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Synthesis of (+)-Vinblastine and Its Analogues†

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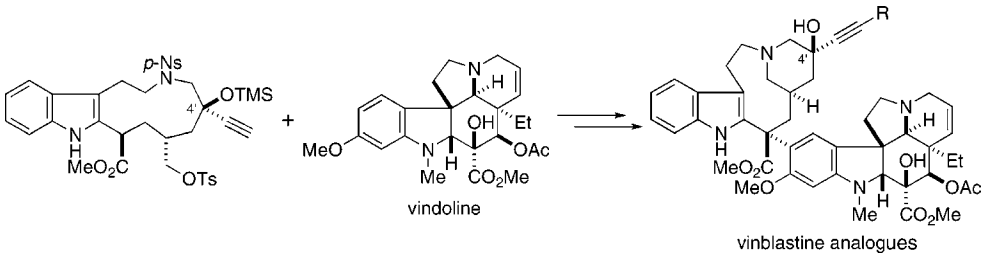
ABSTRACT



A synthetic route to vinblastine and its analogues with an ethynyl group, which features a stereoselective coupling of an 11-membered key intermediate with vindoline, is described. Transformations of the alkynyl moiety including a partial reduction as well as a Sonogashira coupling furnished a variety of analogues.

Vinblastine (**1**), isolated from *Catharanthus roseus*,[1] is known to inhibit the self-assembly of tubulin into microtubles and to prevent cell mitosis. These bioactivities have made vinblastine an effective cancer chemotherapeutic agent especially for treating leukemia and lymphoma patients.[2] The recent disclosure of the X-ray structure of a vinblastine−tubulin complex would help reveal the molecular mechanism of vinblastine and hence would make it possible to develop novel antitumor drugs by structure-based drug design (SBDD).[3] A variety of vinblastine derivatives have been prepared to date through total syntheses of vinblastine[4] as well as syntheses of its analogues,[5] which have revealed that the antitumor activity of vinblastine is highly affected by the substituents at C-4′. Following completion of a total synthesis of vinblastine in 2002,[6] we decided to synthesize a variety of its analogues based on our synthetic route, hoping to find a more effective antitumor agent. Herein we disclose a novel synthetic route to vinblastine and its analogues that is amenable to synthesis of a range of C-4′ derivatives.

To attain the maximum flexibility for modification at the C-4′ position of vinblastine, we opted to introduce an ethynyl group in place of the ethyl group. This would allow Pd-mediated transformations at a later stage of the synthesis, enabling us to synthesize a variety of analogues with minimal effort. The retrosynthetic analysis of the analogue **3** is

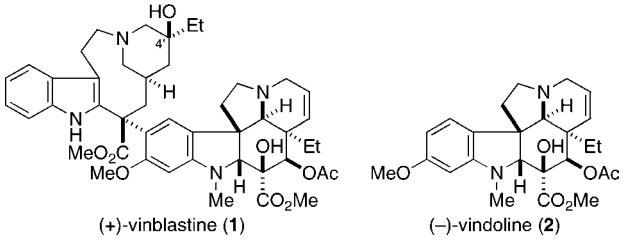


Figure 1. Structures of vinblastine and vindoline.

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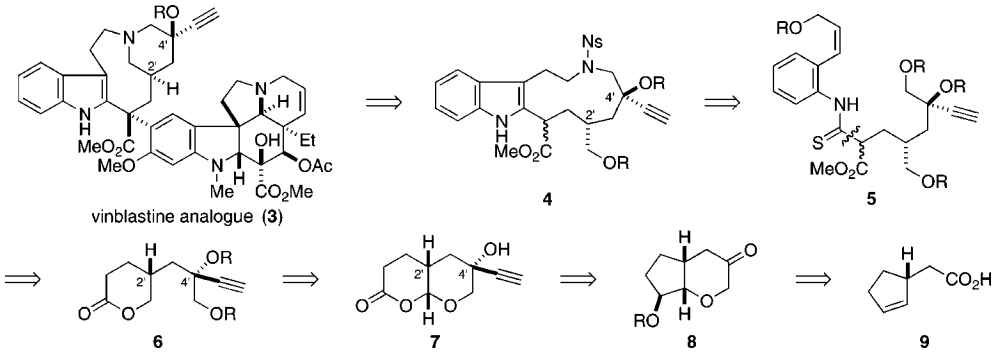
Scheme 1

