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Diastereospecific Synthesis of Ketooxindoles. Potential Intermediates for the Synthesis of Alstonisine as well as for *Voachalotine* Related Oxindole Alkaloids

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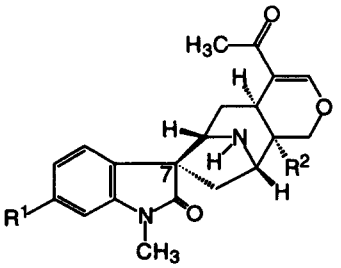
Abstract: *A convenient method has been developed to convert N_a-H tetracyclicketone **1a** into the two corresponding oxindoles[C(7)] diastereospecifically. Treatment of the N_a-H, N_b-benzyl tetracyclicketone **1a** with t-BuOCl provided diastereomer **2a** (related to Voacanga oxindoles), whereas the same process with N_b-H (**1b**) or N_b-benzoyl (**1c**) substituted analogs funished the diastereomers **2b** and **2c** (related to alstonisine), respectively.* © 1997 Elsevier Science Ltd.

Elderfield and Gilman reported the isolation of the first macroline-related oxindole alkaloid from *Alstonia muelleriana* Domin in 1972 and termed it alstonisine **3**.[1] More recently several other macroline-related oxindole alkaloids have been isolated from *Alstonia macrophylla* Wall including N_b-demethylalstophylline oxindole **4**,[2,3] 16-hydroxy-N_b-demethylalstophylline oxindole **5**[4] and alstonal **6**.[5] The structures of oxindole alkaloids **4** and **5** have been determined by NOE spectroscopic experiments[4,6] but the structure of alstonisine **3** has still not been clearly established. LeQuesne demonstrated[7] that the original structure of **3** reported by Nordman was misdrawn;[8] however, the reductive cyclization of **3** to provide talpinine[7] could not be employed to establish the chirality of **3** at C(7). All of the macroline-related oxindole alkaloids **3-6** contain the 8-azabicyclo[3.2.1]nonane substructure. There are several other groups of oxindole alkaloids which contain a substructure related to **3-6**[9,10](voachalotine oxindole **7**, for example); however, interestingly the configuration of the spirojuncture about the spirocyclic carbon[C(7)] in oxindole **7** is opposite to that found in the *Alstonia* oxindoles **3-6**. The absence of an efficient and stereospecific entry into the key ketooxindole templates **2a** and **2b** has, to date, retarded synthetic entry into these alkaloids.

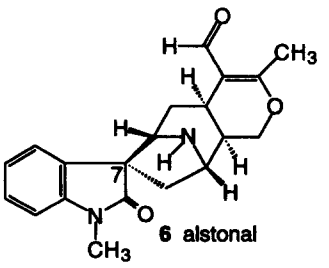
Scheme 1. Potential target oxindole alkaloids



