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Total Synthesis of flinderole A, flinderole B, flinderole C and desmethyl flinderole C

Ramandeep Kaur*

University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India

E-mail address: rddeepraman9@gmail.com

Abstract

*A class of antimalarial bisindole alkaloid flinderole A **1** was isolated from the Papua New Guinean plant Flindersia acuminata, and associated molecules flinderole B **2** and flinderole C **3** were isolated from Flindersia ambionensis. These antimalarial derivatives shows a selective growth inhibition against Dd2 (choroquine-resistant) P. falciparum malaria strain with IC_{50} values ranging from 0.15-1.42 μM.*

Introduction

The Malaria is among the most extensive life-menacing parasitic infectious disease in the tropic and sub-tropic region of the world's today.[1] Bioactive natural occurring products are a rich source of important therapeutics. Natural products are becoming an increasingly valuable resource in the design and development of new drug candidates. From centuries, nitrogeneous heterocycles have been used for medicinal purpose and form the basis for many ordinary drugs such as Captopril which is used for the treatment of hypertension, Morphine used as analgesic, and Vincristine used for cancer chemotherapy. The nitrogen-containing indole ring system is the bases for the chemical structure of the flinderoles (**1**-**4**, Fig 1). After a screening program of natural product in 2008, flinderole alkaloids were found to possess good antimalarial activity against the *Plasmodium falciparum* parasite and compounds from Australian plants and Papua New Guinean plants were found to be a fine front target for the new generation of the antimalarial drugs.[2]

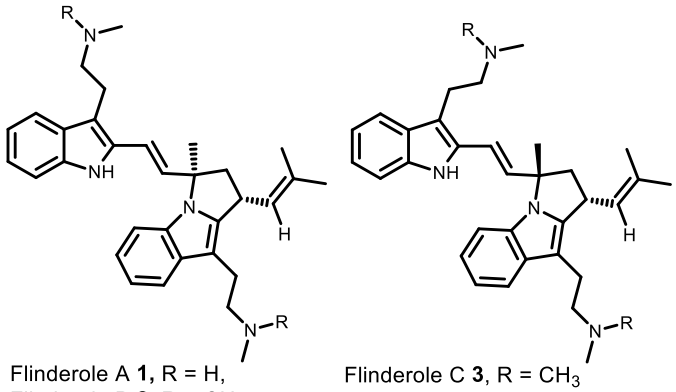
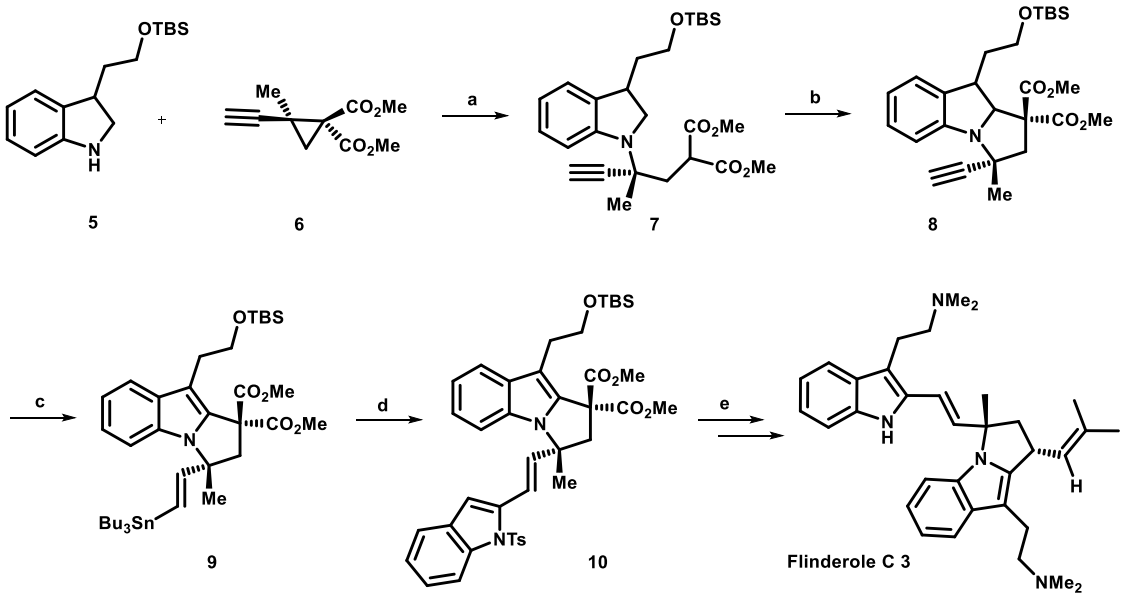


