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Oxindole Alkaloids. A Novel Non-biomimetic Entry to (-)-Horsfiline.

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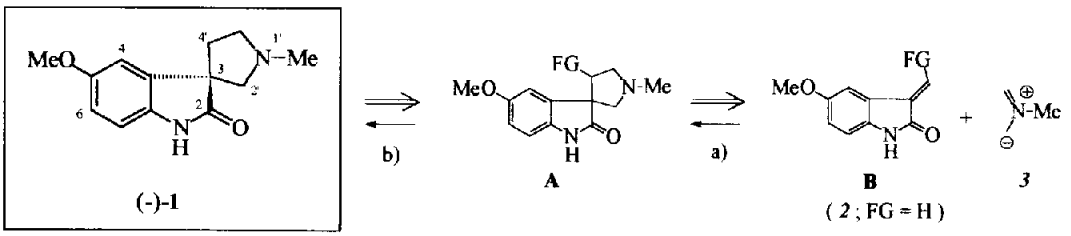
Abstract : A novel non-biomimetic synthesis of horsfiline has been developed. The key pyrrolidine forming reaction is the 1,3-dipolar cycloaddition of the thermally generated *N*-methylazomethine ylide to a suitable 3-alkylidene-indolin-2(3*H*)one. The same strategy was also applied to the synthesis of pure (*R*)-(-)-enantiomer.

The roots of *Horsfieldia superba* native to Malaysia are a rich source of indole-based alkaloids and, among them, (*R*)-(-)-horsfiline **1** is one of the simplest prototype members of the oxindole subfamily.[1] Several routes to both racemic and enantioenriched **1** have been devised.[2] More generally, most of the previous syntheses of oxindole alkaloids are related to an anionic route, aryl radical cyclization, intramolecular Heck reaction and oxidative rearrangement of indole precursors according to a biogenetically patterned approach.[3] Herein, we wish to report a novel non-biogenetic entry to **1** based on a thermal intermolecular 1,3-dipolar cycloaddition.[4]

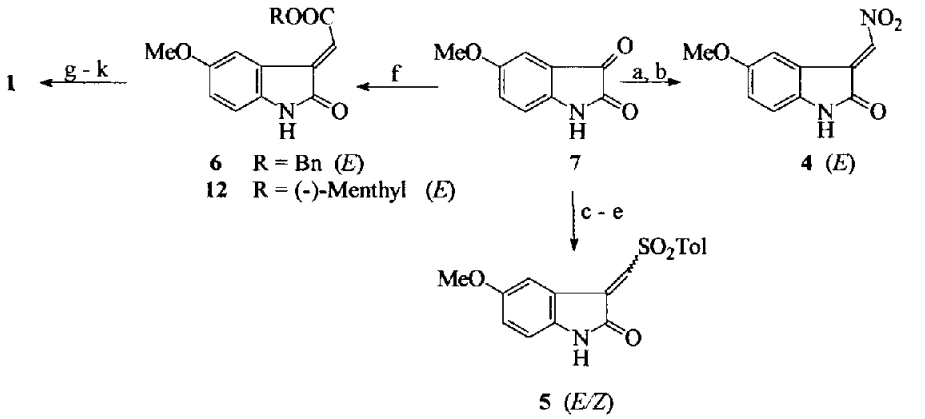


a) [3+2] cycloaddition b) removal of functional group FG

Scheme 1

As outlined antithetically in Scheme 1, the pyrrolidine subunit in the target molecule arose from the two fragments **2** [5-methoxy-3-methylene-indolin-2(3*H*)one] and *N*-methyl-azomethine ylide **3** (thermally generated *in situ* from sarcosine and formaldehyde).[5] Furthermore, a suitable enantiomerically pure dipolarophile **B** (FG: chiral auxiliary) was planned to give access to natural (-)-horsfiline, when stereospecific cycloaddition was expected to induce the requisite *R*-stereochemistry. Previous studies have shown that, in principle, 3-alkylidene-indolin-2(3*H*)ones are readily available by condensation of the corresponding oxindoles with carbonyl compounds.[6] Unfortunately, the ephemeral nature of **2**[7] has made it difficult to obtain and a proclivity toward dimerization compromised its utility as a dipolarophile.[8] On the other hand, non-stabilized ylides (as **3**) are