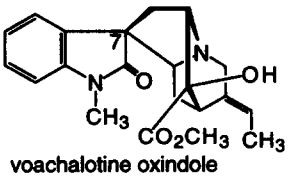
3 $R^1 = R^2 = H$; alstonisine

4 $R^1 = OMe$, $R^2 = H$;
N_b-demethylalstophylline oxindole

5 $R^1 = OMe$, $R^2 = OH$;
16-hydroxy-N_b-demethylalstophylline oxindole



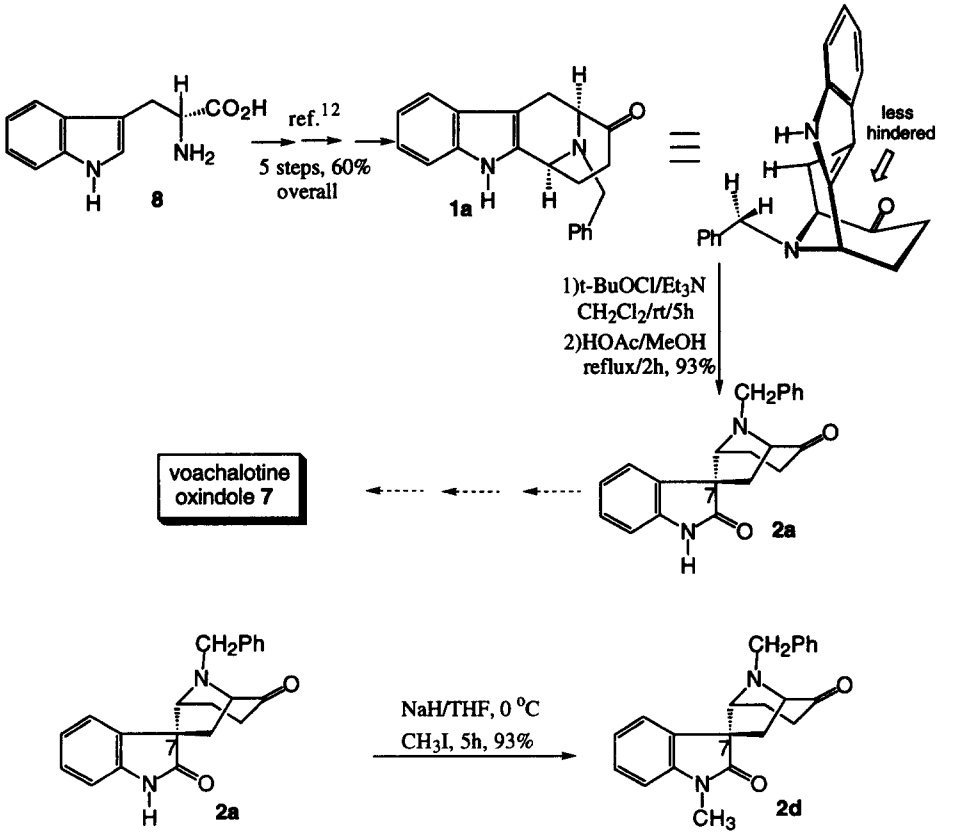
6 alstonal



7 voachalotine oxindole

A highly diastereoselective route for the conversion of N_a-methylated indoloketones into either spirooxindole diastereomer at C(7) by employing the Sharpless osmylation process for asymmetric dihydroxylation was reported recently.[11] However, the yields in the *Alstonia* alstonisine series were modest and a stoichiometric amount of osmium tetroxide was required which limited the usefulness of this approach to alstonisine. In keeping with our interest in a general route to oxindole alkaloids we wish to report here a simple and convienent method to prepare either spiroketooxindole diastereospecifically in high yield.

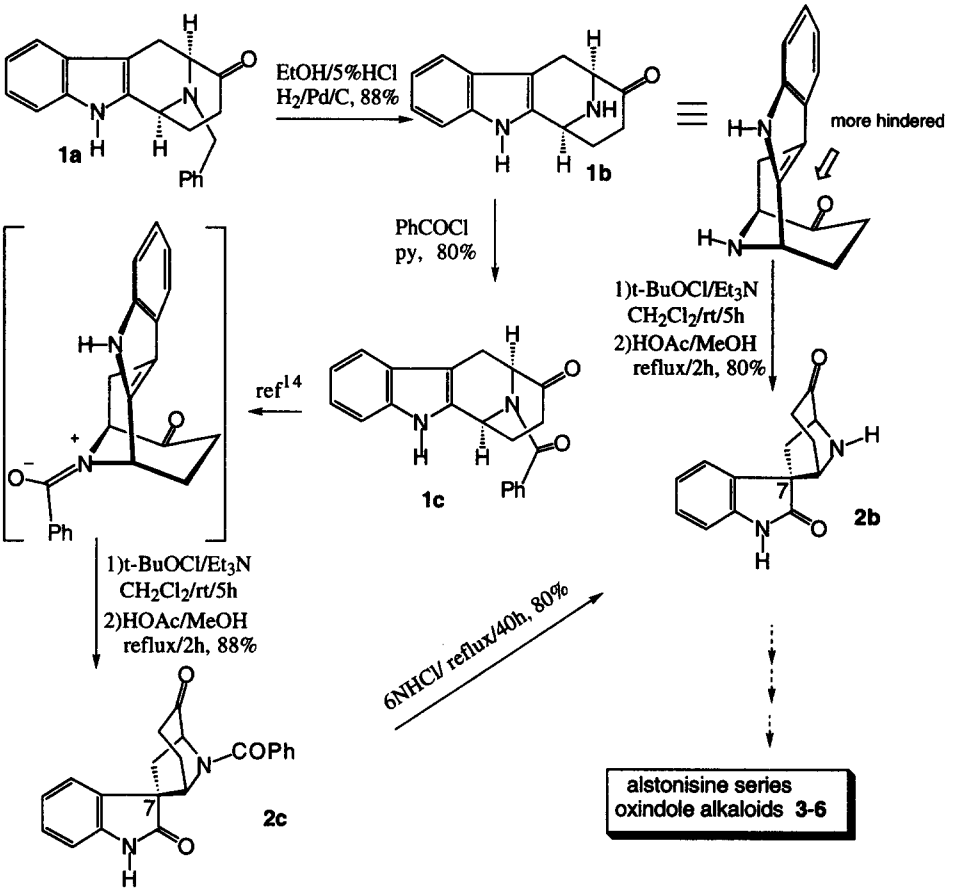
Scheme 2. Conversion of tetracyclicketone **1a** into ketooxindole templates **2a** and **2d**



