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# Efficient Total Syntheses of (±)-Vincadifformine and (–)-Tabersonine

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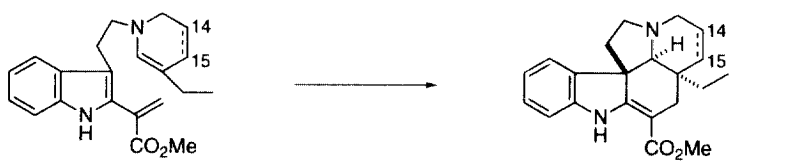
***Abstract:*** Stereocontrolled biomimetic total syntheses of the title compounds are described. Our syntheses feature a highly efficient preparation of the key intermediate **11** using our novel indole synthesis methodology. A novel amine protecting protocol by means of 2,4-dinitrobenzenesulfonamides has been developed to ensure the formation of the elusive secodine (**3**) as well as secodine-type intermediate (**4**) under very mild conditions.


Vincadifformine (**1**) and tabersonine (**2**) are prominent members of aspidosperma alkaloids and have been synthesized several times in the past twenty years.[1] Wenkert and Scott suggested[2] that these alkaloids are biogenetically derived from the hitherto unknown precursors, secodine (**3**) or dehydrosecodine (**4**), via intramolecular Diels-Alder-type reactions (Figure 1). Indeed, experimental support for this intriguing hypothesis was first provided by Kuehne and co-workers in their enantioselective total syntheses of (–)- and (+)-vincadifformine as well as (–)-tabersonine.[1a] In connection with our recent development of a tin-mediated indole synthesis methodology, which is particularly suited for the preparation of 2,3-disubstituted indoles,[3] our efforts have been directed toward efficient total syntheses of indole alkaloids. In this communication we report the straightforward total syntheses of (±)-vincadifformine and (–)-tabersonine, wherein a novel amine activator, 2,4-dinitrobenzenesulfonyl group, plays a decisive role.




**3:** 14,15-dihydro
**4:** $\Delta^{14,15}$

**1:** 14,15-dihydro : Vincadifformine
**2:** $\Delta^{14,15}$ : Tabersonine

**Figure 1**

The indole segment **11**, a key intermediate for **1** and **2**, was first prepared in a highly efficient manner as shown in Scheme 1. A Sonogashira coupling reaction[4] between readily available *o*-iodoformanilide **5**[3] and propargyl alcohol followed by acetylation furnished acetate **6**. Partial hydrogenation of the acetylene **6** over Lindlar catalyst provided olefin **7** and subsequent dehydration of the formamide with phosphorus oxychloride and pyridine afforded isonitrile **8**. Upon treatment with tri-*n*-butyltin hydride and AIBN in acetonitrile at 80 °C, the isonitrile **8** underwent smooth cyclization to give the unstable 2-stannylindole,[5] which was converted to *N*-Boc-2-iodoindole **9** by a one-pot iodination with NIS followed by *N*-Boc protection. The methyl acrylate moiety was introduced to **9** by means of a Stille coupling[6] with 2-tributylstannylacrylate.[7] Hydrolysis of the acetate in **10** then furnished the alcohol **11**.