***Figure 1*:** Structures of flindersial alkaloids (**1**-**4**).

Synthesis of flindersial alkaloids

Kerr, M. A. *et al.* (2016)[3]

M. A. Kerr and co-workers in 2016 reported the formal synthesis of flinderole C **3** using lewis acid mediated nucleophilic ring opening of cyclopropane **6** by indoline **5** as key step (Scheme 1). The acetylenic cyclopropane derivative **6** on treatment with *O*-TBS protected indoline **5** in catalytic amount of $Sc(OTf)_3$ (10 mol%), as catalyst furnished the indoline derivative **7** in 80% yield with 1:1 diaseteromeric ratio. The compound **7** underwent oxidative radical cyclization on treatment with $Mn(OAc)_3$ to furnish the pyrroloindoles **8** in 80% yield.



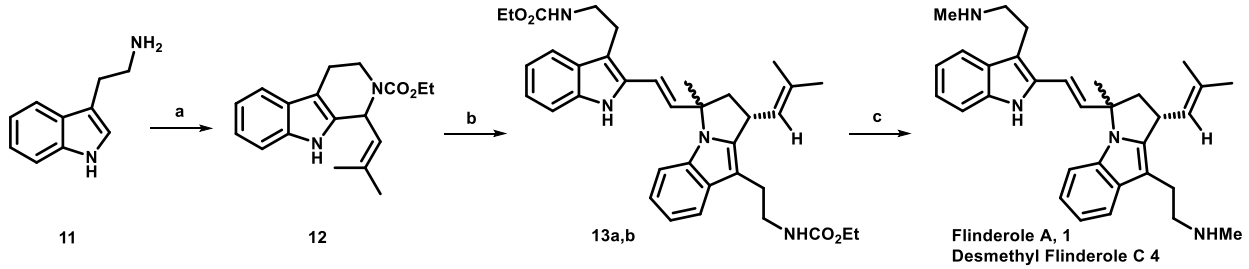
Scheme 1. *Reagents and conditions*: (a) $Sc(OTf)_3$ (10 mol%), toluene, 100 °C, 1.5 h, 80%; (b) $Mn(OAc)_3$, MeOH, 70 °C, 3 h, 80%; (c) $PdCl_2(PPh_3)_2$ (5 mol%), $HSnBu_3$, THF, 0 °C-rt, 30 min, 85%; (d) $Pd(PPh_3)_4$ (5 mol%), toluene, 110 °C, 24 h, 58%; (e) ref 3.

Next, for the synthesis of flinderole moiety, the compound **8** on exposure to $HSnBu_3$ in catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol%) afforded the vinylstannane **9** in 85% yield. The stannane derivative **9** on reaction with *N*-tosylated-2-bromoindole under Stille coupling conditions furnished the bisindole derivative **10** in 58% yield. With compound **10** in hand, a series of functional group manipulations were performed to afford the target molecule **3**.

Dethe, D. H. *et al.* (2014)[4]

In 2014, D. H. Dethe and co-workers reported the synthesis of flinderole A **1** and desmethyl flinderole C **1** starting from commercially available tryptamine **11** in three steps (Scheme 2). The tryptamine **11** on coupling with 3-methylbut-2-enal followed by treatment with methyl chloro formate furnished the

