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A New Route to α-Carbolines Based on 6π-Electrocyclization of Indole-3-alkenyl Oximes

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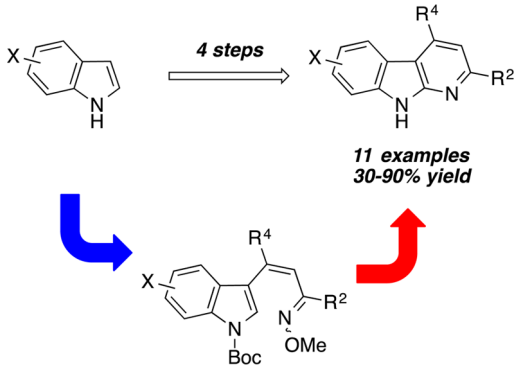
ABSTRACT



Indoles are converted into α-carbolines in four steps by acylation at C-3, Boc-protection, olefination of the resulting 3-indolyl aldehydes or ketones to give *N*-Boc-3-indolyl alkenyl oxime *O*-methyl ethers, which upon heating to 240 °C under microwave irradiation undergo loss of the Boc-group, and 6π-electrocyclization to α-carbolines, following aromatization by loss of methanol (11 examples, 30−90% yield).

In contrast to β-carbolines that are widely represented among natural products and synthetic bioactive compounds,[1−3] α-carbolines (pyrido[2,3-*b*]indoles) are considerably less well investigated.[4,5] Nevertheless there are some important examples such as the naturally occurring anticancer compounds grossularine-1 and -2[6−9] and the neuronal cell protective agent mescengricin (Figure 1).[10] In the medicinal chemistry arena, α-carbolines such as the GABA modulator,[11] and the inhibitor of microsomal triglyceride transport protein implitapide,[12,13] have also been widely studied.

As a consequence, routes for the construction of the α-carboline nucleus are of interest, but unlike their β-carboline counterparts that are almost invariably prepared from tryptophan or tryptamine derivatives, there is no main synthetic access to the isomeric α-carbolines. Thus, α-carbolines have been obtained from 2-aminoindoles,[14−16] by a variation of the Graebe−Ullmann synthesis of

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carbazoles,[17] by intramolecular Diels–Alder reaction of pyrazinones,[18] from palladium-catalyzed reactions of anilines with 2,3-dihalopyridines,[19,20] by cyclization of 2-isocyanato-indoles,[6–8] and of iminyl radicals.[21–24] However, we were attracted by the possibility of developing a more general route based on a 6π-electrocyclic process, and we now report our initial results.

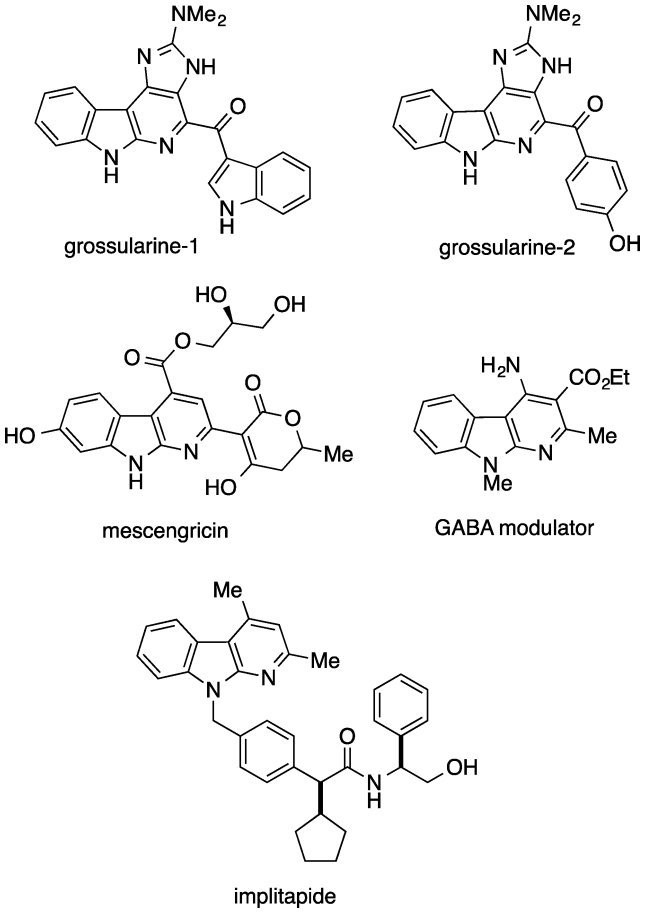
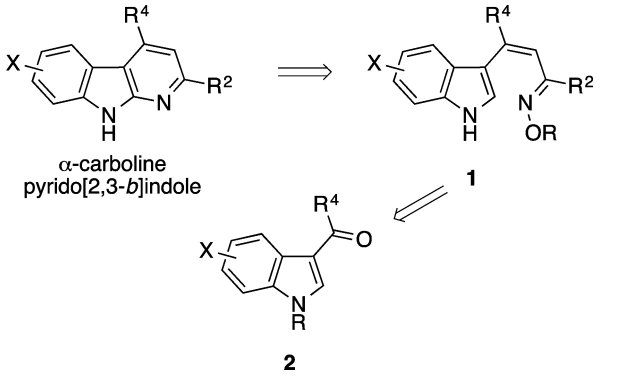


