

# Formal Total Synthesis of (±)-Vindoline by Tandem Radical Cyclization

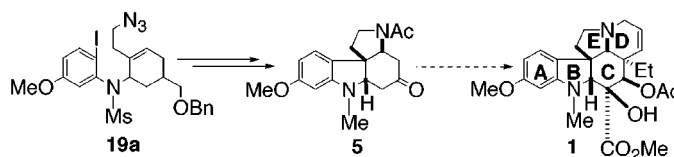
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## ABSTRACT



A formal total synthesis of (±)-vindoline **1** has been achieved featuring the tandem cyclization of radicals produced from the iodoaryl azide **19a**.

Vindoline **1** attracts wide attention among synthetic chemists because of its presence in the clinically important anticancer “*Vinca* dimers” vinblastine **2** and vincristine **3**, which are produced in extremely small quantities in the plant *Vinca rosea*.<sup>1</sup> Our plans to synthesize modified analogues of vinblastine or vincristine required that we undertake the synthesis of vindoline. To date, total syntheses have been achieved by a number of research teams.<sup>2</sup> Although the presence of the condensed ring system makes vindoline an attractive target for a route based on radical cyclization, none of the early synthetic approaches to vindoline was based on the chemistry of free radicals. The recent approach of Fukuyama et al.<sup>2j</sup> uses a radical approach to synthesize an indole **AB** ring precursor, but we now present a tandem

radical cyclization employing an iodoaryl azide<sup>3,4</sup> as the key step which assembles the **ABCE** tetracycle in a formal total synthesis of (±)-vindoline (Scheme 1).

Büchi's seminal synthesis<sup>2a</sup> proceeds through a crucial cyclization step, affording tetracycle **4**. Although the aromatic **A** ring in vindoline carries a methoxy group ( $R' = \text{Me}$ ), the reactivity of the **A** ring meant that Büchi was required to install a group which was substantially less electron-releasing in this position ( $R' = \text{Ts}$ ) for the cyclization reaction; the tosyloxy group was later converted to the desired methoxy group in **5**. Since then, tetracycle **5** has become a key intermediate in vindoline syntheses as shown, for example, by the approach of Ban et al.<sup>2c</sup>

Büchi's problems with substitution of ring **A** by an electron-donating methoxy group arose from generation of highly electrophilic intermediates during the synthesis. The generality of this problem is seen in the fact that other syntheses have also employed sulfonate esters for the **A** ring.<sup>2j</sup> In our case, the use of a methoxy-substituted arene from the outset should not pose problems since we intended to proceed via radical intermediates. Moreover, our strategy for linking the **A** and **C** rings would involve Mitsunobu

