

Stereocontrolled total synthesis of (+)-vinblastine*

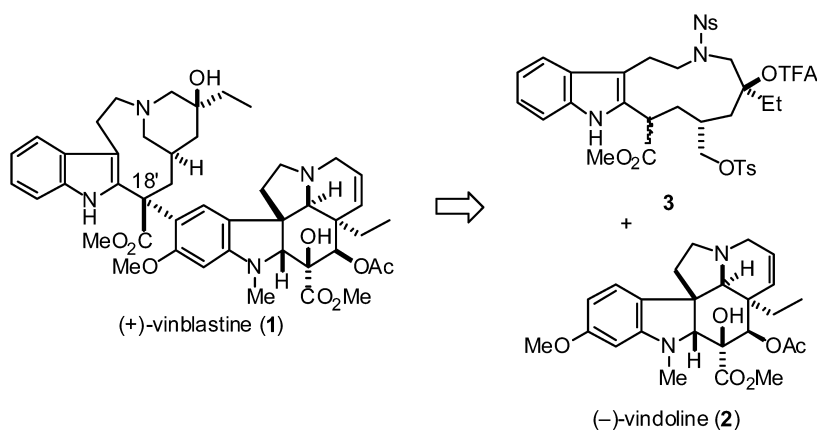
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Abstract: Stereocontrolled total synthesis of (+)-vinblastine (**1**) has been achieved using a novel radical-mediated indole synthesis developed in our laboratories. The isothiocyanate **18**, prepared readily from quinoline **17**, underwent a facile addition of the malonate anion to give **19**. The *o*-alkenylthioanilide **19** was then converted to indole **20** by radical cyclization and protection. (–)-Vindoline (**2**) was prepared from this key intermediate **20** in a highly efficient manner. The indole core of the 11-membered intermediate **3** was constructed similarly from quinoline. The critical coupling reaction between **2** and the chloroindolenine derived from **3** proceeded with complete control of stereochemistry to give the desired product **66** in 97 % yield, which could be successfully converted to (+)-vinblastine (**1**).

Vinblastine (**1**), isolated from *Catharanthus roseus* [1], has been widely known as a prominent agent for cancer chemotherapy. Since chemical modifications of the natural product have been the major means for exploration of the more potent analogs, 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 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 [4] as well as our molecular modeling study strongly suggested that a stereocontrolled coupling with vindoline (**2**) could be per-



Scheme 1

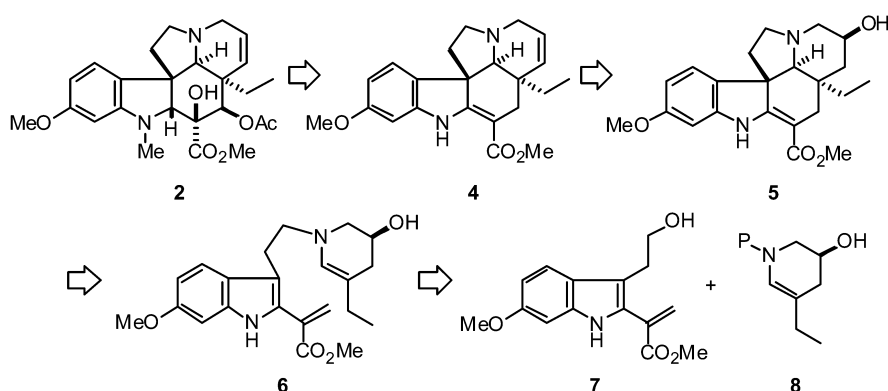
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formed when one employs an 11-membered intermediate such as **3** as a partner. Synthesis of the lower half, vindoline (**2**), would require substantial improvement over our biomimetic total synthesis to supply a sizable amount of the material [5]. On the other hand, we planned to synthesize the upper half by means of our indole synthesis via radical cyclization of *o*-alkenylthioanilide [6].

