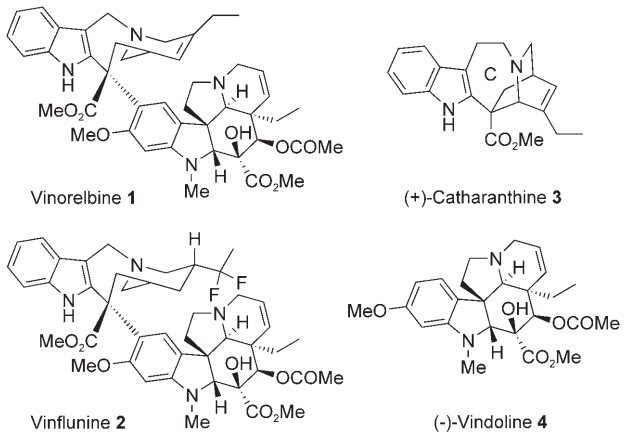

Natural-Products Synthesis

DOI: 10.1002/ange.200601307

Formal Synthesis of (+)-Catharanthine**

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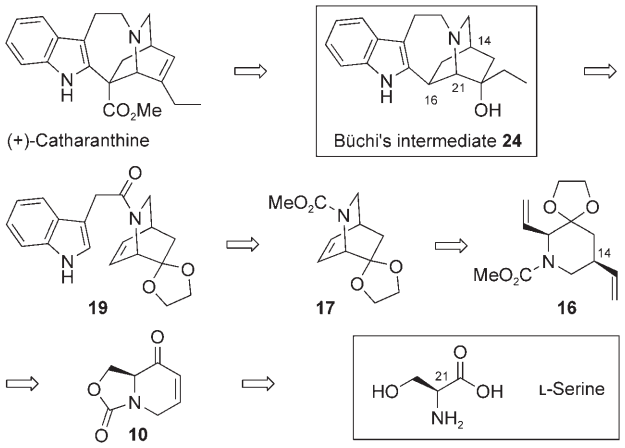
Since the discovery of vinblastine and vincristine in the late 1950s, vinca alkaloids have become one of the most powerful drug types currently in use for the clinical treatment of cancer. Over the past four decades, synthetic efforts[1] have led to the discovery of the major semisynthetic drugs vinorelbine (**1**)[2] and, more recently, vinflunine (**2**).[3] The industrial synthesis of **1** and **2** relies on the biomimetic coupling of catharanthine (**3**) and vindoline (**4**),[1] two alkaloids that are extracted from the leaves of Madagascan periwinkle (*Catharanthus roseus* L. Don). No enantioselective synthesis has yet been reported for catharanthine, which is found in minute amounts in the plant (about 0.0003 % of the dried leaf mass),[4] although numerous racemic approaches have been developed.[5] (+)-Catharanthine has been prepared only once by resolution.[6] Herein we disclose a new and efficient synthesis of a chiral intermediate for the synthesis of (+)-catharanthine.

Catharanthine (**3**) has three stereocenters, C14, C16, and C21 (see **24** in Scheme 1), which are integrated into the isoquinuclidine skeleton. Its structure is further characterized by the seven-membered C ring, which links the indole subunit to the isoquinuclidine moiety. We chose alcohol **24**, in which each stereocenter is unequivocally defined, as the target compound (Scheme 1). In their elegant total synthesis of (±)-catharanthine, Büchi et al. demonstrated that **24** could be transformed readily into catharanthine by introducing the methoxycarbonyl group at C16 and effecting dehydration of the tertiary alcohol.[5a]



Scheme 1. Retrosynthetic analysis of the key intermediate **24** in the synthesis of (±)-catharanthine by Büchi et al.

In that context, our plan was first to design a route to the optically active isoquinuclidine **17** and to couple it to the indole moiety, as shown retrosynthetically in Scheme 1. Since previously reported attempts to obtain optically active isoquinuclidines analogous to **17** by [4+2] cycloaddition had been unsuccessful,[7] we envisaged that the azabicyclo-[2.2.2]alkene system could be prepared by ring-closing metathesis (RCM) of the *cis*-2,5-dialkenyl *N*-acyl piperidine **16**. The stereocenter C14 would derive from the stereocontrolled