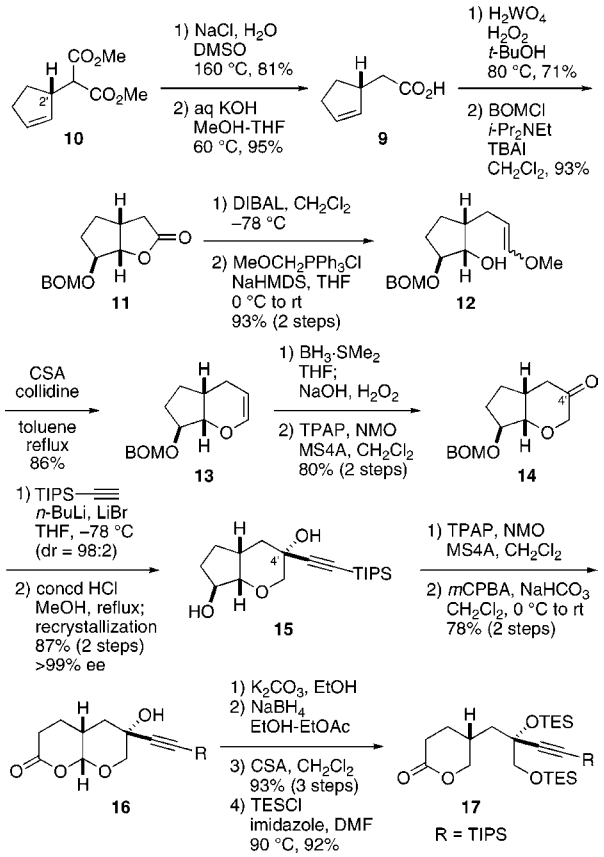


illustrated in Scheme 1. In our previous synthesis of vinblastine, we performed a stereoselective coupling of vindoline (**2**) with the 11-membered upper segment, which was prepared by means of a radical cyclization of *o*-alkenylthioanilides[7] as well as a macrocyclization of nitrobenzenesulfonamide.[8] According to this retrosynthesis, analogue **3** could be obtained from the key intermediate **4**, which in turn would be derived from lactone **6** via thioamide **5**. Lactone **6** could be synthesized from cis-fused bicyclic lactone **7** in a simple operation. Crucial addition of an ethynyl group to ketone **8** is likely to occur from the less hindered, convex face. Finally, ketone **8** would be derived from the readily available carboxylic acid **9**.

Our synthesis commenced with the preparation of the known optically active malonate **10** (96% ee) according to Trost's procedure[9] (Scheme 2). Malonate **10** was converted into carboxylic acid **9** in 77% yield via Krapcho decarbalkoxylation[10] followed by base hydrolysis. Oxidative lactonization of **9** catalyzed by H_2WO_4 afforded a lactone (71%),[11] which was protected as its BOM ether (93%). DIBAL reduction of the lactone **11** followed by Wittig olefination afforded enol ether **12**, which was cyclized under weakly acidic conditions to give dihydropyran **13** in 80% for the three steps. Hydroboration of **13** followed by oxidative workup afforded an alcohol, which was subjected to TPAP oxidation[12] to give the requisite ketone **14** in 80% yield (2 steps). As expected, addition of lithium TIPS acetylide to the ketone of **14** proceeded with excellent diastereoselectivity (98:2) to give the optically pure diol **15** in 87% yield (2 steps), after removal of the BOM group and recrystallization. Oxidation of the secondary alcohol followed by Baeyer–Villiger oxidation of the resulting ketone furnished cleanly the bicyclic lactone **16** in 78% yield (2 steps). Lactone **17** was prepared from **16** in 86% overall yield by way of a four-step sequence involving ethanolysis of the lactone, $NaBH_4$ reduction of the resulting lactol, acid-catalyzed lactonization, and protection of the diol as the TES ethers.

