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Stereocontrolled Total Synthesis of (+)-Vinblastine

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Vinblastine (**1**), isolated from *Catharanthus roseus*,[1] has been widely known as a prominent agent in cancer chemotherapy. Since chemical modifications of the natural product have been the major means for exploration of the more potent analogues, a limited number of its derivatives have so far been accessible.[2a] Total synthesis of vinblastine, on the other hand, has been the subject of intensive investigations in the area of alkaloid synthesis.[2b] Despite the endeavors spanning over the past three decades, only four syntheses have been reported to date.[3] In all cases, however, the supply of the lower half of vinblastine (i.e., vindoline) relied upon the natural sources. The major challenges in the total synthesis of **1** include controlling the stereochemistry of C18′ as well as establishment of efficient routes to the two halves of the indole units.

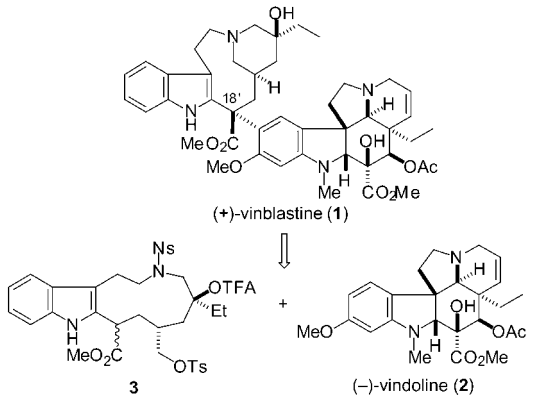
Our synthetic plan is shown in Scheme 1. Model studies by Schill as well as our molecular modeling study strongly suggested that a stereocontrolled coupling with vindoline (**2**) could be performed when one employs an eleven-membered intermediate such as **3** as a partner.[4] Synthesis of the lower half, vindoline (**2**), would require substantial improvement over our biomimetic total synthesis to supply a sizable amount of the mateiral.[5] On the other hand, we planned to synthesize the upper half by means of our indole synthesis via radical cyclization of *o*-alkenylthioanilide.[6]

An improved preparation of the requisite amine unit **8** for the synthesis of vindoline is outlined in Scheme 2. 3-Ethyl-5-phenyl-4-pentenal (**4**), readily derived from 2-pentenal,[7] was transformed into cyanohydrin acetate **5** in 2 steps. Enzymatic hydrolysis of the acetate **5** afforded a diastereomeric mixture of (*S*)-cyanohydrins. Ozonolysis and subsequent dehydration of the resulting hemiacetal gave dihydrofuran **7**. Reduction of the cyano group with $LiAlH_4$ furnished a volatile amine, which was immediately converted to the corresponding 2,4-dinitrobenzensulfonamide (DNs-NHR) **8**.[8]

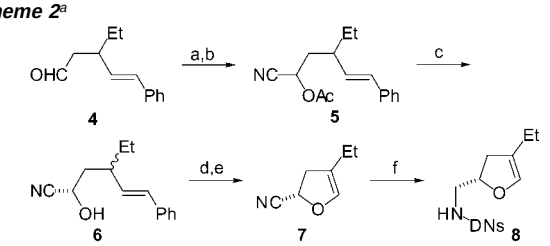
The key indole unit **13** was prepared by means of the protocol developed recently in our laboratories for facile conversion of quinolines to indoles (Scheme 3). Thus, 7-mesyloxyquinoline (**9**)[9] was converted to isothiocyanate **10** by treatment with thiophosgene followed by reduction with $NaBH_4$.[10] After protection of the hydroxyl group as its THP ether, nucleophilic addition of the anion of benzyl methyl malonate to the isothiocyanate afforded thioanilide **11**. The radical cyclization of **11** proceeded smoothly to furnish indole **12**. For conversion to indole acrylate **13**, benzyl ester of Boc-protected **12** was first subjected to hydrogenolysis, and the subsequent decarboxylative Mannich reaction proceeded without incident to give, after deprotection of the THP group, the desired indole unit **13**.