Figure 1. Structures of naturally occurring and bioactive α-carbolines.

The projected precursors to α-carbolines were the 3-indolyl alkenyl oxime ethers **1**, accessible from 3-acylindoles **2** (Scheme 1). 3-Acylindoles are readily available by exploiting the natural reactivity of indoles to undergo facile

Scheme 1. Projected Route to α-Carbolines by 6π-Electrocyclization of 3-Indolyl Alkenyl Oxime Ethers



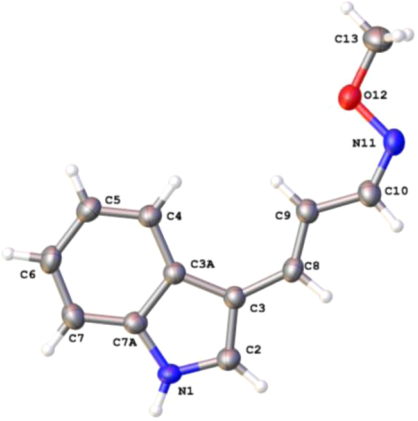


Figure 2. X-ray crystal structure of (*E*)-3-(1-methyl-1*H*-indol-3-yl)-propenal (*Z*)-methyl oxime.

acylation at the 3-position. The participation of oxime ethers in 6π-electrocyclic processes is known from the work of Hibino,[25] and the possible intermediacy of imines related to **1** has been implicated in other work[23] and in a biomimetic synthesis of grossularine-1.[9]

The precursors to the desired oxime ethers were 3-acylindoles **2** and phosphonates **3**. The phosphonates were prepared by reaction of the corresponding carbonyl compound with *O*-methyl hydroxylamine, with the aldoxime precursor being prepared by acid hydrolysis of the commercially available diethyl (2,2-diethoxy)ethylphosphonate. The subsequent Horner–Wadsworth–Emmons reaction with *N*-Boc-protected 3-indolyl aldehydes or ketones gave the required alkenyl oxime ethers **4** generally as mixtures of *E*/*Z*-alkene isomers that could be readily separated and characterized, apart from alkene **4g** which was formed as the *E*-alkene.

In general only one oxime isomer was observed which, on the basis of the chemical shift of the oxime RC**H**=NOMe proton in the ^{1}H NMR spectrum, suggested that

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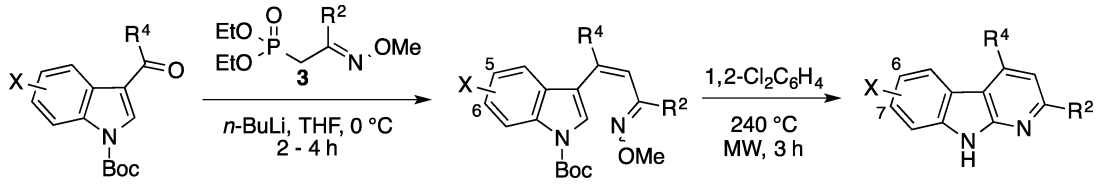
Table 1. Preparation of Indolyl Alkenyl Oxime Ethers **4** [Indoles, Phosphonates, **3a**, R^2 = H; **3b**, R^2 = Me] and Their Conversion into α-Carbolines **5** by 6π-Electrocyclization