With the requisite lactone **17** in hand, we next turned our attention to the construction of the indole core using a radical

Scheme 2



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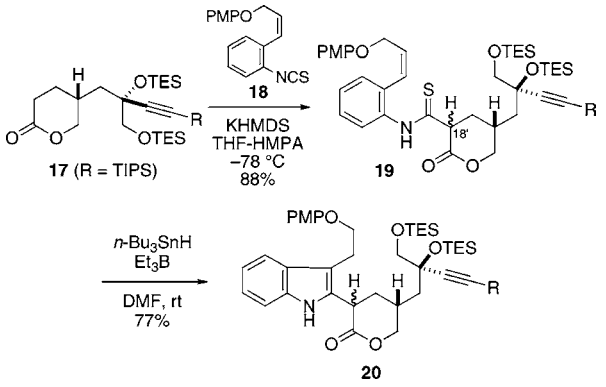
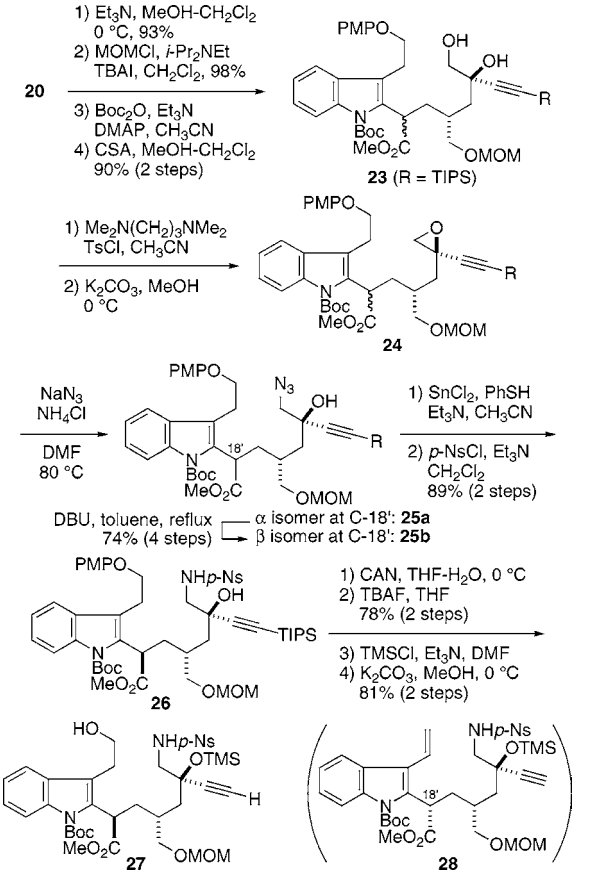
Scheme 3



cyclization of *o*-alkenylthioanilide (Scheme 3).[7] Addition of the enolate derived from lactone **17** to isothiocyanate **18** was effectively performed with use of KHMDS as a base in THF−HMPA (5:1) to give thioanilide **19** in 88% yield as an inseparable diastereomeric mixture at C-18′. The crucial radical cyclization of **19** proceeded smoothly even in the presence of the acetylene moiety to afford indole **20** in 77% yield.

