94%); (f) KHMDS, acryloyl chloride, THF, rt, 1 h (41%); (g) PhSK, MeCN, rt, 48 h (80%); (h) BOC_2O, CH_2Cl_2, reflux, 6 h (100%); (i) methyl acrylate, Hoveyda-Grubbs 2nd generation catalyst (2 mol %), toluene, 60 °C, 24 h (82%); (j) PtO_2, 1 atm of H_2, MeOH, 1 h (99%); (k) NaHMDS, toluene, rt, 2 h (39%); (l) TFA, CH_2Cl_2, 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 $CHCl_3$. Controlled, catalytic $Sn(OTf)_2$-induced cyclization afforded the α-vinyltetrahydro-1*H*-*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 hydrogenation-incompatible *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%. Cross-metathesis 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-1*H*-*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 electron-rich 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-1*H*-*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 NaHMDS: 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 CO_2 ceased. The mixture was concentrated and coevaporated two times with ethyl acetate. Column chromatography (CH_2Cl_2/MeOH/25% NH_3 98:2:½ to 90:10:½) afforded the product as an oil. Yield 0.354 g (1.52 mmol, 67%). R_f 0.58 (CH_2Cl_2/MeOH/25% NH_3 90:10:½). IR ($CHCl_3$) 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). ^{13}C NMR (100 MHz) δ 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 $C_{14}H_{20}NO_2$ (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 K_2CO_3 (0.125 g, 0.912 mmol, 2 equiv) in MeCN (10 mL) was refluxed for 48 h. H_2O (20 mL) was added and the product extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, 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 ($CHCl_3$) ν 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 (m, 1H), 5.30−5.14 (m, 4H), 3.96 (d, J = 8.4 Hz, 1H), 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}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 $C_{16}H_{22}NO_2$ (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 ($CHCl_3$) 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). ^{13}C 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 $C_{17}H_{24}NO_2$ (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 μL, 0.405 mmol, 1.05 equiv) in dichloromethane (10 mL) was added acryloyl chloride (37 μL, 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, ½H), 5.97−5.91 (m, 1H), 5.66 (d, J = 10.3 Hz, 1H), 5.34 (br s, ½H), 5.17−4.97 (m, 2H), 4.50 (br d, J = 11.6 Hz, ½H), 3.89 (br d, J = 11.9 Hz, ½H), 3.80 (s, 3H), 3.88 (s, 3H), 3.49−3.40 (m, ½H), 3.10−3.00 (m, ½H), 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-1*H*-isoquinolin-2-yl)but-3-en-1-one (59). In the same way as for **58**, 6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline (**53**) (160 mg, 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%). R_f 0.62 (CH_2Cl_2/MeOH/25% NH_3 90:10:½). IR ($CHCl_3$) ν 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). ^{13}C 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 $C_{17}H_{22}NO_3$ (MH^+) 288.1600, found 288.1597.

1-(6,7-Dimethoxy-1-vinyl-3,4-dihydro-1*H*-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 (CH_2Cl_2/MeOH/25% NH_3 90:10:½). IR ($CHCl_3$) ν 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, ½H), 5.94−5.81 (m, 1½H), 5.25−4.92 (m, 4½H), 4.60−4.50 (m, ½H), 3.81 (s, 3H), 3.79 (s, 3H), 3.81−3.76 (m, 1H), 3.46−3.41 (m, ½H), 3.05−2.96 (m, ½H), 2.83−2.79 (m, 1H), 2.71−2.62 (m, 1H), 2.51−2.38 (m, 4H). ^{13}C 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 $C_{18}H_{24}NO_3$ (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%). R_f 0.12 (pentane/ethyl acetate). Mp 29.5−29.6 °C. IR ($CHCl_3$) ν 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). ^{13}C 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 $C_{15}H_{18}NO_3$ (MH^+) 260.1287, found 260.1293. Anal. Calcd for $C_{15}H_{17}NO_3$: 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-4*H*-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 ($CHCl_3$) 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). ^{13}C 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 $C_{16}H_{20}NO_3$ (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-1*H*-indol-3-yl)ethyl]-4-nitrobenzenesulfonamide (**65**, 2.99 g, 7.87 mmol) in acetonitrile (40 mL) was added Et_3N (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, 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 = 11.9 Hz, 1H), 3.51−3.43 (m, 1H), 3.39−3.32 (m, 1H), 3.15−3.11 (m, 2H). ^{13}C 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 CH_2Cl_2 (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 Et_3N. The solution was concentrated in vacuo and purified by column chromatography as indicated. The crude reaction mixture was diluted with EtOAc and washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, 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 ($CHCl_3$) ν 1030, 1248, 1708, 3387 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ + 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), 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). ^{13}C NMR (125 MHz, $CDCl_3$ + acetone-d_6) δ 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 $C_{19}H_{17}N_3O_4SCl$ (MH^+) 418.0628, found 418.0628. Anal. Calcd for $C_{19}H_{16}N_3O_4SCl$: 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 × 20 mL). The organic layers were washed with brine, dried over Na_2SO_4, 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%). R_f 0.12 (CH_2Cl_2/MeOH/25% NH_3 90:10:$^1/_2$). IR ($CHCl_3$) ν 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}C NMR (100 MHz) δ 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 $C_{13}H_{14}N_2Cl$ (MH^+) 233.0846, found 233.0835. Anal. Calcd for $C_{13}H_{13}N_2Cl$: 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-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline (**69**) (0.218 g, 0.937 mmol) in dichloromethane (20 mL) was added Boc_2O (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 $NaHCO_3$ (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 ($CHCl_3$) ν 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). ^{13}C NMR (125 MHz) δ 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 ($CHCl_3$) ν 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 PtO_2. The stirred solution was exposed to 1 atm of H_2 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 ($CHCl_3$) ν 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 = 8.5 Hz, 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), 2.13−2.05 (m, 1H), 1.55 and 1.51 (br s, 9H). ^{13}C 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 $NaHCO_3$ (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 Na_2SO_4, 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 ($CHCl_3$) ν 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}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 **73** (50 mg, 0.139 mmol) in CH_2Cl_2 (4 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 $NaHCO_3$ (10 mL) was added. The product was extracted with CH_2Cl_2 (3 × 10 mL) after layer separation. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Column chromatography (CH_2Cl_2/MeOH/25% NH_3 95:5:$^1/_2$) afforded vincantril as a slightly greenish solid. Yield 32 mg (0.123 mmol, 88%). R_f 0.37 (CH_2Cl_2/MeOH/25% NH_3 90:10:$^1/_2$). Mp 171.5−172.6 °C (lit.[28] mp 161−163 °C). IR ($CHCl_3$) ν 1382, 1448, 1602, 1706, 2360, 2928, 3606, 3691 cm^{-1}. ^{1}H 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}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 $C_{14}H_{14}N_2OCl$ (MH^+) 261.0795, found 261.0805. Anal. Calcd for $C_{14}H_{13}N_2OCl$: C, 64.49; H, 5.03; N, 10.74. Found: C, 64.56; H, 4.95; N, 10.66.

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

Acknowledgment. This research was financially supported (in part) by the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO). N.V. Organon (Oss, The Netherlands) is kindly acknowledged for their hospitality during the cyclization experiments in ionic liquids. Dr. G. J. Kemperman (N.V. Organon) is kindly acknowledged for providing the ionic liquids and the practical knowledge necessary to study the cyclizations in ionic liquids.

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.

JO050503T