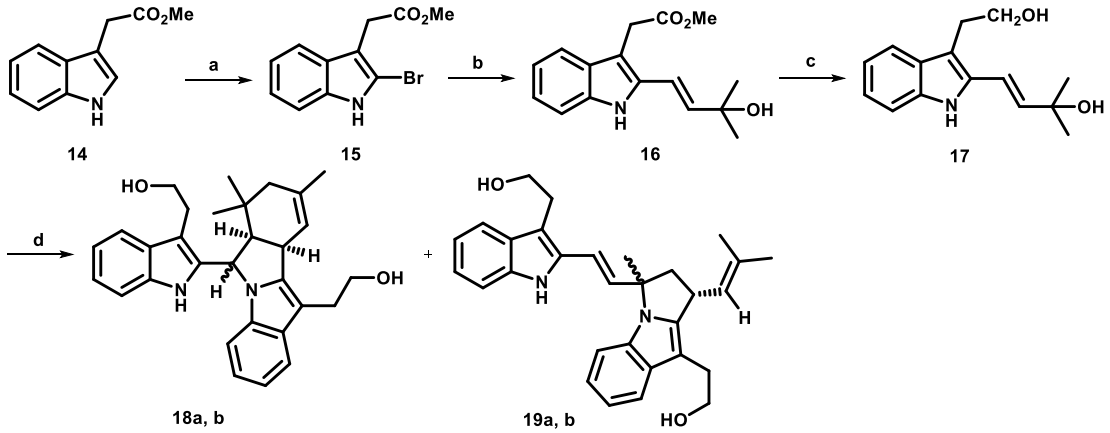
derivative **12** in 87% yield. The olefin **12** on treatment with TFA furnished the derivatives **13a**,**b** in 86% combined yield with 4:5 diastereomeric ratio. Then, LAH reduction of compound **13a**,**b** afforded the target compound flinderole A **1** and desmethyl flinderole C **4** in 83% and 86% yield, respectively.



Scheme 2. *Reagents and conditions*: (a) i) 3-methylbut-2-enal, CH_2Cl_2, 4 Å sieves, 22 °C, 16 h; ii) methyl chloro formate, pyridine, 0 °C-rt, 5 h 87%; (b) TFA, DCM, rt, 30 min, 86%; (c) LAH, THF, rt, 3 h, 83% for **1** and 86% for **4**.

Dethe, D. H. *et al.* (2013)[5]

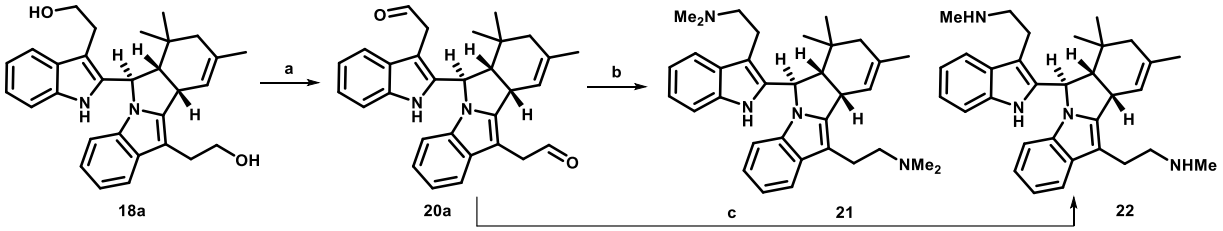
In 2013, D. H. Dethe and co-workers documented the syntheses of antimalarial compounds borreverine **22**, flinderole A **1**, flinderole B **2** and flinderole C **3** (Scheme 3, 4 and 5). The indole derivative **14** on bromination with NBS at C2 position furnished



