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Straightforward access to new vinca-alkaloids *via* selective reduction of a nitrile containing anhydrovinblastine derivative

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ABSTRACT

A procedure to exclusively obtain 3′*S*-cyanoanhydrovinblastine **12** from two naturally occurring vinca-alkaloids (catharanthine and vindoline) in one step with good yield is described. Stereoselective reductions of **12**, providing straightforward access to three new vinca-alkaloids, including two diastereomers 3′*S*-cyano-(4′*R*,5′-dihydro)-anhydrovinblastine and 3′*S*-cyano-(4′*S*,5′-dihydro)-anhydrovinblastine as well as (3′*S*-aminomethyl)-(4′*S*,5′-dihydro)-anhydrovinblastine in good yields is also reported.

The vinca-alkaloids (**1**, **2**) are a family of indole–indoline dimeric compounds which have been used as anticancer agents for more than 40 years. Since then, extensive efforts in both chemistry and pharmacology have been made to identify new vinca-alkaloids which are more active and less toxic, or exhibit a wider spectrum of clinical efficacy.[1] Vinca-alkaloids are complex molecules on which it is challenging to perform selective modification and for which identification of new derivatives is difficult. Although structural changes to the northern part (velbanamine) are less easily accessible, various methods have been developed to introduce new structural features to the D′ ring.[2] Consequently a fluorinated structural analog of vinorelbine, vinflunine[3] (Javlor®), was developed and is now available in several countries (Fig. 1). Recently, Boger and co-workers succeeded in the addition of large aromatic or hetero-aromatic side-chains to the C4′ position (C20′ according to biogenetic numbering) (**4**)[4] or have incorporated the C4′ ethyl group into a C3′–C4′ cis-fused six-membered ring[5] (**5**); this work showed that the introduction of complex structural features to C4′ could lead to highly cytotoxic compounds. In other work, the octahydrophomopsin lateral chain was linked to the tertiary amine (**6**) of the velbenamine moiety, most of these compounds showed good cytotoxicity against the KB cell line.[6] Thus, modification of the velbanamine D′ ring appears to represent a viable approach to alter the cytotoxic activity of vinca-alkaloids.

Langlois and Potier disclosed the first synthetic nitrile vinca-alkaloids derivatives (**8**, **9** and **10**) as a mixture in poor yields (<30%).[7] Nitrile containing compounds can serve as key precursors for a wide-range of synthetic applications, e.g. reduction of the nitrile group to access the aminomethyl group. The resulting nucleophilic amino group can undergo a wide-range of reactions with electrophilic agents. Naturally occurring nitriles such as *bis*-indole alkaloids from *Tabernaemontana elegans*,[8] lahadinines A and B from *Kopsia pauciflora*,[9] saframycin A,[10] and cyanocycline A,[11] exhibit both antimicrobial and antitumor activities. Furthermore, a survey of nitrile-containing pharmaceuticals and clinical candidates indicates the remarkable role of the nitrile group which can act as a bioisostere of carbonyl, halogen, hydroxyl and carboxyl functional groups. Nitrile groups were also showed to improve ADME-toxicology profiles.[12]

Herein, we report the synthesis of new nitrile containing vinca-alkaloids from 3′-cyanoanhydrovinblastine **12**. Langlois and Potier first published the synthesis of 3′-cyanoanhydrovinblastine *via* conjugated iminium intermediate **11** using anhydrovinblastine *N*-oxide. Intermediate **11**, resulting from a modified Polonovski reaction, was subsequently treated with a saturated methanolic solution of KCN, but only afforded 3′-cyanoanhydrovinblastine as a mixture in low yield (32%).[7] In another attempt, the Polonovski reaction to directly couple 21-cyanocatharanthine **8** or