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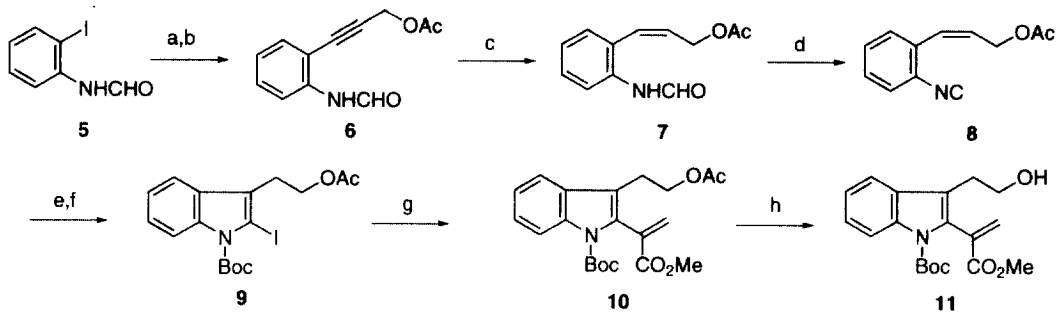
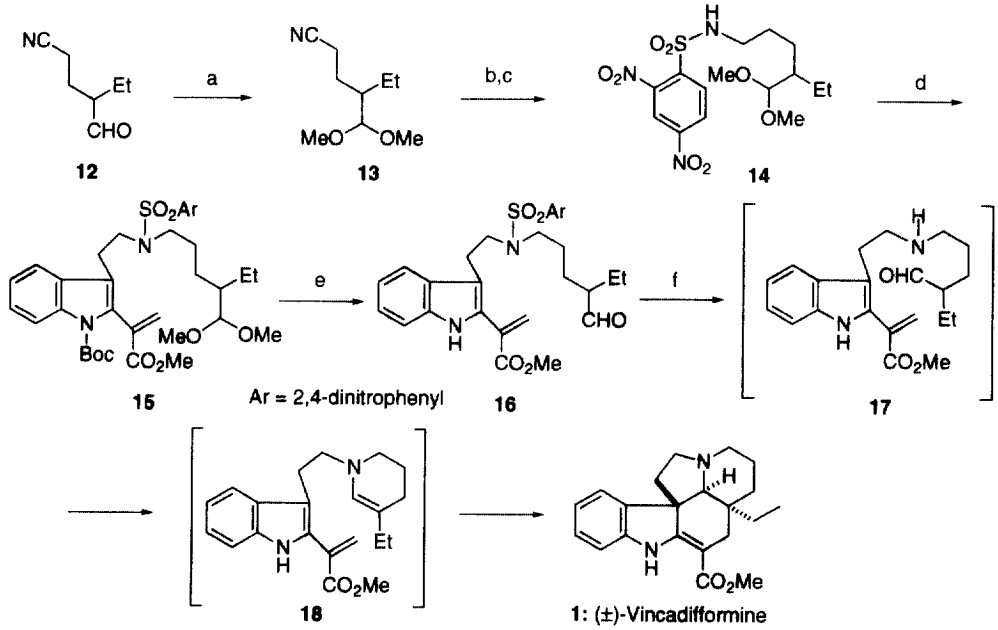


**Scheme 1:** (a) $HC{\equiv}CCH_2OH$, $Pd(PPh_3)_2Cl_2$, CuI, $Et_2NH$, rt, 1 h. (b) $Ac_2O$, pyridine, rt, 30 min, 88% from **5**. (c) $H_2$, Lindlar cat., MeOH, rt, 5 h, 93%. (d) $POCl_3$, pyridine, $CH_2Cl_2$, 40 min, 93%. (e) *n*-$Bu_3SnH$, AIBN, MeCN, 80 °C, then NIS, rt, 20 min. (f) $(Boc)_2O$, $Et_3N$, DMAP, MeCN, rt, 1 h, 71% from **8**. (g) methyl 2-tri-*n*-butylstannylacrylate, $BnPd(PPh_3)_2Cl$, $Ph_3As$, CuI, HMPA/DMF, 85 °C, 3.5 h, 62%. (h) $Na_2CO_3$, $H_2O$/MeOH, rt, 2 h, 90%.