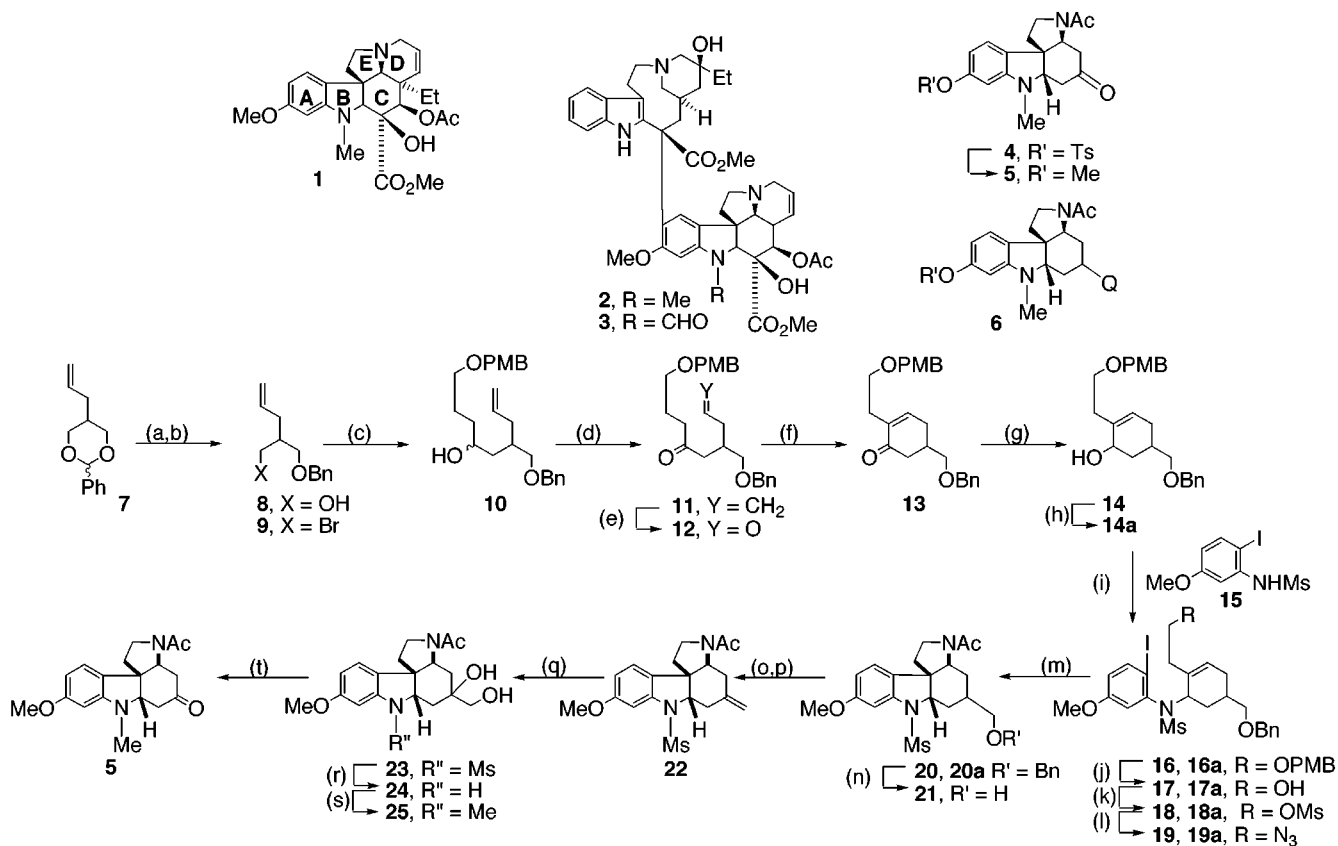
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### Scheme 1<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) DIBAL-H, toluene, rt; (b) CBr<sub>4</sub>, PPh<sub>3</sub>, 2,6-lutidine, THF, rt, 90%; (c) Mg, THF, then 4-(4-methoxybenzyloxy)butyraldehyde, rt, 85%; (d) oxalyl chloride, DMSO, Et<sub>3</sub>N, DCM, -78 °C, 90%; (e) 1. OsO<sub>4</sub> (0.5%), NMO, acetone, H<sub>2</sub>O, rt; 2. NaIO<sub>4</sub>, acetone, H<sub>2</sub>O, rt, 85%; (f) NaOH (1%), H<sub>2</sub>O, 2-propanol, reflux, 84%; (g) CeCl<sub>3</sub>, methanol, NaBH<sub>4</sub>, -15 °C, 95%; (h) *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, DEAD, PPh<sub>3</sub> then NaOH, MeOH, 100%; (i) DEAD, PMe<sub>3</sub>, THF, rt, 92%, 90% for **16**, **16a**; (j) DDQ, DCM, H<sub>2</sub>O, rt, 85%, 87% for **17**, **17a**; (k) MsCl, Et<sub>3</sub>N, DCM, rt, 93%, 90% for **18**, **18a**; (l) NaN<sub>3</sub>, DMF, 60 °C, 90%, 94% for **19**, **19a**; (m) TTMSS, AIBN, benzene, Δ, 35%, 65% for **20**, **20a**; (n) H<sub>2</sub>, Pd/C, EtOAc, rt, 99%; (o) 2-nitrophenylselenocyanate, Bu<sub>3</sub>P, THF, rt, 95%; (p) NaIO<sub>4</sub>, NaHCO<sub>3</sub>, MeOH, 50 °C, 86%; (q) OsO<sub>4</sub> (1%), NMO, acetone, H<sub>2</sub>O, rt, 91%; (r) NH<sub>3</sub>, Na, 2-propanol; (s) HCHO (36% in H<sub>2</sub>O), NaCNBH<sub>3</sub>, pH = 3 (with HCl), MeOH/DCM/H<sub>2</sub>O, 85% from **23**; (t) NaIO<sub>4</sub>, acetone, H<sub>2</sub>O, 84%.

chemistry where the key nitrogen of ring **B** would be present as a sulfonamide. [The sulfonyl functionality would be more than a protecting group: the acidity it imparts to the nitrogen would be key to the success of the Mitsunobu reaction.] The sulfonamide should modulate the electron-donating powers of this nitrogen and could be converted to an *N*-methyl group at the appropriate time.