known to react most efficiently with electron-deficient dienophiles since such a pair of addends possesses a narrow dipole HOMO (-7.91 eV for **3**) /dipolarophile LUMO gap [9] (Sustmann's Type I classification)[10]; *i. e.*, the placement of an EWG on the π-bond lowers the dipolarophile LUMO energy. Accordingly, three candidates **4**, **5** and **6**, that differ from **2** by the presence of a *sacrificial*[11] EWG, were considered with the hope of i) obviating the intrinsic lability of the dipolarophile and ii) eventually, opening a route to non-racemic **1**. The designed starting materials were prepared from the easily accessible 5-methoxyisatin **7**[12] in satisfactory yields (Scheme 2). We first elected *(E)*-nitroalkene **4** to serve as a dipolarophile, mainly because of its known reactivity in cycloaddition reactions[13] and the possibility of subsequently removing the nitro group (*e.g.*, Bu_3SnH, AIBN).[14] This initial approach had to be abandoned due to the instability of **4** under the conditions designed for thermal generation of **3** according to the Tsuge protocol.[5] We found that treatment of vinylsulfone **5** (as a *E/Z* mixture) (Scheme 2) with sarcosine (2.5 equiv) and paraformaldehyde (6 equiv) in refluxing toluene (Dean-Stark) for 7 h, resulted in the clean formation of a mixture of (3*R**,4′*S**)-**8** and (3*R**,4′*R**)-**9** in 60% combined yield. Since the sulfone group in **8** and **9** is excised in the subsequent step, separation of **8** and **9** was not routinely performed. We were disappointed to find that reductive cleavage with either 6% Na(Hg) in MeOH in the presence of Na_2HPO_4[15] or powdered Mg/$HgCl_2$(cat)[16] in MeOH led to intractable product mixtures.

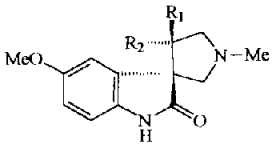


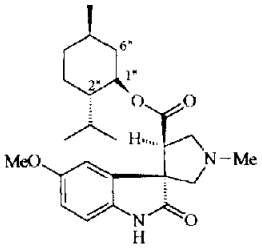
Scheme 2

Reagents and conditions. **a)** $MeNO_2$, EtOH, DBU, rt (66%); **b)** MsCl, TEA, CH_2Cl_2, 0°C, (89%); **c)** N_2H_4, EtOH, rfx (81%); **d)** HCOOEt, EtONa, Et_2O, rt, then AcOH (79%); **e)** $TolSO_2Na$, n-Bu_4NBr (cat), CH_2Cl_2-TFA (cat), rt (63%);**f)** Ph_3P=CHCOOBn, diglyme, rfx (→**6**; 85%);**g)** $(CH_2O)n$, **3**, 3Å, PhMe (Dean-Stark), rfx (77%), **h)** 10% Pd/C, H_2 (304kPa), MeOH, rt (95%), **i)** 2-MercaptoPy-*N*-Ox, DCC, DMAP, CH_2Cl_2, dark; **j)** 3-Hydroxy-4-methylthiazole-2-(3*H*)thione, DCC, 2-PyrrolidinoPy, CH_2Cl_2, dark; **k)** Bu_3SnH, AIBN, C_6H_6, rfx [65% (*via* **i**), 74% (*via* **j**)].

We turned our attention to the alternate candidate **6**.[17,18] Despite the less favourable electronic arrangement of **6** *vs* **4** and **5**, we found that by refluxing a mixture of **6** with sarcosine and $(CH_2O)_n$ in toluene for 4 h under the same conditions as for **5**, a clean and stereospecific cycloaddition took place delivering pure (3*R**, 4′*S**)-**10** (54%). Interestingly, *addition of powdered, oven-dried 3-Å molecular sieves*[19] *to the reaction medium accelerates the cycloaddition reaction* [about 2 h for disappearance (TLC) of **6**] *improving the chemical yield (77%).*[20] With the crucial assembly of the pyrrolidine subunit accomplished , the stage was set for decarboxylative elimination to provide *rac*-**1**. Hydrogenolysis of **10** [10%Pd/C, MeOH, H_2 (304 kPa), rt] gave the aminoacid **11**, which was immediately converted to either *N*-hydroxy-2-thiopyridine ester[21] (DCC, DMAP, 2-