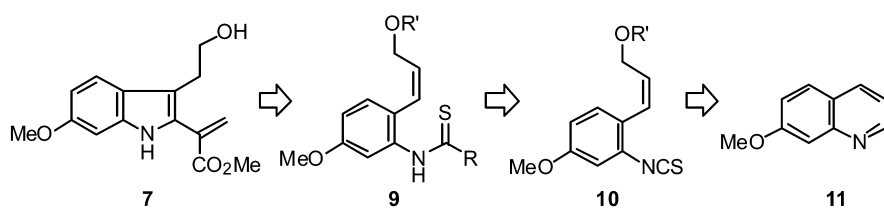
TOTAL SYNTHESIS OF (–)-VINDOLINE (**2**)

Our retrosynthetic analysis of vindoline is illustrated in Scheme 2. Vindoline in racemic as well as optically active forms has already been synthesized by several groups [7]. The key intermediate **4** was common in the total syntheses by both Danieli's [7d] and Kuehne's [7g] groups. It should be noted that Kuehne was the first to demonstrate that the chiral center of the secondary alcohol in **6** is responsible for controlling the entire stereochemistry of the aspidosperma-type skeleton in **5**. Therefore, our task was to establish an efficient synthetic route to the indole part **7** and the amine part **8**.



Scheme 2

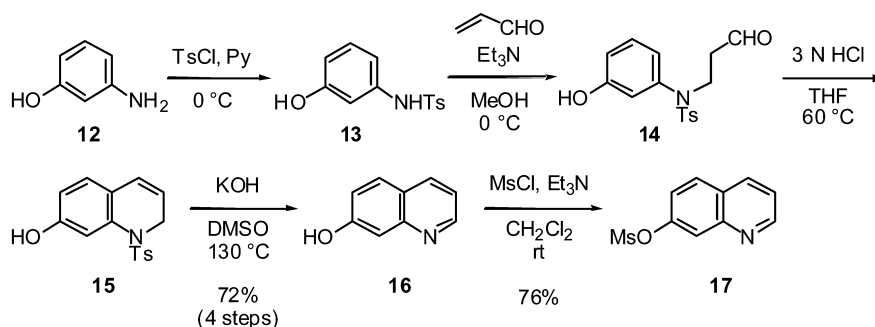
As shown in Scheme 3, synthesis of the indole part **7** could be derived from 7-methoxyquinoline **11** by means of the protocol established recently in our laboratories [8].



Scheme 3

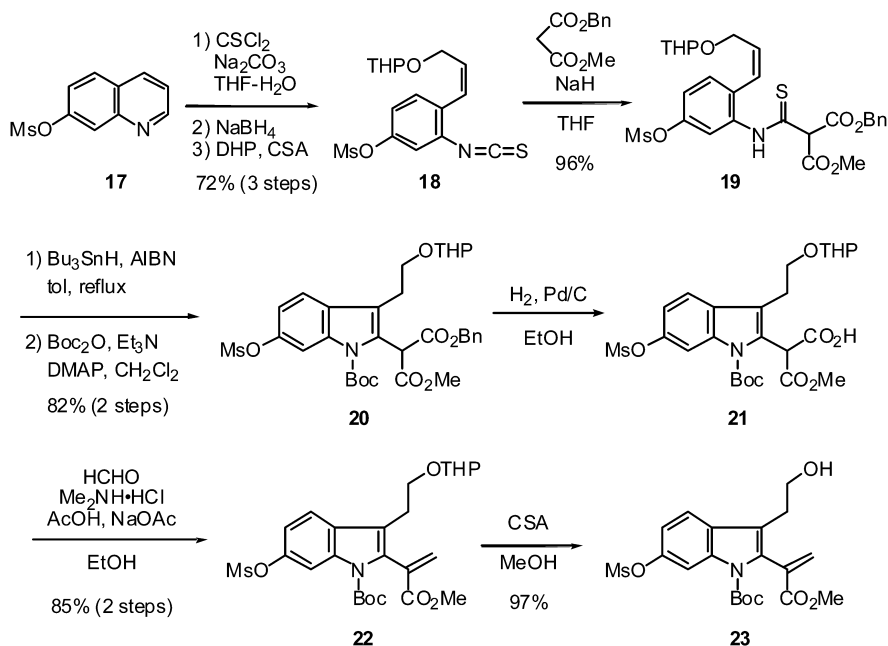
Our initial attempt at total synthesis of (–)-vindoline commenced with the preparation of quinoline **11** according to the well-known Skraup quinoline synthesis. Unfortunately, only 30 % yield of the desired 7-methoxyquinoline along with 8 % yield of 5-methoxyquinoline was obtained from *m*-anisidine under the standard conditions. Furthermore, it was very difficult to scale up the reaction. We therefore decided to devise our own method for preparation of quinolines (Scheme 4) [9]. Thus, the amino group of 3-aminophenol **12** was selectively tosylated to give **13**, which was then treated with acrolein and triethylamine to give the Michael adduct **14**. Upon heating with dilute aqueous HCl, a facile cyclization proceeded to afford the dihydroquinoline derivative **15** as the predominant product. Elimination of toluenesulfonate from **15** was facilitated by treatment with potassium hydroxide (KOH) in dimethyl sulfoxide (DMSO) at 130 °C. The crude product thus obtained was purified by crystallization as a nitric acid salt from ethanol. One hundred-gram quantities of pure 7-hydroxyquinoline **16**