Extensive investigations to construct the 11-membered ring[13] led us to the conclusion that cyclization of **27** by means of the Mitsunobu reaction[14] would be the most effective route. Thus, **20** was converted into the macrocyclization precursor **27** as shown in Scheme 4. Opening the lactone followed by a sequence of protecting group manipulations gave diol **23** in 82% overall yield, which was converted into epoxide **24** via a selective tosylation of the primary alcohol.[15] Regioselective opening of the epoxide with sodium azide furnished **25**. Since preliminary studies of the macrocyclization under Mitsunobu conditions revealed that the α isomer at C-18′ of **25a** suffered from substantial elimination to give the undesired dehydrated product **28**, the mixture of the epimers at C-18′ was separated at this stage by silica gel column chromatography. The undesired α isomer **25a** thus obtained was subjected to epimerization with DBU to give a 1:1 mixture of the α and *β* epimers. Iteration of the separation−epimerization procedure four times furnished the desired *β* isomer **25b** in 74% combined yield from **23**. Reduction of the azide of **25b**[16] and subsequent nosylation

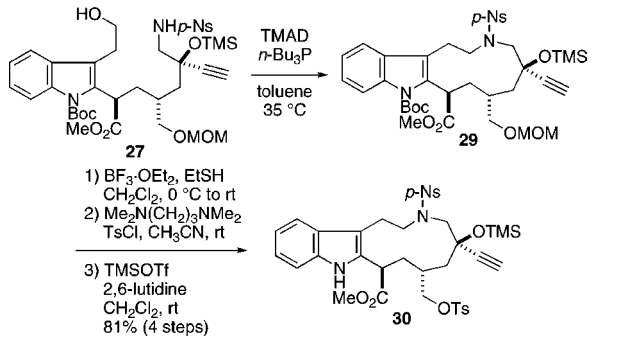
Scheme 4



with *p*-NsCl afforded **26**, which was converted into the cyclization precursor **27** through a series of protecting group manipulations in 56% overall yield.

The crucial Mitsunobu cyclization was successfully performed by treatment of **27** with TMAD and *n*-Bu_3P in toluene,[17] giving the desired 11-membered cyclic compound **29** (Scheme 5). Global cleavage of the TMS, MOM, and Boc

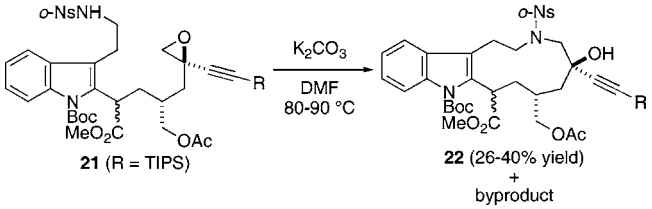
Scheme 5



groups, introduction of a Ts group at the primary alcohol, and a subsequent protection of the tertiary alcohol furnished the key intermediate **30** in 81% yield for the four steps.

With use of the key intermediate **30**, the critical coupling reaction with the lower half, (−)-vindoline, was performed

(13) The attempted macrocyclization of the nosyl amide and the epoxide in **21**, according to the strategy employed in our previous total synthesis, resulted in a low-yield formation of the desired macrocyclic compound **22** along with a substantial amount of a byproduct. While the structure of the byproduct could not be determined, its ^{1}H NMR suggested a decomposition of the Ns moiety.