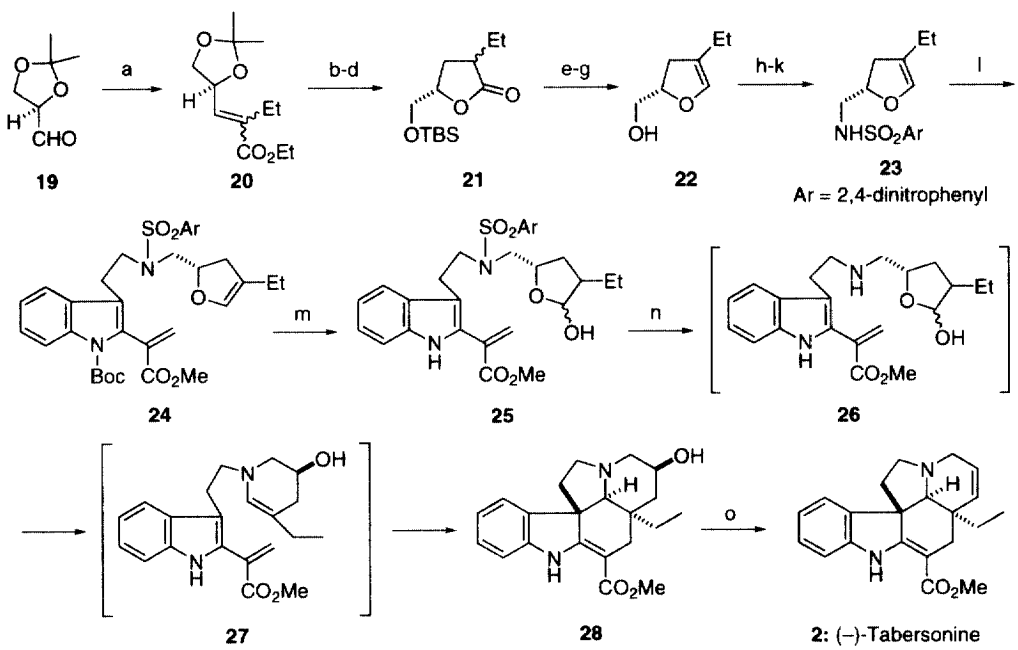
Cyano aldehyde **12** was prepared according to the procedure described by Ziegler (Scheme 2).[8] Protection of the aldehyde as dimethyl acetal **13**, hydrogenation of the nitrile over Raney nickel at high pressure ($H_2$, 1500 psi), and subsequent treatment of the resultant primary amine with 2,4-dinitrobenezenesulfonyl chloride furnished sulfonamide **14**.[9] Much to our delight, the sulfonamide **14** underwent smooth Mitsunobu coupling[10] with indole alcohol **11** to give **15** in 91% yield.[11] In order to prepare for the critical biomimetic cyclization, both the dimethyl acetal and the Boc group in **15** were deprotected by treatment with trifluoroacetic acid in dichloromethane to give aldehyde **16**. As we have recently reported,[9b] ordinary 2,4-dinitrobenzenesulfonamides can easily be deprotected by treatment with PhSH-$Et_3N$, $HSCH_2CO_2H$-$Et_3N$, or *n*-$PrNH_2$ at room temperature. However, these conditions could not be employed for



**Scheme 2:** (a) $CH(OMe)_3$, CSA, MeOH, rt, 20 min, 95%. (b) $H_2$ (1500 psi), Raney-Ni (W-2), $NH_3$-EtOH, 80 °C, 4 h. (c) 2,4-dinitrobenzenesulfonyl chloride, pyridine, $CH_2Cl_2$, rt, 30 min, 82% from **13**. (d) **11**, diethyl azodicarboxylate (40% in toluene), $PPh_3$, benzene, rt, 40 min, 91%. (e) TFA, $CH_2Cl_2$, rt, 15 min. (f) PhOK, MeCN, rt, 4 h, 67% from **15**.

the deprotection of **16** due to the unusually facile Michael addition of the nucleophiles to the acrylate moiety. To circumvent these difficulties, less reactive, harder nucleophiles were sought. When treated with potassium phenoxide in MeCN at room temperature, the 2,4-dinitrobenzenesulfonamide **16** underwent smooth deprotection with concomitant cyclization to give (±)-vincadifformine (**1**) in 67% yield from **15**. Although the reaction was expected to proceed via the presumed intermediate secodine **18**, we could not detect it in the reaction mixture.