was prepared from **12** in 72 % overall yield without chromatographic separations. The hydroxy group of **16** was then protected as the mesylate **17**.



Scheme 4

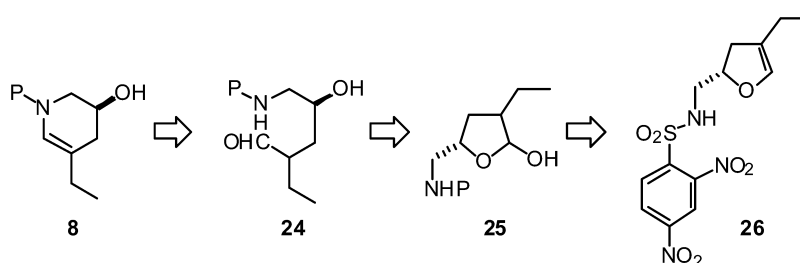
7-Mesyloxyquinoline **17** was converted to isothiocyanate **18** by treatment with thiophosgene [10] followed by reduction with NaBH_4 and protection of the resulting alcohol as the tetrahydropyranyl (THP) ether (Scheme 5). Nucleophilic addition of the anion of benzyl methyl malonate to the isothiocyanate **18** afforded thioanilide **19**. The radical cyclization of **19** proceeded smoothly to furnish, after protection of the nitrogen with a Boc group, the desired indole **20** in high yield. For the conversion of **20** into the indole acrylate **23**, benzyl ester of Boc-protected **20** 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 **23**.



Scheme 5

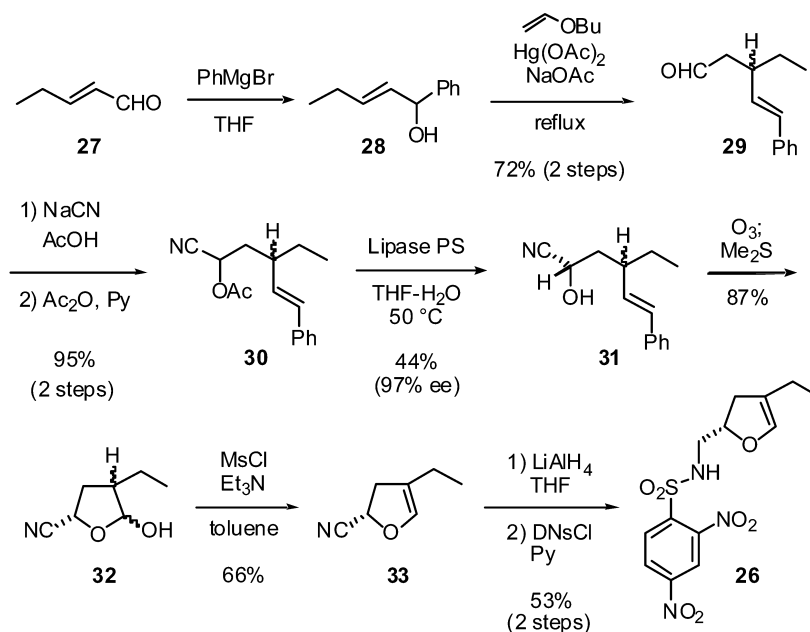
As illustrated in Scheme 6, we reasoned that 2,4-dinitrobenzenesulfonamide **26** would serve as a synthetic equivalent of the amine part **8**.

