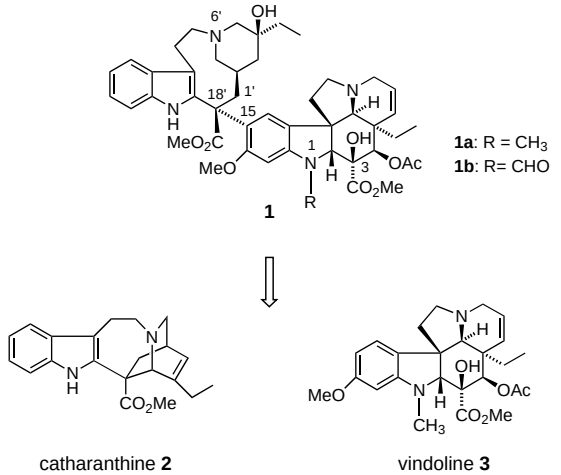
First De Novo Synthesis of the Bisindole Alkaloid Vinblastine

Christoph Schneider*

As a result of their extremely potent cytotoxic activity the bisindole alkaloids vinblastine (**1a**) and vincristine (**1b**) (see Scheme 1), isolated at the end of the 1950s independently by the groups of Noble and Svoboda,[1a] have become one of the most attractive research targets in medicine, biology, and chemistry[2] and are currently used in the therapy of particularly fast growing tumor types (leukemia, lymphoma). The complete chemical structure of **1b** was completely solved relatively early by Lipscomb and Moncrief by crystal structure analysis of the methiodide[1b] and applied to **1a** because of the known relationship of the two natural products. A pentacyclic, relatively rigid vindoline alkaloid is connected to a tetracyclic, conformationally flexible velbanamine fragment through a central C–C bond buried in the interior of the molecule.

Extensive biosynthetic investigations have suggested the monomeric indole alkaloids catharanthine (**2**) and vindoline (**3**) as direct biogenetic precursors (Scheme 1),[2] which after oxidative activation of catharanthine—presumably as the 7-hydroperoxyindolenine—are coupled to anhydrovinblastine and finally converted into vinblastine. The potent cytotoxic action derives from an antimitotic activity which comprises an inhibition of tubulin polymerization and consequent prevention of cell division.[2] Problematic and in the final instance dose-limiting are the side effects on hemopoiesis (vinblastine) and the nervous system (vincristine).



Scheme 1. Vinblastine (**1a**) and vincristine (**1b**) and the biogenetic precursors of **1a**.

Whereas the monomers catharanthine (**2**) and vindoline (**3**) can be obtained in significant amounts from *Catharanthus roseus*, vinblastine and vincristine themselves are present there only in traces. It is for this reason that semi-synthetic strategies were initially followed for their construction, when usually vindoline from natural sources was used as starting material. Difficulties soon arose in constructing the correct stereochemistry at the quaternary C(18′) chiral center essential for the biological activity. The groups of Potier and Langlois,[3] Kutney,[4] Kuehne,[5] and Magnus[6] were able to solve this problem elegantly in their respective vinblastine syntheses, but they all used natural vindoline as the starting material for their syntheses.

After more than 40 years of intensive vinblastine research Fukuyama et al. have now successfully achieved the first total synthesis from simple starting materials, which provides the natural product in an overall yield of 1 %[7] and thus for the first time makes it possible to carry out broadly based structure-activity studies which also include the vindoline fragment of the natural product.

Sufficient amounts of synthetic vindoline (**3**) were obtained by means of a new indole synthesis that uses quinolines as starting materials (Scheme 2).[8] The reaction of 7-(methylsulfonyloxy)quinoline (**4**) with thiophosgene/$NaBH_4$ led to a reductive ring opening of the heterocycle to give the isothiocyanate **5**, from which the thioanilide **6**, the actual substrate for the indole synthesis, was obtained by the addition of an unsymmetrical malonate ester. The known thiophilic nature of the tributyltin radical was now used to produce an N,S-substituted carbon radical from **6** under classical Bu_3SN/AIBN conditions. This radical reacted in a 5-*exo* cyclization with the neighboring double bond after which in situ elimination of BuSnSH gave the complete indole framework **7** of vindoline.