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[**] This research is part of a collaboration between "CEA/Direction des Sciences du Vivant" and "Pierre Fabre Médicament".
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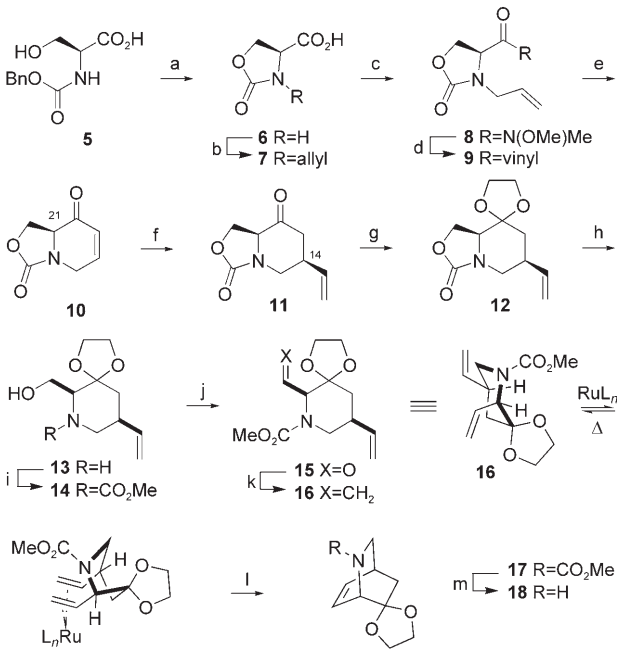
Michael addition of a vinyl group to the cyclic enone **10**. Compound **10** could in turn be prepared in five steps starting from protected L-serine, our source of chirality.

Our synthesis started from *N*-benzyloxycarbonyl-L-serine (**5**; Scheme 2). Upon treatment with sodium hydroxide, **5** was converted in 73% yield into oxazolidinone **6**, which was subsequently allylated to give **7** in 61% yield. The conversion of **7** into the corresponding Weinreb amide **8** was carried out in 76% yield under standard EDCI-mediated peptide-coupling conditions. Measurement of the *ee* value of **8** indicated little erosion of the enantiomeric excess (< 5%) over these last three steps.[8] Recrystallization from Et_2O/CH_2Cl_2 provided material of > 99% *ee*. The addition of vinylmagnesium bromide, followed by careful quenching of the reaction with anhydrous acetic anhydride, provided enone **9** in 81% yield. Enone **10** was then obtained in 87% yield by the treatment of **9** with the second-generation Grubbs catalyst (G2).[9] The rapid filtration of crude **10** through a short pad of silica was found to be the most efficient procedure for its purification, as epimerization of the stereogenic center C21 was thus avoided.

With enone **10** in hand, we next had to install the C14 stereocenter by the conjugate addition of vinylmagnesium bromide. The 1,4-nucleophilic attack of the vinyl group proceeded smoothly in the presence of a stoichiometric amount of CuI at −78 °C to afford a 9:1 mixture of diastereomers. As the hydrogen atom at C21 proved to be labile, the carbonyl group of **11** was directly protected to give the corresponding dioxolane **12** in 70% yield (two steps). At this stage, chromatography over silica permitted the isolation of the major diastereomer, whose *cis* configuration was established unambiguously by X-ray crystallographic analysis (Figure 1).[10]



Scheme 2. Synthesis of the optically active isoquinuclidine **18**: a) NaOH, H_2O, room temperature, 73%; b) allyl iodide, NaH, DMF, 61%; c) HN(OMe)Me·HCl, EDCI, DIPEA, CH_2Cl_2, 76%; d) 1) vinylmagnesium bromide, THF, 0 °C; 2) acetic anhydride, 81%; e) G2 (10 mol%), CH_2Cl_2, reflux, 87%; f) vinylmagnesium bromide, CuI, THF, −78 °C; g) ethylene glycol, CH_2Cl_2, TsOH, 70% (2 steps); h) NaOH, H_2O/MeOH, reflux, 18 h; i) $ClCO_2Me$, $NaHCO_3$, THF, 81% (2 steps); j) TPAP, NMO, CH_2Cl_2, 75%; k) Tebbe reagent, Et_2O, −10 °C, 83%; l) G2 (10 mol%), CH_2Cl_2, reflux, 20 h, 84%; m) MeLi, Et_2O, 0 °C, 1 h, 74%. Bn = benzyl, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarboiimide, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate, Ts = *p*-toluenesulfonyl.

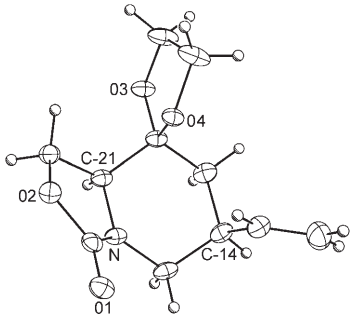
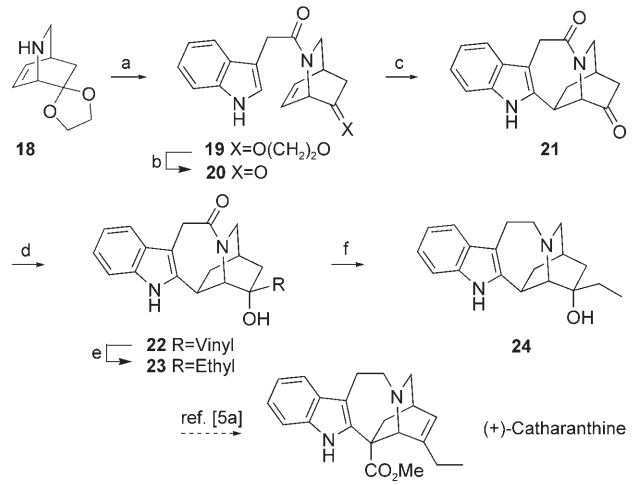


Figure 1. Molecular structure of **12**. Displacement ellipsoids are drawn at the 30% probability level.