For the synthesis of **26**, commercially available 2-pentenal **27** was first treated with phenylmagnesium bromide, and the resulting adduct **28** was subjected to a one-pot Claisen rearrangement reaction



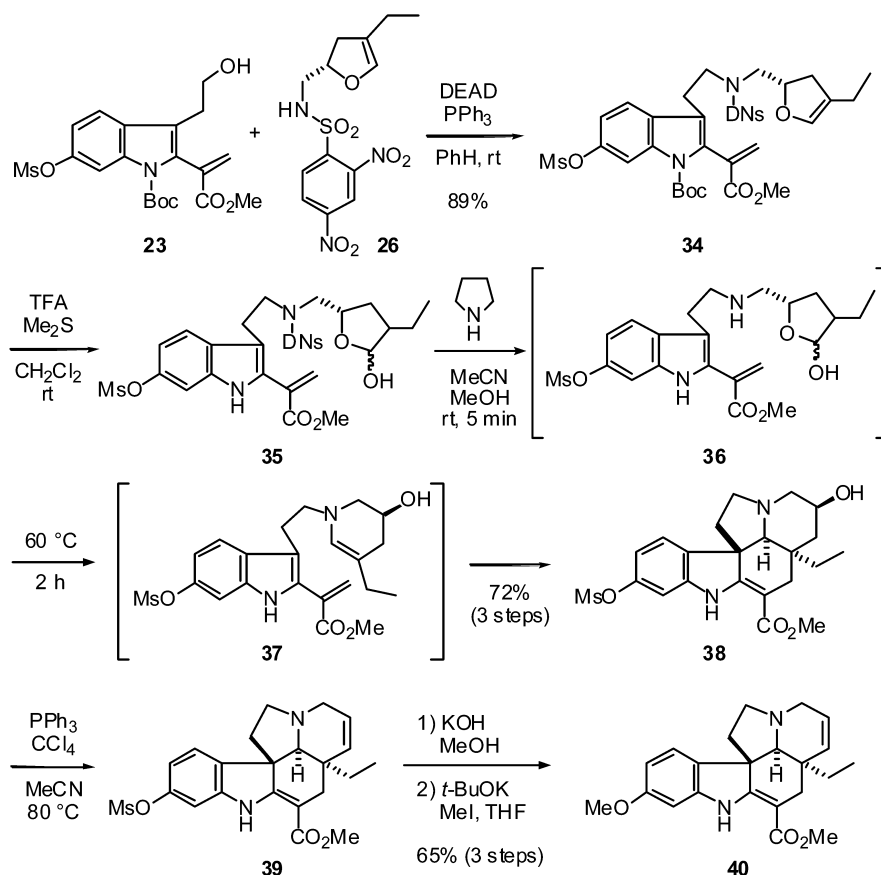
Scheme 6

to give the aldehyde **29** [11] (Scheme 7). 3-Ethyl-5-phenyl-4-pentenal **29** thus obtained was transformed into cyanohydrin acetate **30** in the usual manner. Enzymatic hydrolysis of the acetate **30** using Amano lipase polystyrene (PS) afforded a diastereomeric mixture of (*S*)-cyanohydrins **31** in excellent enantiomeric purity. Ozonolysis and subsequent dehydration of the resulting lactol **32** gave the dihydrofuran **33**. Reduction of the cyano group with LiAlH_4 furnished a volatile amine, which was immediately converted to the corresponding 2,4-dinitrobenzenesulfonamide (DNs-NHR) **26** [12].