Having established much more efficient processes for the preparation of both the indole unit **13** and the amine unit **8**, the coupling reaction of the two units and subsequent transformations

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) NaCN, AcOH, room temperature; (b) Ac_2O, pyridine, room temperature, 95% (2 steps); (c) Lipase PS, THF−H_2O, 50 °C, 44%, 97% ee; (d) O_3, MeOH, CH_2Cl_2, −78 °C; Me_2S, 91%; (e) MsCl, Et_3N, toluene, 0 to 80 °C, 71%; (f) $LiAlH_4$, THF, −10 °C to room temperature; H_2O, NaOH; DNsCl, CH_2Cl_2, 75%.

were performed according to the synthetic pathway reported earlier[5] to provide (−)-vindoline (**2**) in several hundred-milligram quantities (Scheme 3).[11]

With synthetic (−)-vindoline in hand, we next focused on the synthesis of the upper half (**3**) of vinblastine. The synthesis of the requisite ester **23** commenced with introduction of (*R*)-4-benzyl-2-oxazolidinone to 4-ethylpent-4-enoic acid (**16**)[12] via its mixed anhydride (Scheme 4).[13] According to Evans' method,[14] diastereoselective cyanoethylation of the resulting imide **17** afforded adduct **18** as a sole isomer. Reduction of **18**[15] followed by protection of the resulting alcohol as its TBDPS ether furnished **19**. Reduction of the nitrile **19** with DIBAL followed by treatment of the resulting aldehyde with hydroxylamine gave the oxime, which, upon exposure to sodium hypochlorite, underwent facile intramolecular 1,3-dipolar cycloaddition via the nitrile oxide to afford isoxazoline **20** as a single diastereomer. Subsequent reductive cleavage of the N−O bond gave hydroxyketone **21**. Baeyer−Villiger oxidation of **21** was best effected by treatment with *m*CPBA in acetic acid, leading to lactone **22**. Finally, methanolysis of the lactone and protection of the resultant diol furnished the desired ester **23**.

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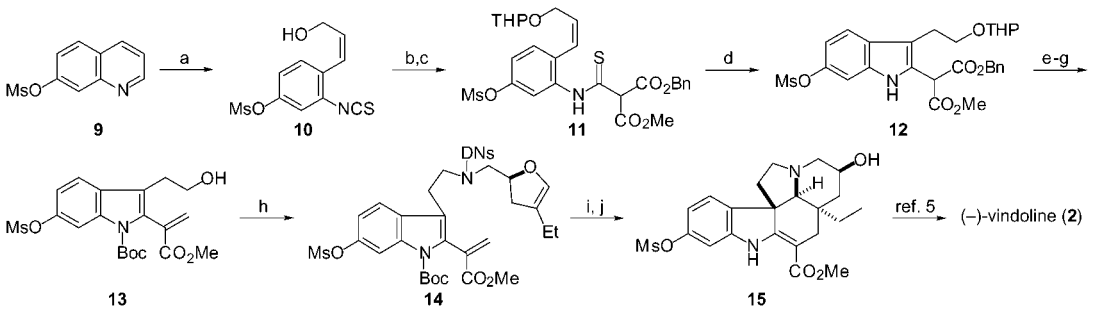
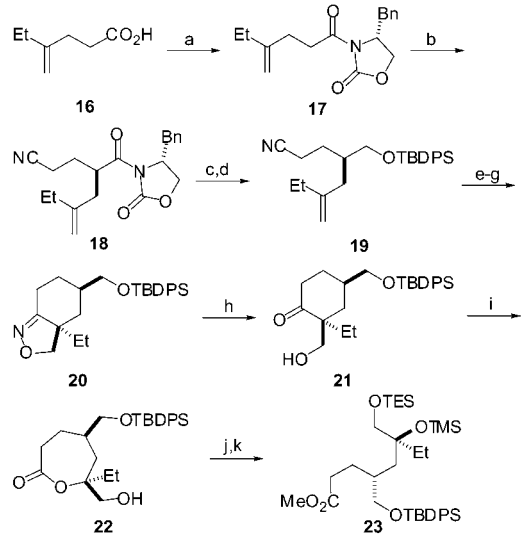
Scheme 3[a]