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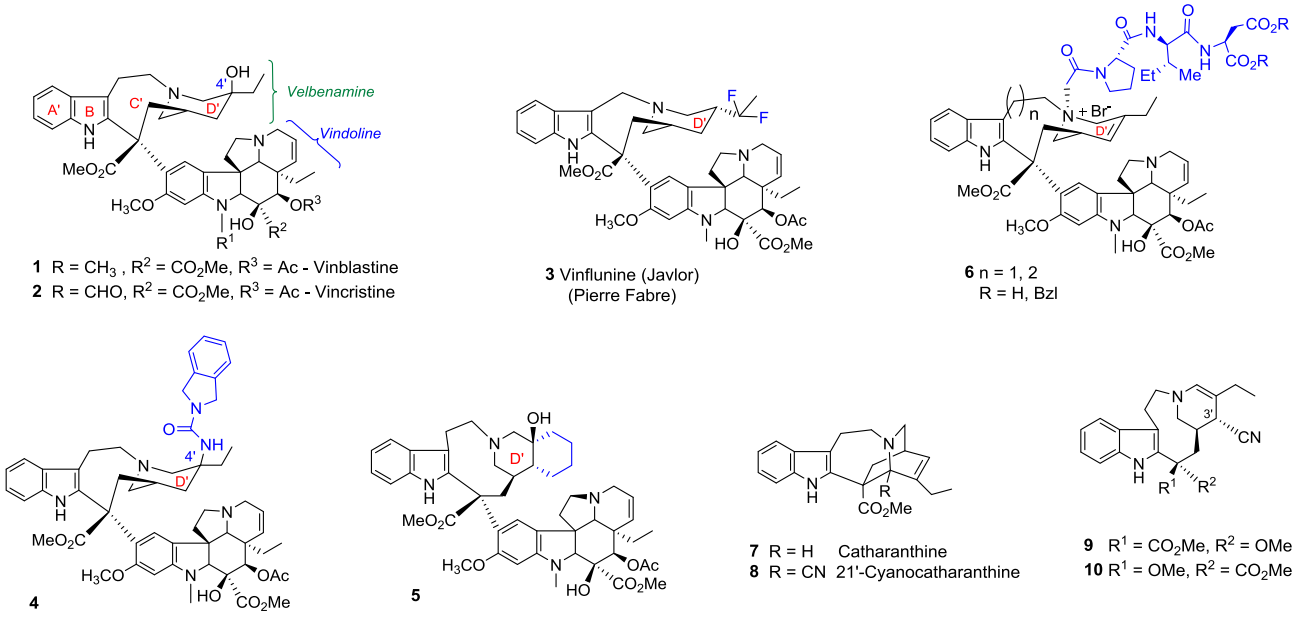
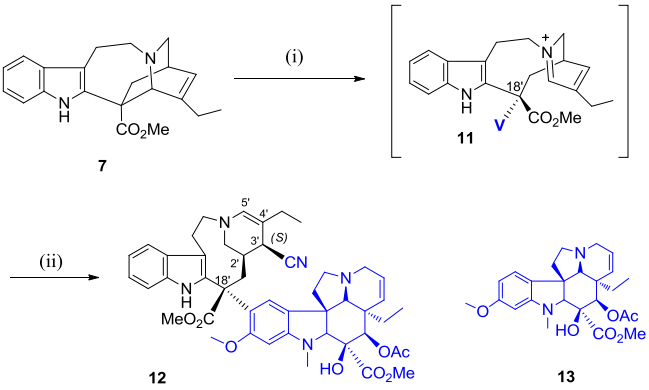


Fig. 1. Representative examples of vinca-alkaloids.