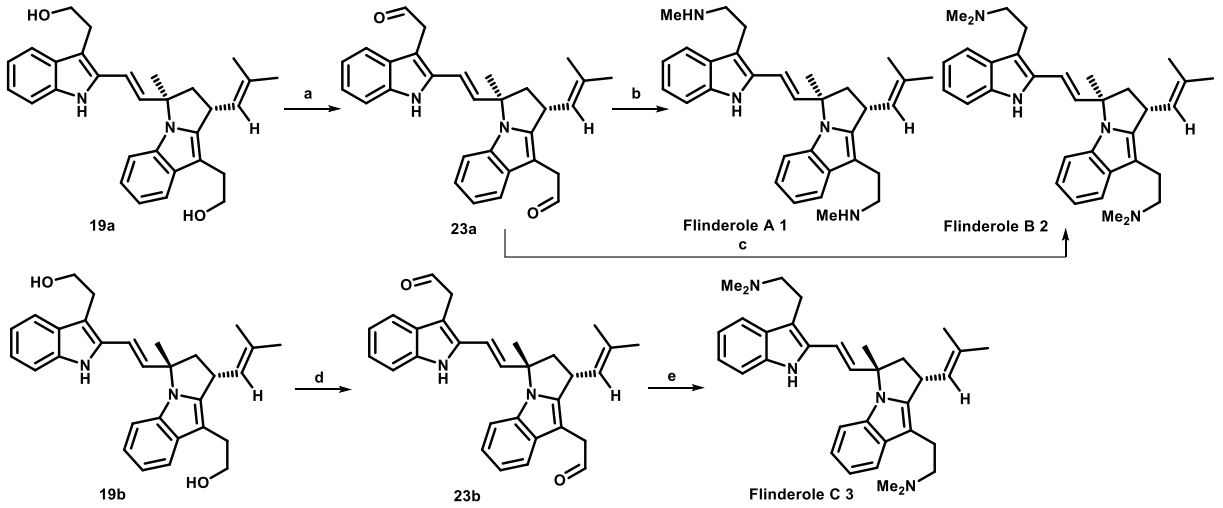
Scheme 3. *Reagents and conditions*: (a) NBS, CCl_4, heat, 1 h, 67%; (b) 2-methyl-4-(tributyl-stannyl)but-3-en-2-ol, Bu_4NCl, $Pd(OAc)_2$, DMF, heat, 3 h, 77%; (c) $LiAlH_4$, Et_2O, 0 °C to rt, 3 h, 75%; (d) $BF_3{\cdot}OEt_2$ (10 mol%), DCM, rt, 15 min, 82%.

the derivative **15** which on stille coupling with 2-methyl-4-(tributylstannyl)but-3-en-2-ol afforded the alcohol derivative **16** in 77% yield. The LAH reduction of compound **16** furnished the alcohol derivative **17** which further on lewis acid mediated dimerization furnished the cyclized products **18a**,**b** and **19a**,**b** with a combined yield of 82% in 5:1 and 4:1 diastereomeric ratios, respectively. The alcohol **18a** on

oxidation with IBX afforded the aldehyde **20a** which on $NHMe_2$ mediated reductive amination furnished dimethylisoborreverine **21** in 82% yield (Scheme 4). And reductive amination of above synthesized aldehyde in presence of iron triflate furnished the isoborreverine **22** in 89% yield.



Scheme 4. *Reagents and conditions*: (a) IBX, ethyl acetate, heat, 1 h, 80%; (b) $NHMe_2$, $NaCNBH_3$, AcOH, CH_3OH, rt, 12 h, 82%; (c) NH_2Me, $Fe(OTf)_3$, $NaBH_4$, CH_2Cl_2, rt, 30 min, 89%.