For the synthesis of (–)-tabersonine (Scheme 3), optically pure sulfonamide **23** needed to be prepared. Readily available (*R*)-glyceraldehyde acetonide **19**[12] was subjected to a Horner-Wadsworth-Emmons reaction with triethyl 2-ethylphosphonoacetate to give a 2:3 mixture of the *E*/*Z* esters **20**. Catalytic hydrogenation of the olefin **20** followed by an acid-catalyzed hydrolysis of the acetonide led to the exclusive formation of the γ-lactone, which was isolated as a diastereomeric mixture of its TBS ether **21**. Reduction of the lactone **21** with DIBAL, dehydration of the resultant lactol by treatment with a catalytic amount of camphorsulfonic acid (CSA)-quinoline (1:2) in benzene,[13] and subsequent deprotection of the TBS ether with TBAF furnished the alcohol **22**. Alcohol **22** was converted to 2,4-dinitrobenzenesulfonamide **23** in 81% overall yield by a four-step sequence involving mesylation, displacement of the mesylate with sodium azide, selective hydrogenation of the azide over Lindlar catalyst, and protection of the amine with 2,4-dinitrobenzenesulfonyl chloride. Once again, the coupling of sulfonamide **23** and alcohol **11** proceeded exceptionally smoothly under the Mitsunobu conditions[9] to give the desired product **24** in 95% yield. Upon treatment with TFA in $CH_2Cl_2$, **24** underwent simultaneous deprotection of the Boc group and hydration of the enol ether to give lactol **25**, which




**Scheme 3**: (a) triethyl 2-ethylphosphonoacetate, LiCl, DBU, THF, rt, 5 h, 81%. (b) $H_2$, 10% Pd/C, EtOH, rt, 1 h. (c) concd HCl, EtOH, rt, 30 min. (d) TBSCl, imidazole, DMF, rt, 30 min, 99% from **20**. (e) DIBAL (0.95 M in hexane), $Et_2O$, -78 °C, 10 min. (f) CSA, quinoline, benzene, reflux, 2.5 h. (g) *n*-$Bu_4NF$, THF, 0 °C, 30 min, 79% from **21**. (h) MsCl, pyridine, rt, 15 min. (i) $NaN_3$, DMF, 100 °C, 3 h. (j) $H_2$, Lindlar cat., EtOH, rt, 3 h. (k) 2,4-dinitrobenzenesulfonyl chloride, pyridine, $CH_2Cl_2$, rt, 1 h, 81% from **22**. (l) **11**, diethyl azodicarboxylate (40% in toluene), $PPh_3$, benzene, rt, 30 min, 95%. (m) TFA, $CH_2Cl_2$, rt, 15 min. (n) pyrrolidine, MeOH/MeCN (5/1), rt, 5 min, then reflux, 4 h, 58% from **24**. (o) $PPh_3$, $CCl_4$, MeCN, 70 °C, 30 min, then $NH_4OH$ workup, 73%.

was used for the subsequent sulfonamide deprotection without purification. While potassium phenoxide was the reagent of choice for the deprotection of sulfonamide **16** into the corresponding vincadifformine (**1**), it failed completely for the conversion of **25** to **26**. Fortunately, treatment of the crude sulfonamide **25** with 5 equivalents of pyrrolidine in MeOH-MeCN (5:1) for 5 min at room temperature cleanly furnished the amine **26** which, after refluxing for 4 h, gave 14-(*S*)-hydroxyvincadifformine **28** as a single isomer in 58% overall yield from **24**.[14,15] As in the case of vincadifformine, the intermediate hydroxysecodine **27** remained elusive. Dehydration of **28** was performed according to literature procedures[1a] to give (–)-tabersonine (**2**) in 73% yield. The spectroscopic data of synthetic (±)-vincadifformine and (–)-tabersonine were in complete agreement with those reported in the literature.

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