entry	**2**	X[a]	R^4	**3**	R^2	**4**	*E* yield/%	*Z* yield/%	X[b]	**5**	yield/%
1	**a**	H	H	**a**	H	**a**	46	38	H	**a**	73
2	**b**	5-OMe	H	**a**	H	**b**	37	25	6-OMe	**b**	36
3	**c**	6-OMe	H	**a**	H	**c**	38	60	7-OMe	**c**	30
4	**d**	5-Cl	H	**a**	H	**d**	49	42	6-Cl	**d**	55
5	**a**	H	H	**b**	Me	**e**	11	22	H	**e**	90
6	**c**	6-OMe	H	**b**	Me	**f**	28	62	7-OMe	**f**	77
7	**b**	5-OMe	H	**b**	Me	**g**	34[c]	–	6-OMe	**g**	41
8	**e**	H	CO_2Me	**a**	H	**h**	38[c]	49	H	**h**	52
9	**f**	H	Me	**a**	H	**i**	49	16[c]	H	**i**	62
10	**f**	H	Me	**b**	Me	**j**	45	23	H	**j**	65
11	**e**	H	CO_2Me	**b**	Me	**k**	52	29	H	**k**	51

[a] Indole numbering. [b] α-Carboline numbering. [c] Mixture of oxime geometric isomers.

the oximes have the (*Z*)-geometry. In the case of oxime **4a**, removal of the Boc-protecting group gave the crystalline *E*-alkene-*Z*-oxime (Figure 2), confirming the *Z*-stereochemistry of the oxime double bond. The olefination reaction was then extended to indole-3-carbaldehydes bearing chloro- and alkoxy-groups, and indolyl ketones with methyl or ester groups (Table 1).

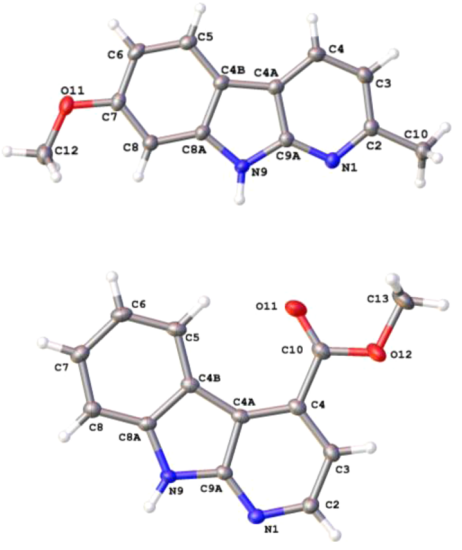


Figure 3. X-ray crystal structures of α-carbolines **5f** and **5h**.

With a range of oxime ethers **4** in hand, their thermal cyclization reactions were studied. Initially, these were investigated leaving the Boc-group in place since it was assumed that it would be cleaved under the high temperature conditions. In the event, heating **4a**, as a mixture of geometric isomers, to 180 °C in 1,2-dichlorobenzene gave a mixture of the desired α-carboline **5a** (12%) plus the Boc-deprotected starting material. Increasing the temperature to 240 °C under microwave irradiation delivered the α-carboline **5a** in 73% yield. We assume that the reaction involves initial thermal removal of the Boc-group to give the NH indole in which isomerization of the alkene into the *cis*-isomer required for electrocyclization is facilitated. In support of this, prior removal of the Boc-group in **4a** under hydrolytic conditions (82%) gave the corresponding NH indole that cyclized to α-carboline **5a** (54%) upon heating to 240 °C. It would appear that the NH is essential for cyclization since the corresponding *N*-methyl compound does not give 9-methyl-α-carboline under the same conditions. Electrocyclization of the indolyl alkenyl oxime ethers **4b**–**4k**, starting with either (*Z*)- or (*E*)-alkene isomers, proceeded similarly to give a range of α-carbolines **5** in 30–90% yield (Table 1). The structures of the carbolines **5f** and **5h** were confirmed by X-ray crystallography (Figure 3).

In conclusion, we have developed a new general route to α-carbolines that proceeds in just four steps from indoles.

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Supporting Information Available. All experimental procedures, copies of ^1H and ^{13}C NMR spectra, and cif files for X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.