Selective cleavage of the malonate ester paved the way for a Mannich reaction with concomitant decarboxylation to form the conjugated ester **8**, which was coupled through the subsequently liberated OH function with the enantiomerically pure sulfonamide **9** (synthesis not shown here) under Mitsunobu conditions to yield **10**. The dinitrosulfonyl (DNs)

[*] Priv.-Doz. Dr. C. Schneider
Institut für Organische Chemie
Georg-August-Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399660
E-mail: cschnei1@gwdg.de

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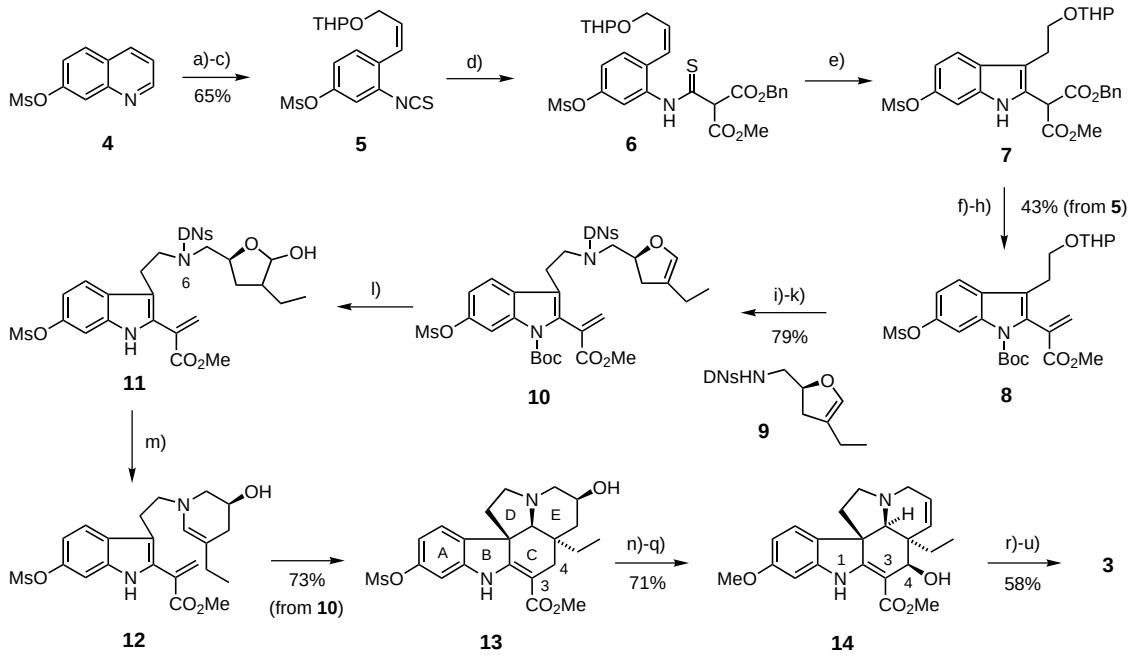

Scheme 2. Synthesis of vindoline (**3**) by a novel indole synthesis according to Fukuyama et al. a) $CSCl_2$, Na_2CO_3; b) $NaBH_4$, MeOH; c) dihydropyran, H^+; d) benzylmethylmalonate, NaH; e) Bu_3SnH, AIBN; f) Boc_2O, NEt_3; g) $Pd/C/H_2$; h) $Me_2NH \cdot HCl$, HCHO; i) MeOH, H^+, k) DEAD, PPh_3, **9**; l) TFA, Me_2S; m) pyrrolidine, $0 \rightarrow 50\,^{\circ}C$; n) PPh_3, CCl_4; o) KO*t*Bu, MeI; q) $(PhSeO)_2O$; r) mCPBA, MeOH; s) HCl, $Na(CNBH_3)$; t) HCHO, $Na(CNBH_3)$; u) Ac_2O, NaOAc. AIBN = azobisisobutyronitrile, DEAD = diethylazodicarboxylate, Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid, mCPBA = *meta*-chloroperbenzoic acid; Ms = methylsulfonyl, THP = tetrahydropyranyl, Bn = benzyl.