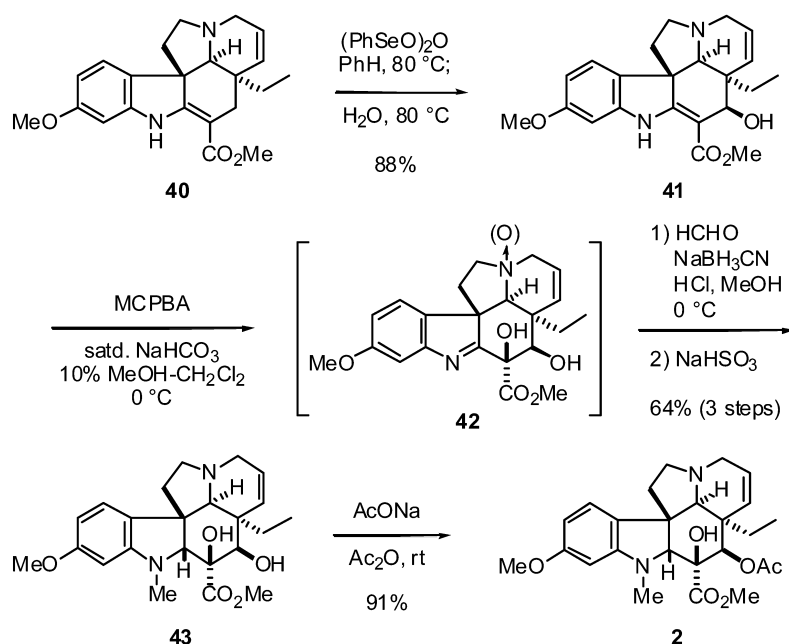
Scheme 7

Coupling of the 2,4-dinitrobenzenesulfonamide **26** and the indole part **23** by means of the Mitsunobu reaction [13] proceeded uneventfully to give the desired product **34** in 89 % yield (Scheme 8). Upon treatment with trifluoroacetic acid (TFA) in dichloromethane, **34** underwent simultaneous deprotection of the Boc group and hydration of the enol ether to give the lactol **35**, which, without purification, was subjected to the sulfonamide deprotection. Thus, treatment of the crude lactol **35** with 5 equiv of pyrrolidine in MeOH–MeCN (5:1) for 5 min at room temperature cleanly furnished the amine **36** which, after refluxing for 4 h, gave (–)-14-hydroxy-11-mesyloxyvincadifformine **38** as the major product in 72 % overall yield from **34**. Dehydration of **38** with carbon tetrachloride and triphenylphosphine furnished (–)-11-mesyloxytabersonine **39**. Alkaline hydrolysis of the mesylate in **39** followed by methylation of the resulting phenol at 0 °C to avoid quaternization of the tertiary amine afforded (–)-11-methoxytabersonine **40**.



