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New Method of Synthesis of *Vinca* Alkaloid Derivatives

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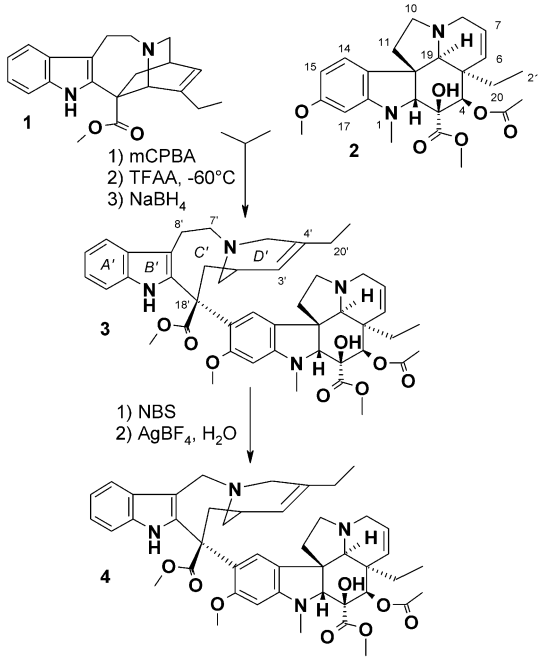
Abstract—Vinblastine and vinorelbine analogues have been synthesised by reacting new versatile electrophilic vindoline derivatives with various 3-substituted indoles. The resulting compounds have been evaluated for their antimitotic properties, but exhibited less potent activities in comparison with the standard binary *Vinca* alkaloids. © 2002 Elsevier Science Ltd. All rights reserved.

Biomimetic coupling of catharanthine **1** and vindoline **2**, leading to 3′,4′-anhydrovinblastine **3**, permitted the chemists to prepare for the first time large quantities of antimitotic *Vinca* alkaloids.[1] Further investigations resulted in the synthesis of vinorelbine **4**, obtained by *C′* ring contraction of 3′,4′-anhydrovinblastine **3** (Scheme 1).[2] Vinorelbine (Navelbine®) represents a new class of vinblastine derivatives modified in its 'upper' velbenamine moiety. Its recent advent continues and adds to the clinical success story of the *Vinca* alkaloid family, widely used in cancer chemotherapy for more than 30 years.[3]

Over the years, extensive chemistry on *Vinca* alkaloids has led to numerous compounds, obtained either by total synthesis or hemisynthesis starting mainly from the naturally occurring vinblastine.[4] Some of these derivatives have been obtained by structural modifications in the vindoline part of the molecule bearing several reactive functions.

Modifications in the velbenamine 'upper' moiety, resulting from the rearrangement of catharanthine **1**, are less easily accessible and would require a large number of steps.[5] For example, Kuehne and co-workers synthesised a series of 20′-modified vinblastine derivatives exhibiting original in vitro properties.[6] On the other hand, a non-oxidative method based on the coupling of vindoline **2** with a tertiary amine in the presence of chloroformate has been applied by Magnus et al. for a new synthesis of vinblastine.[7] In these different strategies, the vindoline unit is incorporated by nucleophilic attack of its highly reactive C_{15}.

In the course of our search for new vinorelbine analogues, we have focused on the less exploited upper part of the molecule and have developed a method based on the synthesis of versatile vindoline derivatives, which could act as electrophilic species.



Scheme 1. Structure of *Vinca* alkaloids and synthesis of vinorelbine **4**.