protecting group for N(6) was chosen for two reasons: it allowed a facile N-alkylation with the Mitsunobu reaction, and it could be readily cleaved with nucelophiles under extremely mild conditions. Its use was developed specially as part of the synthesis of this natural product.[9]

Compound **10** constitutes the complete vindoline carbon framework in a partly acyclic form. The stereochemically correct construction of the ABCDE ring system now followed in only two simple, elegant synthetic operations. Under acidic conditions the enol ether was first hydrated to the lactol **11**, followed by deprotection of the central N(6) by reaction with pyrrolidine by which the aminolactol was transformed into the cyclic hydroxyeneamine **12** (E ring). This on heating underwent a Diels–Alder reaction with inverse electron demand with the opposing diene unit and afforded the pentacyclic vindoline ring system **13** stereoselectively in 73% yield. Thus in their synthesis of the CD ring system the authors followed the biogenic pathway proposed by Wenkert and Scott[10] and the biomimetic synthesis of a whole series of indole alkaloids by Kuehne et al.[11]

The conversion of **13** into vindoline (**3**) follows closely work by Danieli et al.[12] for the stereoselective introduction of hydroxy groups at C(3) and C(4). After regioselective elimination of the secondary hydroxy function in the E ring and protective group exchange at the phenolic hydroxy group of the A ring dehydration with benzeneseleninic anhydride gave the conjugated imine which was hydrated at C(4) and yielded **14**. By treatment with *meta*-chloroperbenzoic acid, **14** was first oxidized at C(3) and then methylated at N(1) by imine reduction and reductive amination. Remarkably, both the introduction of the hydroxy groups and the imine reduction occurred stereoselectively in each case on the β side of the vindoline framework, presumably because the neighboring ethyl group sterically shielded the α side. Vindoline (**3**) is thus very efficiently accessible in an overall yield of more than 6% (starting from **4**).

For attachment of the velbanamine fragment an 11-membered N-heterocycle **21** was envisaged in which after successful coupling with vindoline cyclization to the piperidine ring should occur by intramolecular S_N reaction at the tosylate (Scheme 3). In-depth investigations by Schill et al. on similar model compounds had shown that aromatic substitution on vindoline with such a substrate should give the correct configuration at C(18′).[13]

Again, for the synthesis of the indole fragment **21** the reliable Fukuyama method under radical conditions was used. For this purpose the required thioanilide **17** was generated from the isothiocyanate **15** by addition of ester **16** (synthesis not shown here), and radical cyclization with Bu_3SnH/Et_3B gave the indole **18** in 67% yield even at room temperature. A number of protective group manipulations and renewed Mitsunobu reaction with 4-nitrobenzenesulfonamide ultimately gave the sulfonamide **19** which underwent an intramolecular S_N2 reaction at the epoxide with K_2CO_3 in refluxing DMF to give the 11-membered N-heterocycle **20** in 82% yield. Further standard reactions led finally to the second key compound **21** (2% overall yield over the longest linear sequence).

For the critical coupling of fragments **3** and **21** to form the central C(15)–C(18′) bond in vinblastine use was made of the established *t*BuOCl indole activation introduced by the groups of Kutney and Neuss[14] which produced the chloroindolenine **22** from **21**. By reaction with trifluoroacetic acid **22** was activated to the iminium salt **23** (Scheme 4). In an