Scheme 8

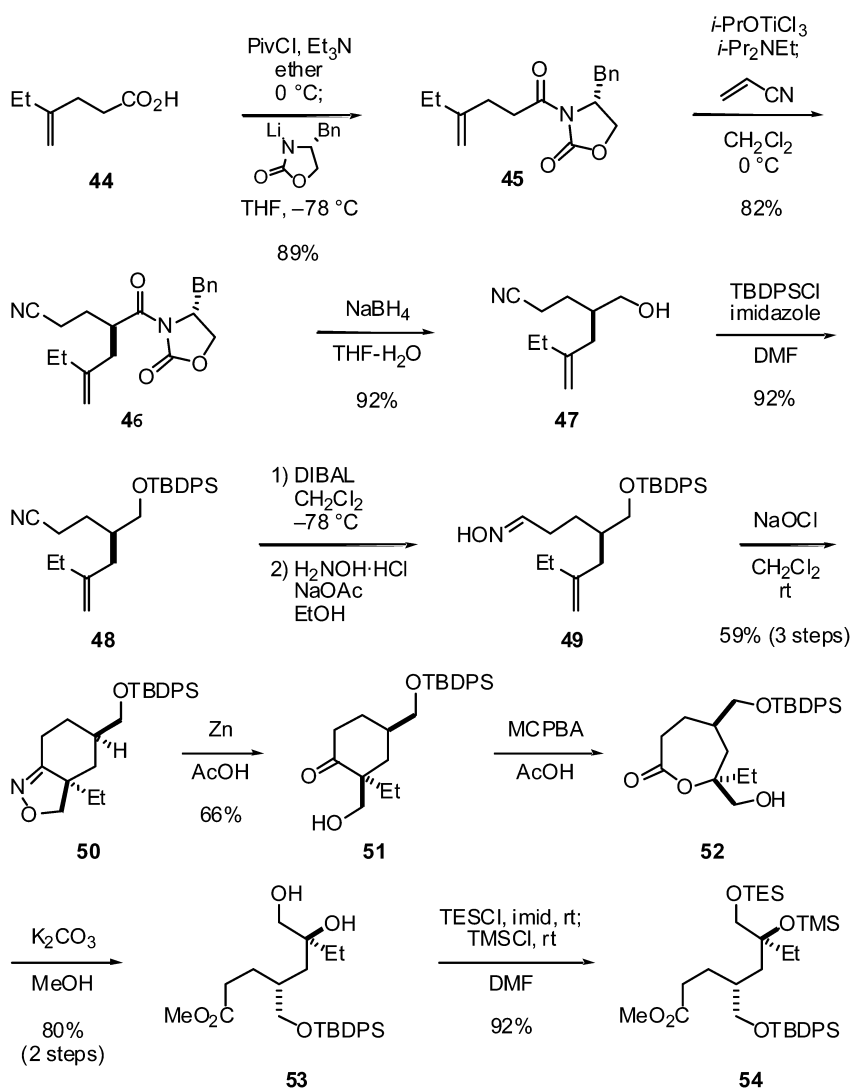
Oxidation of (–)-11-methoxytabersonine **40** was performed according to Danieli's procedures [7d] to give (–)-17 β -hydroxy-11-methoxytabersonine **41** in 88 % yield (Scheme 9). While conversion of **41** to (–)-deacetylvindoline **43** has been achieved by two groups to date [7d,g], the reported methods gave, in our hands, traces or a very low yield of **43** and are far from being practical. In order to establish a practical synthesis of (–)-vindoline, substantial improvements need to be made for the critical steps. After extensive investigation, we could finally find the reproducible conditions for the transformation. Thus, conversion of vinyllogous urethane **41** to **43** was achieved in 64 % yield via **42** through a one-pot, three-step sequence involving oxidation with 2.0 equiv of *m*-chloroperoxybenzoic acid (MCPBA) at 0 °C in a mixture of 10 % methanol in dichloromethane and a saturated sodium bicarbonate solution, adjustment of pH to 3.0 with 10 % hydrochloric acid/methanol, and reduction/reductive methylation with sodium cyanoborohydride and formaldehyde. Deoxygenation of a small amount of *N*(4)-oxide product formed during the oxidation could easily be done by a brief exposure to a sodium hydrogensulfite solution during the final workup. Selective acetylation of the 17-hydroxy group in **43** furnished (–)-vindoline **2**.