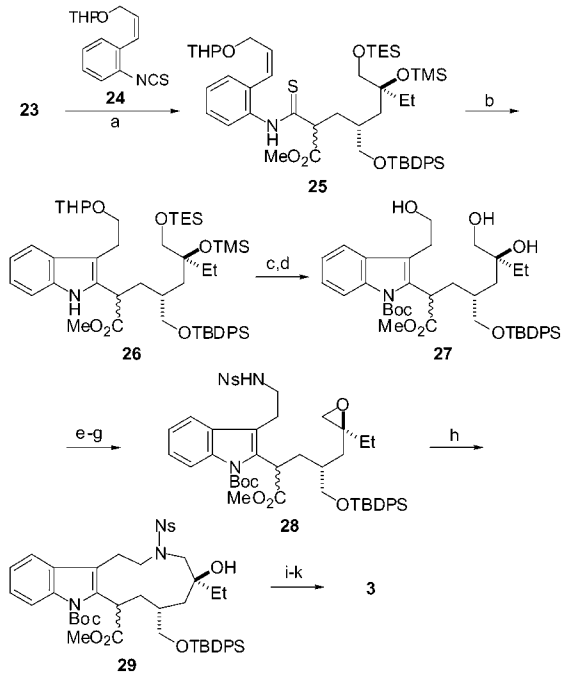
[a] Reagents and conditions: (a) thiophosgene, Na_2CO_3, THF−H_2O, 0 °C; $NaBH_4$, MeOH, 0 °C; (b) DHP, CSA, CH_2Cl_2, room temperture, 65% (2 steps); (c) benzyl methyl malonate, NaH, THF, 0 °C; (d) AIBN, Bu_3SnH, toluene, 110 °C; (e) Boc_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 60% (3 steps); (f) H_2, Pd/C, EtOH, room temperature; Me_2NH·HCl, HCHO, AcONa, AcOH-EtOH, room temperature, 72% (2 steps); (g) CSA, MeOH, room temperature, 99%; (h) **8**, DEAD, Ph_3P, benzene, 79%; (i) TFA, Me_2S, CH_2Cl_2, room temperature; (j) pyrrolidine, MeOH−CH_3CN, 0 °C to 50 °C, 73% (2 steps).

Scheme 4[a]



[a] Reagents and conditions: (a) PivCl, Et_3N, Et_2O, 0 °C; *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, −78 °C, 89%; (b) (*i*-PrO)$TiCl_3$, *i*-Pr_2NEt, acrylonitrile, CH_2Cl_2, 0 °C, 82%; (c) $NaBH_4$, THF−H_2O, room temperature, 92%; (d) TBDPSCl, imidazole, DMF, room temperature, 92%; (e) DIBAL, CH_2Cl_2, −78 °C; (f) H_2NOH·HCl, NaOAc, EtOH, room temperature; (g) NaClO aqueous, CH_2Cl_2, room temperature, 59% (3 steps); (h) Zn, AcOH, 66%; (i) *m*CPBA, AcOH, room temperature; (j) K_2CO_3, MeOH, room temperature, 80% (2 steps); (k) TESCl, imidazole, DMF, room temperature; TMSCl, room temperature, 92%.

Scheme 5[a]