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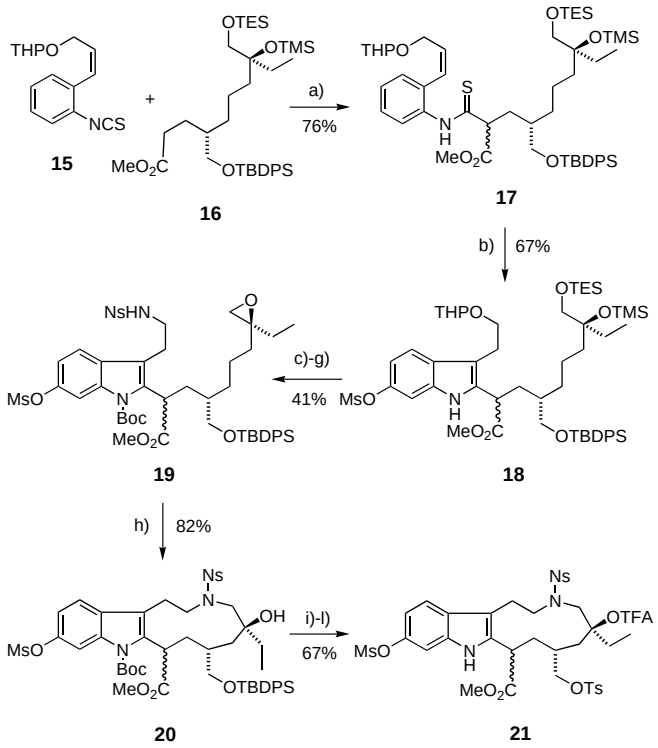
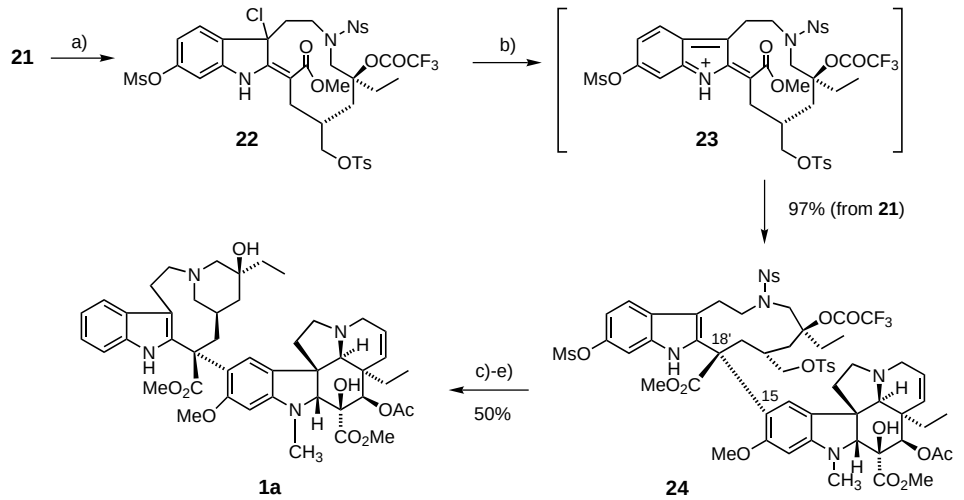


Scheme 3. Synthesis of the 11-membered N heterocycle **21** as velbanamine fragment. a) LDA; b) Bu_3SnH, Et_3B; c) Boc_2O, NEt_3; d) $AcOH/H_2O$; e) TsCl, Bu_2SnO, NEt_3; f) $NaHCO_3$, DMF; g) $NsNH_2$, DEAD, PPh_3; h) K_2CO_3, DMF; i) TFA; k) TsCl, $Me_2N(CH_2)_3NMe_2$; l) TFAA, pyridine. LDA = lithium diisopropylamide, Ts = tolylsufonyl, DMF = dimethylformamide, Ns = 4-nitrobenzenesulfonyl, TFAA = trifluoroacetic anhydride; TES = triethylsilyl, TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

electrophilic aromatic substitution reaction coupling with vindoline (**3**) occurred almost quantitatively, and the vinblastine precursor **24** was formed with correct and uniform (18′*S*) configuration. This stereochemical result is in agreement with the formation of an *E*-configured C(17′)–C(18′) double bond in **23** and the subsequent nucleophilic addition of vindoline on the front of the molecule controlled by the ring conformation of the 11-membered heterocycle.[13] Deprotection of the alcohol and amino groups in the velbanamine fragment led then directly to cyclization to the piperidine ring by which the synthesis of **1a** was completed.

The synthesis described here has not only made the biologically highly active and pharmacologically interesting bisindole alkaloid vinblastine accessible for the first time by total synthesis, thus opening the way for the syntheses of analogues and potentially "better" compounds by this route. Also it has led to the development of versatile new methods which equally will provide valuable service in the solution of other synthetic problems.



Scheme 4. Final synthesis of vinblastine (**1a**). a) *t*BuOCl; b) TFA, vindoline **3**; c) NEt_3, MeOH; d) $HSCH_2CH_2OH$, DBU; e) $NaHCO_3$, *i*PrOH. DBU = 1,6-diazabicycloundecene.

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