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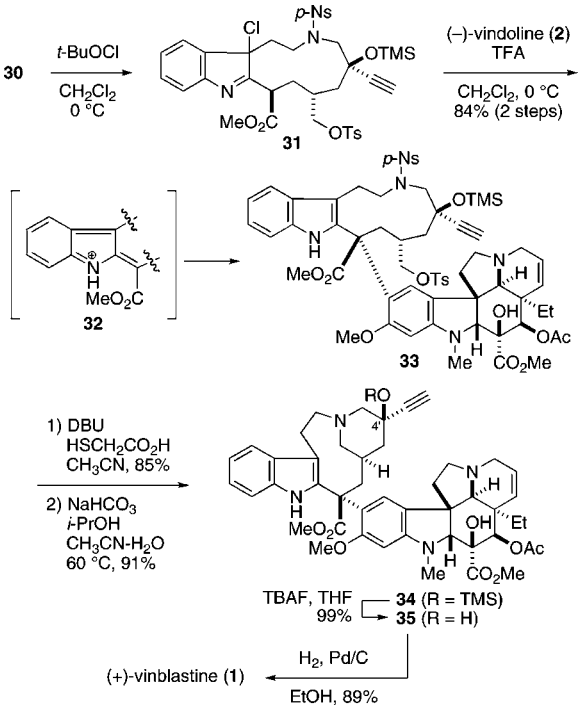
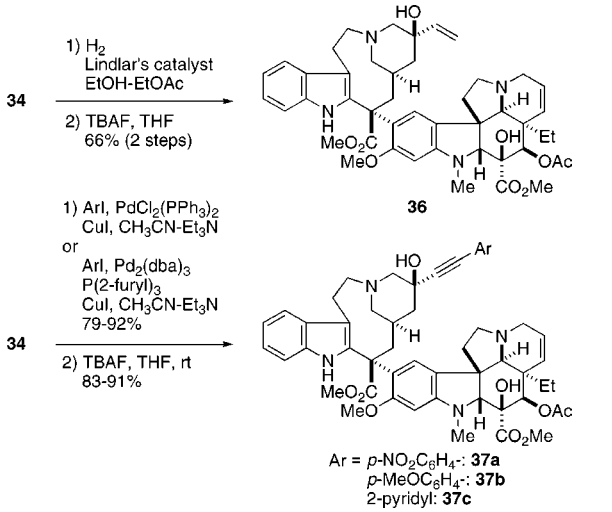
Scheme 6



Scheme 7



(Scheme 6). Chlorination of **30** with *t*-BuOCl afforded chloroindolenine **31**, which was immediately treated with TFA in the presence of (−)-vindoline (**2**) to provide the desired coupling product **33** in 84% yield (2 steps) as the single detectable product. This coupling reaction is believed to proceed via the iminium intermediate **32**. Removal of the *p*-Ns group followed by heating at 60 °C in the presence of sodium bicarbonate provided vinblastine analogue **34** in 77% yield (2 steps) with an ethynyl moiety at C-4′. To confirm the structure including the absolute configuration, **34** was converted into (+)-vinblastine (**1**) in 89% yield via a conventional two-step process. The physical data of the synthetic product were identical with those of natural (+)-vinblastine.

With the requisite vinblastine analogue **34** possessing the ethynyl moiety at C-4′ in hand, we next investigated the synthesis of vinblastine analogues by manipulation of the ethynyl moiety (Scheme 7). Partial reduction of **34** followed by desilylation provided vinyl analogue **36**. Sonogashira coupling of **34** afforded a variety of analogues. For example, coupling with *p*-nitroiodobenzene proceeded under conventional conditions to give **37a**. While other aryl iodide such as *p*-methoxyiodobenzene or 2-iodopyridine gave a considerable amount of the acetylene dimer of **34**, use of $P(2\text{-furyl})_3$ as the ligand instead of $PdCl_2(PPh_3)_2$ effectively suppressed the undesired dimerization to give **37b** and **37c**, resepectively, in good yields.

Using the analogues thus obtained, cell growth assay with the K562 cell line was conducted (Table 1).[18] While the IC_{50}-value of the vinyl analogue **36** was almost the same as that of vinblastine, the ethynyl analogue **35** slightly decreased the cell growth inhibitory activity. The analogues **37a**−**c** with the arylacetylene moieties lost the activity.

Table 1. Cell Growth Inhibitory Activity of the Vinblastine Analogues against K562 Cell Line

compd	IC_{50} (nM)
35	27
36	0.89
37a	>10000
37b	3900
37c	6600
vinblastine (**1**)	0.76

In conclusion, we have successfully developed a versatile synthetic route to vinblastine and its analogues, which is amenable to the preparation of a range of analogues at C-4′. The further bioassay of the analogues is currently underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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