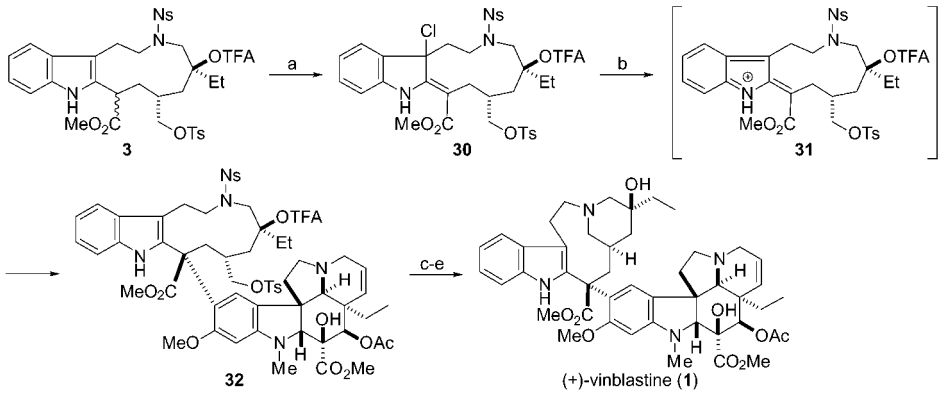
[a] Reagents and conditions: (a) LDA, THF, −78 °C; **24**, −78 to 0 °C, 76%; (b) Bu_3SnH, Et_3B, THF, room temperature, 67%; (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 87%; (d) AcOH−H_2O (95:5), 80 °C, 71%; (e) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, room temperature, 84%; (f) $NaHCO_3$, DMF, 80 °C, 90%; (g) $NsNH_2$, DEAD, Ph_3P, toluene, room temperature, 88%; (h) K_2CO_3, DMF, 90 °C, 82%; (i) TFA, CH_2Cl_2, room temperature, 85%; (j) TsCl, $Me_2N(CH_2)_3NMe_2$, CH_3CN-toluene, room temperature, 88%; (k) TFAA, pyridine, CH_2Cl_2, room temperature, 90%.

Construction of the key intermediate **3** features an indole formation of the fully functionalized thioanilide **25** and a macrocyclization using 2-nitrobenzenesulfonamide (Ns amide) (Scheme 5).[16] First, addition of the enolate of **23** to isothiocyanate **24** afforded an inconsequential mixture of thioamides **25**, which was subjected to the radical conditions to furnish indole **26**. At this stage, it became necessary to differentiate the three hydroxyl groups. Protection of the indole NH and acid-catalyzed deprotection of the hydroxyl groups gave triol **27**. Upon treatment of the triol **27** with TsCl and triethylamine in the presence of dibutyltin oxide, tosylation occurred selectively at the primary alcohol of the1,2-diol.[17] After conversion of the resulting tosylate into epoxide, the remaining primary alcohol was treated with $NsNH_2$ under Mitsunobu conditions[18] to give **28**. Upon heating with potassium carbonate in DMF, **28** underwent a critical macrocyclization to yield the eleven-membered-ring product **29**. Acid-catalyzed deprotection of the Boc group and the TBDPS ether, tosylation[19] of the resulting primary alcohol, and subsequent protection of the tertiary alcohol as its trifluoroacetate afforded the key intermediate **3**.[20]

The final stages of the total synthesis of (+)-vinblastine are illustrated in Scheme 6. Chlorination of the indole nucleus of **3** with *tert*-butyl hypochlorite furnished chloroindolenine **30**. To our great satisfaction, upon treatment of the mixture of **30** and vindoline (**2**) with trifluoroacetic acid, the coupling reaction proceeded smoothly to furnish the desired product **32** as a sole isomer in 97% yield. After deprotection of the tertiary alcohol, the Ns group was removed under mild conditions to liberate the secondary amine, which formed the piperidine ring to give (+)-vinblastine (**1**). The synthetic product was identical in all respects to natural (+)-vinblastine.

In conclusion, an efficient total synthesis of (+)-vinblastine has been accomplished through the use of the radical cyclization of *o*-alkenylthioanilides as well as the chemistry of 2-nitro- and 2,4-

Scheme 6[a]



[a] Reagents and conditions: (a) *t*-BuOCl, CH_2Cl_2, 0 °C; (b) (−)-vindoline (**2**), TFA, CH_2Cl_2, 0 °C to room temperature, 97%; (c) Et_3N, MeOH, room temperature, quantitative; (d) $HSCH_2CH_2OH$, DBU, CH_3CN, room temperature, 76%; (e) $NaHCO_3$, *i*-PrOH−H_2O, room temperature, 66%.

dinitrobenzenesulfonamides that have been developed in our laboratories for the synthesis of indole alkaloids. We believe that the present synthetic pathway could be applied to the synthesis of a wide variety of vinblastine analogues.

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Supporting Information Available: Experimental details and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Overall yield of the 22-step synthesis of **3** from the known **16** was 2.0%.

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