We speculate that the observed stereoselectivity of the 1,4-addition could originate from the nitrogen lone-pair electrons, which may direct the *syn* attack of the vinyl group. With the desired *cis* isomer in hand, the second olefinic side chain was introduced. First, the oxazolidinone was hydrolyzed under alkaline conditions followed by protection of the resulting secondary amine as a methyl carbamate. Subsequent TPAP/NMO[11] oxidation of the alcohol provided aldehyde **15** in 75% yield. Finally, the methylenation of **15** occurred in 83% yield in the presence of the Tebbe reagent.

The stage was thus set for the intramolecular alkene metathesis. Despite the prolific use of RCM for the synthesis of bridged azabicyclic structures,[12] no example of the synthesis of azabicyclo[2.2.2]alkene systems has been reported. Indeed, RCM is performed in most cases on *N*-acyl *cis*-2,6-dialkenyl piperidines, as 1,3 allylic strain[13] favors the required axial-like orientation of the alkenyl side chains. In the case of the *N*-acyl *cis*-2,5-dialkenyl piperidine **16**, a less-favored boat conformation is required to bring the substituents at the 2- and the 5-position of the ring into an axial orientation. Nevertheless, upon treatment with the second-generation Grubbs catalyst (10 mol%) in refluxing CH_2Cl_2, piperidine **16** was converted smoothly into isoquinuclidine **17** in 84% yield and with > 99% *ee*.

Isoquinuclidine **17** was next coupled to the indole moiety. First, the secondary nitrogen atom was deprotected with MeLi. The product (**18**) was then treated with 3-indoleacetatic acid in the presence of EDCI (→**19**, 94% yield; Scheme 3), the ketal protecting group removed under acidic conditions (→**20**, 88% yield), and the C ring closed by using the Pd^{II}/Ag^{I} mixed-metal-mediated cyclization developed by Trost and co-workers.[5c] Controlled reduction of the σ C–Pd bond in the resulting intermediate with $NaBH_4$ in MeOH



Scheme 3. Completion of the synthesis: a) 3-indoleacetic acid, EDCI, CH_2Cl_2, 94%; b) TsOH, H_2O, acetone, reflux, 96 h, 88%; c) 1) $[(CH_3CN)_2PdCl_2]$, $AgBF_4$, CH_3CN, RT→70°C, 18 h; 2) MeOH, $NaBH_4$, 0°C; d) vinylmagnesium bromide, THF, 0°C, 48% (2 steps); e) H_2, PtO_2, THF, room temperature, 70%; f) $AlCl_3$–$LiAlH_4$, THF, 0°C, 77%.

afforded ketone **21** as the major product, together with a small amount of the corresponding alcohol (< 5%). The addition of vinylmagnesium bromide to **21** gave the tertiary alcohol **22** as a single diastereomer. Subsequent hydrogenation over PtO_2 furnished **23** with the desired ethyl side chain in 70% yield. As previously observed by others, a direct introduction of the side chain by using ethylmagnesium bromide was unsuccessful owing to competing reduction of the ketone by hydride transfer from the Grignard reagent.[5a] Finally, the amide was reduced to the corresponding amine with $AlCl_3$–$LiAlH_4$ to give the key intermediate **24**. In our case, the Büchi intermediate **24**, which can be transformed in five steps into (+)-catharanthine, was obtained in virtually optically pure form with greater than 99% *ee*.

In summary, we have disclosed herein the formal synthesis of (+)-catharanthine, the crucial intermediate for the industrial synthesis of the major antitumor drug vinorelbine. Our approach starts from naturally occurring L-serine and is based on two key steps, namely, the stereocontrolled *cis* addition of a vinyl group to the cyclic enone **10** and unprecedented RCM of an *N*-acyl *cis*-2,5-dialkenyl piperidine system. The strategy we have developed to meet this synthetic challenge may be viewed as a general route for the synthesis of optically active isoquinuclidines.

Received: April 3, 2006
Published online: July 17, 2006

Keywords: alkaloids · antitumor agents · metathesis · natural products · synthetic methods

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