Scheme 9

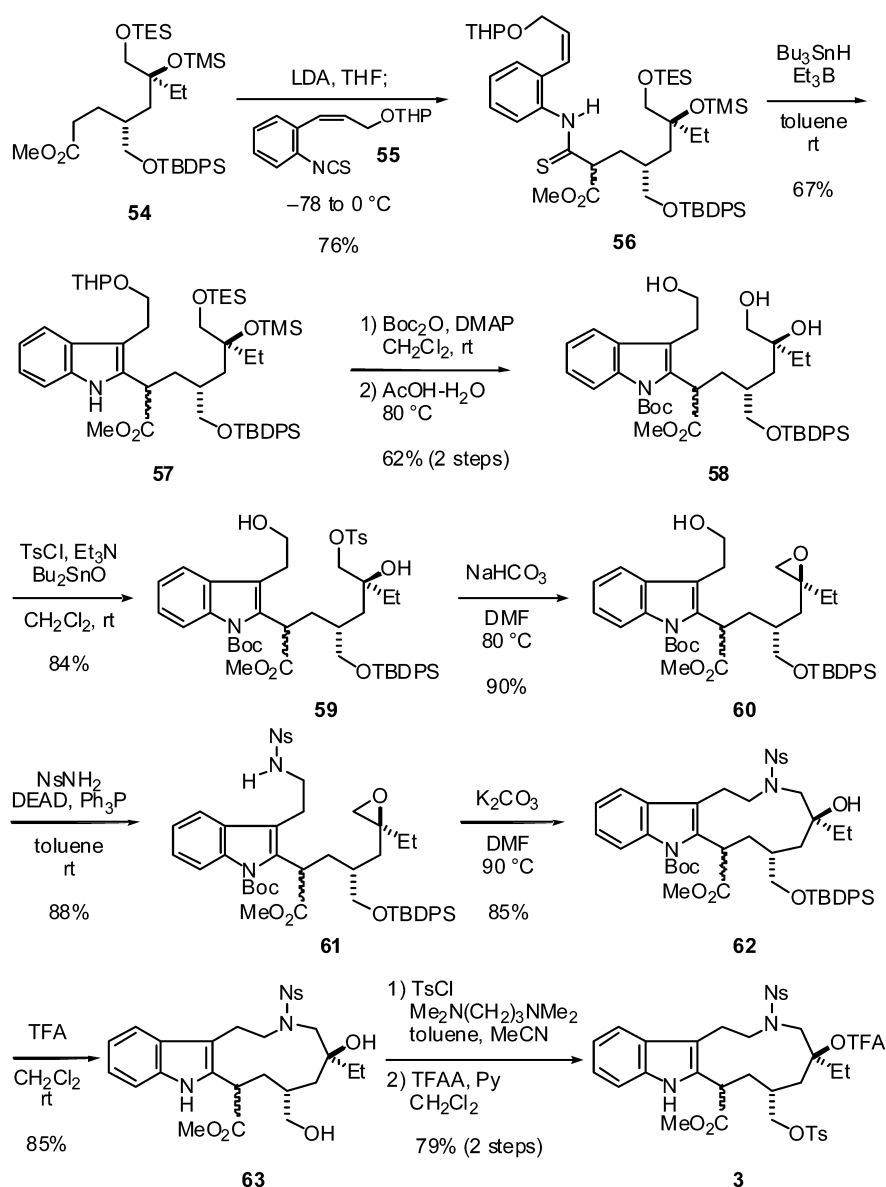
TOTAL SYNTHESIS OF (+)-VINBLASTINE (1)

With synthetic (–)-vindoline in hand, we next focused on the synthesis of the upper half **3** of vinblastine. The synthesis of the requisite ester **54** commenced with introduction of (*R*)-4-benzyl-2-oxazolidinone to 4-ethylpent-4-enoic acid **44** [14] via its mixed anhydride (Scheme 10) [15]. According to Evans' method [16], diastereoselective cyanoethylation of the resulting imide **45** afforded the adduct **46** as the sole isomer. Reduction of **46** [17], followed by protection of the resulting alcohol **47** as its *t*-butyldiphenylsilyl (TBDPS) ether furnished **48**. Reduction of the nitrile **48** with diisobutylaluminum hydride (DIBAL) followed by treatment of the resulting aldehyde with hydroxylamine gave the oxime **49**, which, upon exposure to sodium hypochlorite, underwent facile intramolecular 1,3-dipolar cycloaddition via the nitrile oxide to afford isoxazoline **50** as a single diastereomer. Subsequent reductive cleavage of the N–O bond gave hydroxyketone **51**. Baeyer–Villiger oxidation of **51** was best effected by treatment with MCPBA in acetic acid, leading to lactone **52**. Finally, methanolysis of the lactone and protection of the resulting diol **53** furnished the desired ester **54**.