Our plan envisaged a synthesis of **6**, bearing a Q-substituent, which could be converted to the desired ketone in **5**. In principle, Q might most conveniently be a protected alcohol or ketone, but intermediates bearing such structures would be highly unstable toward elimination from ring **C**. Instead, a benzyloxymethyl group was chosen, because of its stability under a broad range of experimental conditions.

The present synthesis started with reduction of diethyl allylmalonate and protection of the resulting diol, affording benzylidene acetal **7** without purification. Treatment with DIBAL-H in toluene afforded the monoprotected diol **8** in excellent yield (75% from diethyl allylmalonate). The free hydroxyl group in **8** was transformed to bromide **9** (90%), which was used in a Grignard reaction to couple with 4-(4-

methoxybenzyloxy)butyraldehyde to give adduct **10** (85%). Swern oxidation of the secondary alcohol afforded ketone **11** in 90% yield. Oxidative cleavage provided aldehyde **12** (85%), which, on treatment with base, underwent aldol condensation smoothly (84%), to afford cyclohexenone **13**. This was followed by Luche reduction, yielding the alcohol **14** (95%). Gratifyingly, the stereoselectivity of the reduction was excellent (95/5), although the relative stereochemistry at the two carbon centers is not yet determined. Alcohol **14** has now been prepared on a 30 g scale by this practical route.

Conversion to the cyclization precursor was straightforward. Coupling of sulfonamide **15** and alcohol **14** by Mitsunobu reaction gave **16** in excellent yield (92%). Deprotection of the 4-methoxybenzyl group in **16** by DDQ (85%), mesylation of the resulting hydroxyl group (93%), and transformation of the mesylate to azide **19** (90%) all went smoothly. However, tandem radical cyclization with tris(trimethylsilyl)silane (TTMSS) followed by acetylation gave 35% yield of the desired tetracycle **20**. Judging that the stereochemistry of the benzyloxymethyl group in **19** might be the cause of this low yield, it was decided to invert

the stereochemistry of the hydroxy group in **14** by coupling it with 4-nitrobenzoic acid under Mitsunobu reaction conditions. Hydrolysis of the resulting benzoate gave **14a** in quantitative yield. This was efficiently converted to **19a** as above (through steps i–l) and subjected to the same cyclization conditions. This time, the product **20a** was isolated in a more acceptable 65% yield.

The next tasks were to convert the *N*-Ms group to an *N*-Me group and to introduce the ketone in ring **C**. In our initial studies, the *N*-methanesulfonyl group in **20a** was converted to an *N*-methyl group, but the product proved to be highly reactive. [For example, under Swern oxidation conditions, the aromatic ring was observed to undergo electrophilic substitution, recalling the problems of Büchi et al.] Therefore it was judged best to keep the methylsulfonamide protecting group on the nitrogen to stabilize the aromatic ring, until the final stages of the synthesis.

Accordingly our attention was directed to cleaving one carbon from the hydroxymethyl group to introduce the ketone group of the Büchi intermediate. Hydrogenolysis at atmospheric pressure removed the benzyl group in **20a** (99%). The resulting alcohol **21** reacted with 2-nitrophenylselenocyanate and tributylphosphine in THF to give the phenyl-seleno derivative in 95% yield. Oxidation with sodium periodate in methanol gave the corresponding selenoxide, which underwent facile elimination in situ to afford alkene

**22** in excellent yield (86%). Dihydroxylation was performed in acetone and water with a catalytic amount of osmium tetroxide as oxidant and NMO as co-oxidant. The reaction gave **23** (91%) as a mixture of diastereomers in excellent yield. Deprotection of the methylsulfonyl group was then performed with sodium in liquid ammonia with 2-propanol (proton donor). The crude product was used directly without purification in the next reaction, in which formaldehyde solution in water and sodium cyanoborohydride were used at pH < 3 to effect methylation on nitrogen in very good combined yield (85% from **23**). Finally sodium periodate cleavage of the diol afforded Büchi intermediate **5** in excellent yield (84%). This approach therefore constitutes a high-yielding synthesis of the crucial tetracyclic intermediate **5**, and hence a formal total synthesis of (±)-vindoline. This synthesis promises to be adaptable to the synthesis of enantiomerically pure (–)-vindoline by starting with a single enantiomer<sup>5</sup> of **8**.

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