mercapto-pyridine *N*-oxide, CH_2Cl_2, dark) or the *N*-hydroxy-2-thiazolinethione ester[22] (DCC, 4-pyrrolidinopyridine, 3-hydroxy-4-methylthiazole-2(3*H*)thione, CH_2Cl_2, dark). Treatment of the respective esters with Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing benzene for 2 h[23] afforded *rac*-**1** in 38 % and 41% overall yields (from **10**), respectively. Toward the goal of accessing (-)-**1**, we reasoned that 1,3-dipolar cycloaddition involving (5*R*)-menthyl ester **12** as an enantiomerically pure dipolarophile would proceed with π-facial diastereoselectivity. The requisite **12** was prepared in 76% yield by Wittig homologation of **7** with (5*R*)-menthyl (triphenylphosphoranylidene)acetate in refluxing diglyme. In fact, repetition of our protocol with **12**[24]produced two chromatographically separable oxindoles identified as (-)-(3*S*,4'*R*)-**13**[25](39 %) and (-)-(3*R*,4'*S*)-**14**[25](41%). The 400-MHz ^1H NMR spectra of **13** and **14** were fully assigned with the aid of COSY, NOESY and HMBC results. More specifically, the 'wrong' diastereomer **13** was identified on the basis of i) strong shielding of one of H-6"(menthol moiety) (δ = -0.089 ppm) resulting from the low-energy conformation in which it is located above the center of the benzene ring, and ii) cross-peaks (NOESY) of H-6" with the aromatic protons H-4/H-6. In **14** the presence of NOESY correlations between Me-C(8")(menthol subunit) and H-4/H-6 supports that the major population conformer is with the *i*-propyl appendage and benzene ring overlaid. The preference of **13** and **14** for these conformations has been conclusively demonstrated using molecular mechanics calculations.





8 (3*R**, 4'*S**) R_1=H; R_2=SO_2Tol
9 (3*R**, 4'*R**) R_1=SO_2Tol; R_2=H
10 R_1=H; R_2=COOBn
11 R_1=H; R_2=COOH
14 R_1=H; R_2=COO-(-)-Menthyl

13 (3*S*, 4'*R*)

Correlation to natural horsfiline (-)-**1** provided proof of the *R* configuration at C-3 of the more polar diastereomer **14**. This was accomplished, after much experimentation, in 65% overall yield by cleavage of the chiral auxiliary [powdered KOH, 18-crown-6(cat), THF, rt, 18 h; then Dowex 50Wx8] and subsequent removal of the CO_2H function according to the Barton radical protocol.[21] The synthetic material was compared with an authentic sample of (-)-horsfiline, kindly provided by Dr. Borschberg (ETH, Zürich), and was found to be identical by ^1H NMR and CD spectra. The reported specific rotation for the natural product is $[\alpha]_D$ -7.2 (c 1, MeOH) , [1] that found for our material is $[\alpha]_D$ -7.0 (c 0.55, MeOH). In conclusion, the use of azomethine ylides with 3-alkylidene-indolin-2(3*H*)-ones as dipolarophiles provides a rapid assembly of the pyrrolidine subunit in oxindole alkaloids. Although the diastereoselection was disappointingly low, the high yields, coupled with the simple chromatographic separation of the more polar diastereomer, provided the natural enantiomer (-)-**1** in good optical purity. The above chiral auxiliary strategy[26] should be readily adapted to prepare other oxindoles and ways to maximize stereocontrol are presently being explored.

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25. All new compounds gave satisfactory spectroscopic data.Representative data for some new compounds: **13** [α]D -184.7 (c 0.5, $CHCl_3$); CD(CH_2Cl_2) λ(Δε) 240(+3.83), 250(0), 262(-4.56), 281(0), 307(+3.07),344(0); ^{1}H NMR (400 MHz, $CDCl_3$) -0.089(1H, d, J 7.1, H-6"), 0.65 & 0.67 (2 x 3H, 2 x d, J 7.1, H-7"/H.9"), 0.81(3H, d, J 7.1, H-10"), 2.85 & 2.95(2H, AB syst, J 9.1, H-2'). 3.50(1H, dd, J 9.4, 6.9; H-5'), 3.68(1H, dd, J 9.4, 6.9; H-4'), 4.34(1H, dt, J 10.8, 4.4; H-1"); CMR(100 MHz, $CDCl_3$) 16.2 & 20.3(C-9"/C-10"), 21.5(C-7"), 38.7(C-6"), 51.5(C-4'), 56.1(C-5"), 56.5(C-3), 74.1(C-1"), 109.1 & 111.7(C-4/C-6), 155.7(C-5), 169.5(CO_2), 179.5(CON). **14** [α]D -25.7(c 0.5, $CHCl_3$); CD λ(Δε) 241(-2.42), 248(0), 260(+2.82), 277(=), 306(-2.32); 1H NMR 0.34 & 0.65(2 x 3H,2 xd,J 7.0, H-9"/H-10"), 0.84(3H,d,J 7.0, H-7"), 2.44(3H,s,NMe), 2.74 & 2.98(AB syst, 2H, J 9.1, H-2'), 3.69(1H,dd; J 8.9, 7.2; H-4"), 3.77(3H, s,OMe), 4.40(1H,dt; J 10.8, 4.4; H-1"); CMR 15.2 & 22.4(C-9"/C-10"), 21.6(C-7"), 40.3(C-6'), 51.8(C-4'), 56.5 & 56.7(C-3/C-5'), 67.0(C-2'), 74.6(C-1"), 109.3 & 111.7(C-4/C-6), 169.6(CO2), 179.2(CON).
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