Scheme 10

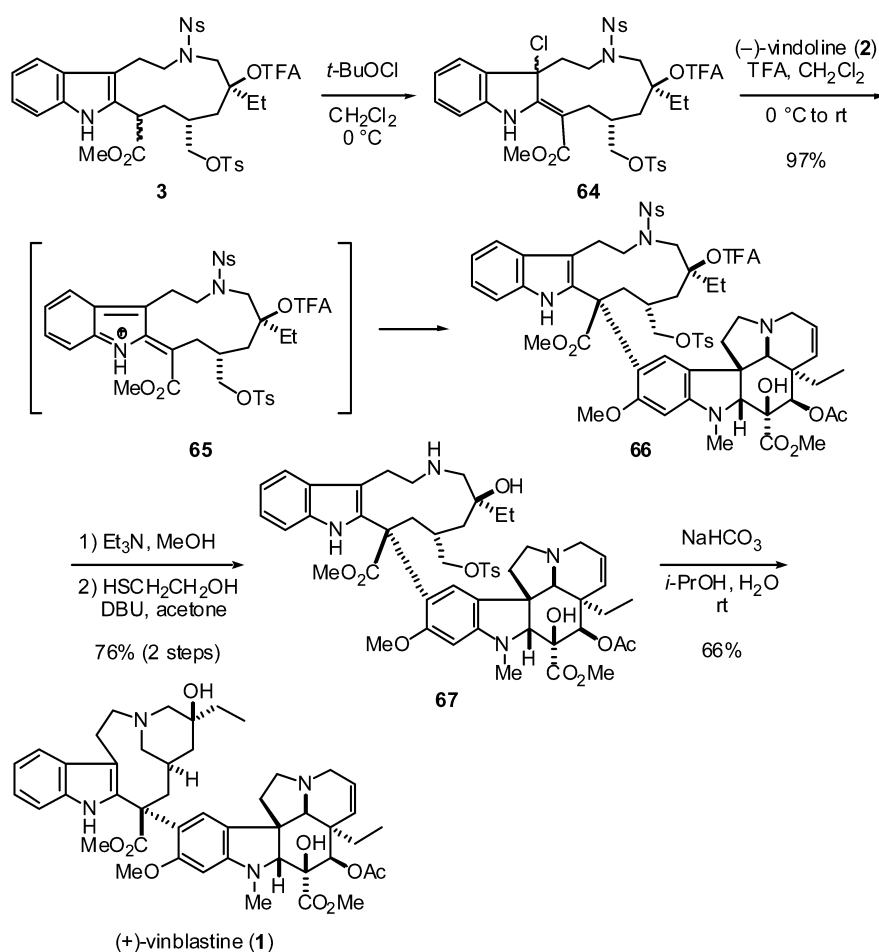
Construction of the key intermediate **3** features an indole formation of the fully functionalized thioanilide **56** and a macrocyclization using 2-nitrobenzenesulfonamide (Ns amide) (**5**) (Scheme 11). First, addition of the enolate of **54**, generated by treatment with lithium diisopropylamide (LDA), to isothiocyanate **55** afforded an inconsequential mixture of thioamides **56**, which was subjected to the radical conditions to furnish indole **57**. At this stage, it became necessary to differentiate the three hydroxyl groups. Protection of the indole NH with the Boc group and acid-catalyzed deprotection of the hydroxyl groups gave triol **58**. Upon treatment of the triol **58** with TsCl and triethylamine in the presence of dibutyltin oxide, tosylation occurred selectively at the primary alcohol of the 1,2-diol to give **59** [18]. After conversion of the resulting tosylate into the epoxide **60** under slightly basic conditions, the remaining primary alcohol was treated with NsNH₂ under Mitsunobu conditions to give **61**. Upon heating with potassium carbonate in *N,N*-dimethylformamide (DMF), **61** underwent a critical macrocyclization to yield the 11-membered ring product **62** [19]. Acid-catalyzed deprotection of the Boc group



Scheme 11

and the TBDPS ether, tosylation [20] of the resulting primary alcohol **63**, and subsequent protection of the tertiary alcohol as its trifluoroacetate afforded the key intermediate **3**.

The final stages of the total synthesis of (+)-vinblastine are illustrated in Scheme 12. Chlorination of the indole nucleus of **3** with *t*-butyl hypochlorite furnished the relatively stable chloroindolenine **64**. To our great satisfaction, upon treatment of the mixture of **64** and synthetic vindoline (**2**) with trifluoroacetic acid, the coupling reaction proceeded smoothly to furnish the desired product **66** as a sole isomer in 97 % yield. After methanolysis of the trifluoroacetate, the Ns group was removed under mild conditions to liberate the secondary amine **67**, which gradually formed the piperidine ring on standing at room temperature to give (+)-vinblastine (**1**). The synthetic product was identical in all respects to natural (+)-vinblastine [21].



Scheme 12

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-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 analogs.

ACKNOWLEDGMENTS

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