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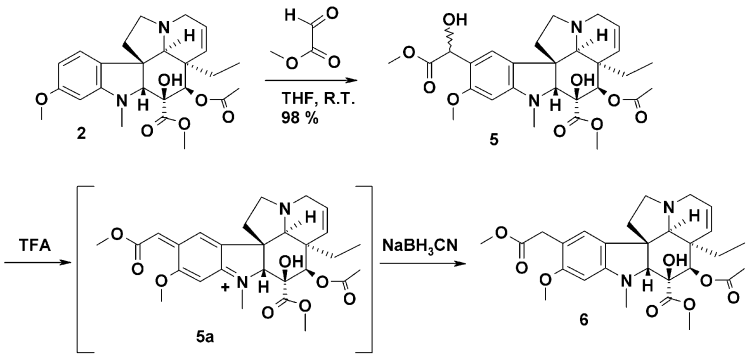
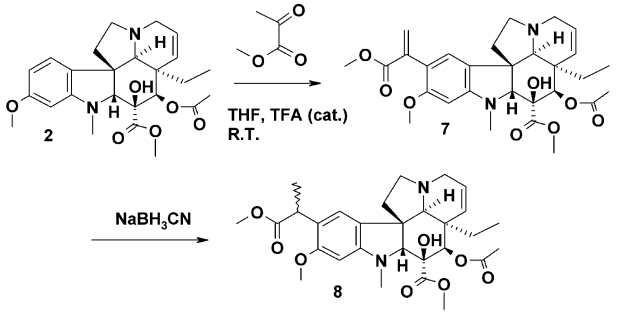
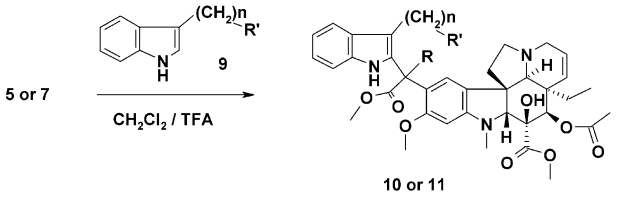


Scheme 2.



Scheme 3.



Compound	n	R	R'	Yield
10a	2	H	NH_2	90 %
10b	1	H	$N(CH_3)_2$	19 %
10c	2	H	N	42 %
10d	1	H	N	37 %
10e	1	H	N	19 %
11	2	CH_3	NH_2	44 %

Scheme 4.

Chemistry

Vindoline **2** reacts readily with methyl glyoxylate leading to the 15-substituted product **5** in quantitative yield (Scheme 2).[8]

The newly introduced methoxycarbonyl group corresponds to that present at the 18′ position included in the natural binary molecules, and was demonstrated essential for the antimitotic activity.[9] We postulated that under acidic condition, compound **5** would be dehydrated to the intermediate ion **5a**, which could react with a nucleophile. As expected, reduction of **5** by sodium cyanoborohydride in trifluoroacetic acid provided compound **6** in 72% yield. The deep blue colour of the solution before the addition of the reducing agent is in favour of the presence of ion **5a**. Similarly, reaction of vindoline **2** with methyl pyruvate afforded directly the ethylenic **7** in 70% yield, which results likely from spontaneous dehydration of the alcohol function. Also compound **7** was reduced to **8** (58%) by sodium cyanoborohydride under the same conditions (Scheme 3). These results validated our hypothesis on the possible functionalisation of the carbon equivalent to $C_{18'}$ in the binary *Vinca* alkaloids.

The reactivity of compounds **5** and **7** in the presence of nucleophiles such as indole derivatives was studied subsequently. Indole itself is known to react predominantly at its 3 position. However, when 3-substituted, the 2 position is sufficiently nucleophilic to condense with a convenient substrate.[10] Compound **5** or **7** was added to various substituted indoles **9**[11] in a mixture of methylene chloride and trifluoroacetic acid (1:1), leading to the product **10** or **11**, respectively (Scheme 4).[12]

HPLC analysis of **10a** (R = H) showed the formation of two products, presumably due to the formation of the two epimers of the junction carbon. This interpretation was consistent with the fact that certain signals in the ^{1}H NMR spectra, namely the vindoline H_{14} aromatic hydrogen were doublets. No doublets were observed for the methyl-derivative **11** ($R = CH_3$), for which only one product has been isolated in each experiment. Nevertheless, in the absence of crystallographic data, the configuration of the junction carbon has not been established.

Compounds **10a**–**e** and **11** can be considered as *seco-C′ Vinca* alkaloid analogues. Their cytotoxicity and their ability to inhibit tubulin polymerisation in vitro were evaluated. Only the tetrahydroisoquinoline derivative **10e** exerted a marginal activity on the tubulin polymerisation inhibition test under our experimental conditions. Furthermore, compared to standard *Vinca* alkaloids, none exhibited a significant level of cytotoxic activity against tumoral cell lines. Similar results have been obtained previously in the course of a study on the reactivity of vinorelbine, where derivatives lacking the $C_{7'}$–$C_{8'}$ bond in the *C′* ring were found inactive.[13]

Conclusion

A new strategy to synthesise *Vinca* alkaloid analogues has been established. The intermediate vindoline derivatives **5** and **7** can be used as electrophilic reagents, offering new opportunities for the preparation of novel compounds. Our preliminary pharmacological results, however, suggest that the integrity of the velbanamine skeleton in the *Vinca* alkaloids is important for maintaining their pharmacological properties.

Acknowledgements

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