With the availability of key intermediate (-)-N_a-H, N_b-benzyltetracyclicketone **1a** on large scale,[12] t-BuOCl[13,14] was employed to convert the N_a-H ketone **1a** into either oxindole **2a** (required for the *Voacanga* alkaloids) or into **2b** (via **1b**) for the alstonisine series. Interestingly, when N_a-H, N_b-benzylketone **1a** was employed directly, the oxindole **2a**[15](see Scheme 2), which is structurally related to the voachalotine oxindoles, was obtained in 93% yield as the sole diastereomer. When N_a-H, N_b-H ketone **1b** or N_a-H, N_b-benzoyl ketone **1c** were employed, oxindole **2b** or **2c** which are structurally related to alstonisine **3** were diastereospecifically formed in 88% and 80% yields, respectively, as depicted in Scheme 3. The structures of

2a and **2b** were confirmed by NOE experiments and single crystal X-ray analysis. Oxindole **2a** was N_a-methylated (NaH, CH_3I) to provide oxindole **2d** in 93% yield.

Scheme 3. Conversion of tetracyclicketones **1b** and **1c** into ketooxindoles **2b** and **2c**, respectively



The 100% diastereoselectivity here is a result of the difference in reactivity of t-butyl hypochlorite with the N_b-benzyl (**1a**) vs [N_b-H (**1b**) or N_b-benzoyl (**1c**)] tetracyclicketones. The N_b-benzyl group presumably blocks one face of the indole double bond and directs the Cl^+ to attack from the concave face resulting in a pinacol type rearrangement wherein the migrating group must attack from the face opposite the C-Cl bond to provide oxindole **2a**. Meanwhile, in the N_b-H (**1b**) and N_b-benzoyl(**1c**, imine form) cases, this concave face is more hindered when compared to **1a**. In **1b** and **1c** the indole double bond is presumably attacked from the convex face to form the chloroindolenine intermediate which can only rearrange to provide oxindole **2b** or **2c**, respectively. It is believed the effect of the N_b-benzoyl group on the stereoselectivity (see

1c) is primarily steric in nature. Additional experiments are underway to determine the stereochemical preference for attack of Cl^+ on **1a** vs **1b/1c** to provide this important diastereoselectivity at C(7).

In summary, a cheap and convenient diastereospecific conversion of the (-)-N_a-H tetracyclicketone **1a** into both ketooxindoles **2a** and **2b** was achieved. Either diastereomer at C(7) can now be readily formed from **1a** in high yield via a simple change in the N_b-substituent.These oxindoles should serve as templates for the total synthesis of alstonisine as well as for the voachalotine related oxindole alkaloids, respectively.

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References and notes

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15. **2a**: mp 203-204°C $[\alpha]_D^{28}$ = +182.3° (c= 0.95, $CHCl_3$), IR(KBr) 3236, 1707, 1676, 1466 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.30-2.41(m, 2H, H-14), 2.41-2.43 (m, 1H, H-15β), 2.43-2.56 (m, 2H, H-6), 3.15 (d, J = 2.56Hz, 1H, H-3), 3.41(dt, J = 8.8 and 10.4Hz, 1H, H-15α), 3.55 (d, J = 7.20Hz, 1H, H-5), 3.89 (dd, J = 4.1 and 13.1Hz, 2H, H-17), 6.89 (d, J = 7.5Hz, 1H, H-12), 7.11(t, J = 7.5 Hz, 1H, H-10), 7.24 (t, J = 7.5 Hz, 1H, H-11), 7.26-7.42 (m, 5H, aromatic Bn protons), 7.77(d, J = 7.5 Hz, 1H, H-9), 8.66(s, 1H, N_a-H); ^{13}C NMR ($CDCl_3$) δ, 23.72 (C-14), 34.33 (C-15), 39.64 (C-6), 51.72 (C-17), 55.81(C-7), 65.30 (C-3), 67.55 (C-5), 109.16 (C-12), 122.92 (C-10), 123.48 (C-9), 128.41 (C-11), 137.53(C-8), 137.60(C-13), 179.50 (C-2), 212.69 (C-16); MS(EI)m/z(%) 333(M^++1, 100%), 304(7%), 189(6%).

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