21-cyano-15,20-dihydrocatharanthine with vindoline failed to afford the corresponding *bis*-indolic compounds.[7]

In our case, 3′-cyanoanhydrovinblastine **12** was prepared exclusively in good yield (74%) *via* a modified Vukovic coupling reaction, followed by treatment with KCN in NH_4OH (Scheme 1). Vukovic and co-workers previously developed a method for coupling catharanthine **7** and vindoline **13** in the presence of Fe^{3+} in an acidic aqueous medium. They justified the exclusive obtention of the 18′*S* configuration by a concerted reaction mechanism.[13] Addition of alkali metal cyanides such as potassium cyanide, in this case, lead exclusively to 1,4-addition. The regioselectivity of addition to α,β-unsaturated iminium ion **11** is normally attributed to the hard/soft character, with soft nucleophiles preferring 1,4-addition.[14] Conducting the reaction at high temperature under basic conditions also favored 1,4-adducts.

It is noteworthy that compound **12** is relatively stable, which enabled its isolation in the crystalline form. Langlois and Potier did not establish the configuration of the C-3′ carbon bearing the nitrile group in compound **12**, although the C-3′ stereochemistry in compound **9** was reported as *R* by single-crystal X-ray analysis.[7] In our case, compounds **12** was selectively obtained as a simple diastereomer, and its C-3′ configuration determined by a NOESY experiment. According to the X-ray structure of vinblastine,[15] the



Scheme 1. Reagents and conditions: (i) vindoline (**V**) (1 eq.), $FeCl_3$ (4 eq.), glycine buffer (10 mL), HCl 0.1 N (10 mL), 35 °C, 3 h, (ii) KCN (30 eq.), NH_4OH (8 mL), 74%.

absolute configuration at C-2′ is *R*. A nuclear Overhauser effect (NOE) between H2′ and H3′ was observed, such correlations are only consistent with an absolute *S* configuration for the nitrile group (Scheme 1).

The reduction of **12** for the straightforward access to new vinca-alkaloids which can be readily functionalized, thus enabling the production of novel derivatives that may be of biological interest, was also examined. Initially, we explored the reduction of **12** in the presence of Pd/C (10%) with formic acid–triethylamine as a hydrogen donor under previously optimized conditions.[16] The catalytic transfer hydrogenation reaction using Pd/C is only selective for reducing aromatic nitriles to the corresponding primary amines and attempts to hydrogenate acrylonitrile derivatives often affords a mixture of products.[16] In this case, although formation of the amine product was not detected, compound **14a** was formed as the main product in excellent yield (Table 1, entry 1). The IR spectrum of **14a** showed a loss of absorption bands at 1650 cm^{-1} for the enamine, while the cyano band at 2229 cm^{-1} was still present. The ^1H NMR spectrum of **14a** also indicated the absence of proton H5′ at 5.92 ppm. The combination of ESI-MS, ^1H NMR, ^{13}C NMR, and 2D-NMR spectroscopic data indicated hydrogenation of the double bond in the C4′ position. Additionally, a NOESY correlation between H-4′ and H-3′ confirmed the absolute *S* configuration of C-4′ in **14a**.

Next, we examined catalytic reduction using different strong hydride donors, including $NaBH_4$, $NaBH_3CN$ and $LiAlH_4$ in the presence of cobalt(II) and nickel(II) halides or their corresponding borides, to selectively reduce nitrile, ester and olefin functional groups. These functional groups are known to be inert to such reducing agents alone.[17] Interestingly, in the presence of $NaBH_3$-CN/Ni_2B, the reduction did not lead to the methylamino product but rather to hydrogenation products **14a** and **14b** (10:90) (Table 1, entry 2). Unlike compound **14a**, no NOESY correlation between H-4′ and H-3′ was observed for **14b**, suggesting the *R* absolute configuration of C-4′ (Scheme 2). Notably, high chemoselectivity and stereoselectivity were achieved for olefin versus ester and nitriles functionalities in the case of **14a**,**b**. Treating compound **12** with $NaBH_4$ and $CoCl_2$, $NiCl_2$ or their corresponding borides in EtOH, afforded a novel amine product along with the products of olefin hydrogenation (**14a**), ester reduction (**14e**) or deacetylation (**14d**) in different ratios (Table 1, entries 3–6). To our delight, amine