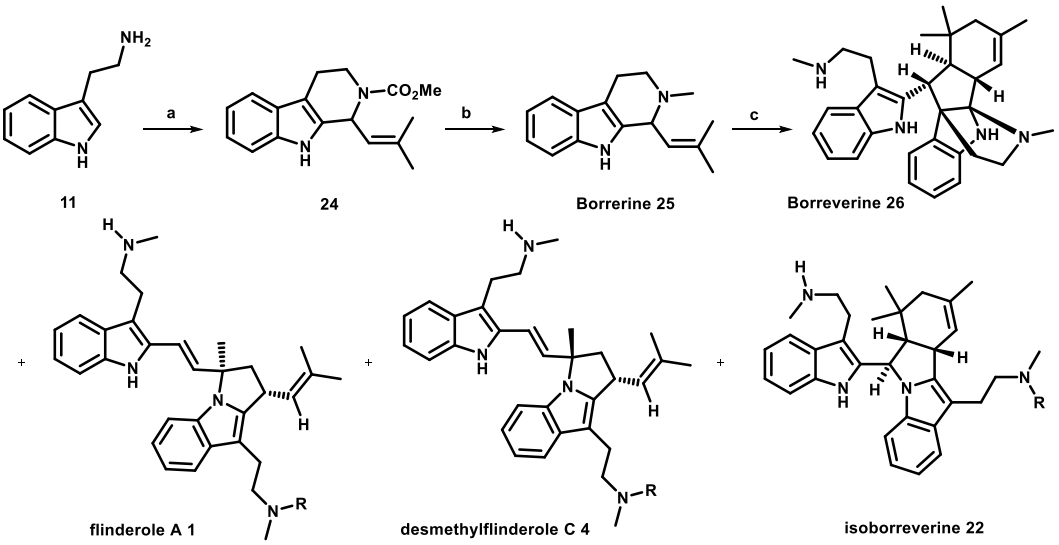


Scheme 5. *Reagents and conditions*: (a) IBX, ethyl acetate, reflux, 1 h, 74%; (b) NH_2Me, $Fe(OTf)_3$, $NaBH_4$, CH_2Cl_2, rt, 30 min, 75%; (c) $NaCNBH_3$, $NHMe_2$, AcOH , MeOH, rt, 12 h, 85%; (d) IBX, ethyl acetate, heat, 1 h, 81%; (e) $NaCNBH_3$, $NHMe_2$, AcOH, CH_3OH, rt, 12 h, 81%.

By following an analogous series of reactions flinderole A **11**, B **12** and C **13** were afforded in 17%, 85%, 81% yield, respectively (Scheme 5).

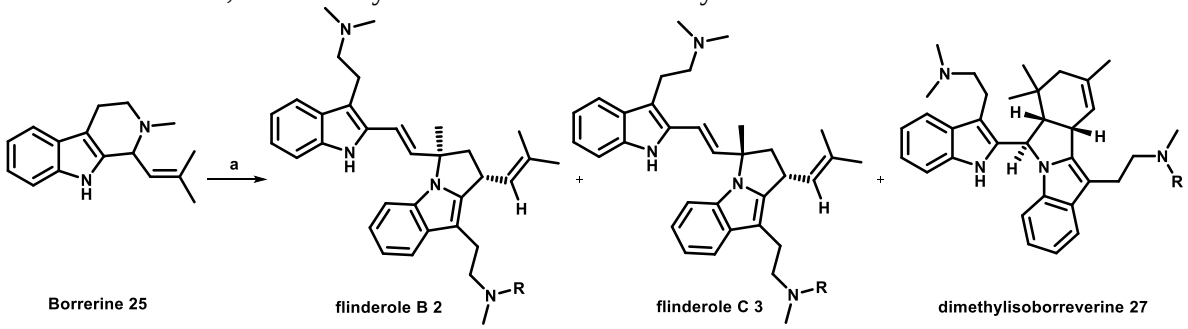
May, J. A. *et al.* (2012)[6]

J. A. May and co-workers documented the total synthesis of flinderole A **1**, flinderole B **2**, flinderole C **3**, desmethylflinderole C **4**, borreverine **26**, isoborreverine **22**, and dimethylisoborreverine **27** employed the acid-mediated dimerization of the natural occurring product borrerine starting from commercially available tryptamine **11** (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) i) 3-methylbut-2-enal, DCM, 4 Å sieves, 22 °C, 16 h; ii) methyl chloro formate, pyridine, 0 °C to rt, 5 h, 87%; (b) LAH, THF, reflux, 2 h, 88%; (c) different conditions of acid, solvent, time, temperature.

The reaction of tryptamine **11** with 3-methylbut-2-enal followed by treatment with methyl chloroformate furnished the amine derivative **24** which on LAH reduction afforded the borrerine **25** in 88% yield. The synthetic borrerine **25** on acid mediated dimerization under different conditions furnished the borreverine **26**, flinderoles A **1**, desmethylflinderole C **4** and isoborreverine **22** (Scheme 7). The treatment of borrerine **25** first with methyl triflate in CH_2Cl_2 followed by reaction with TFA furnished the flinderole B **2** in 21%, flinderole C **3** in 19%, and dimethylisoborreverine **27** in 30% yield.

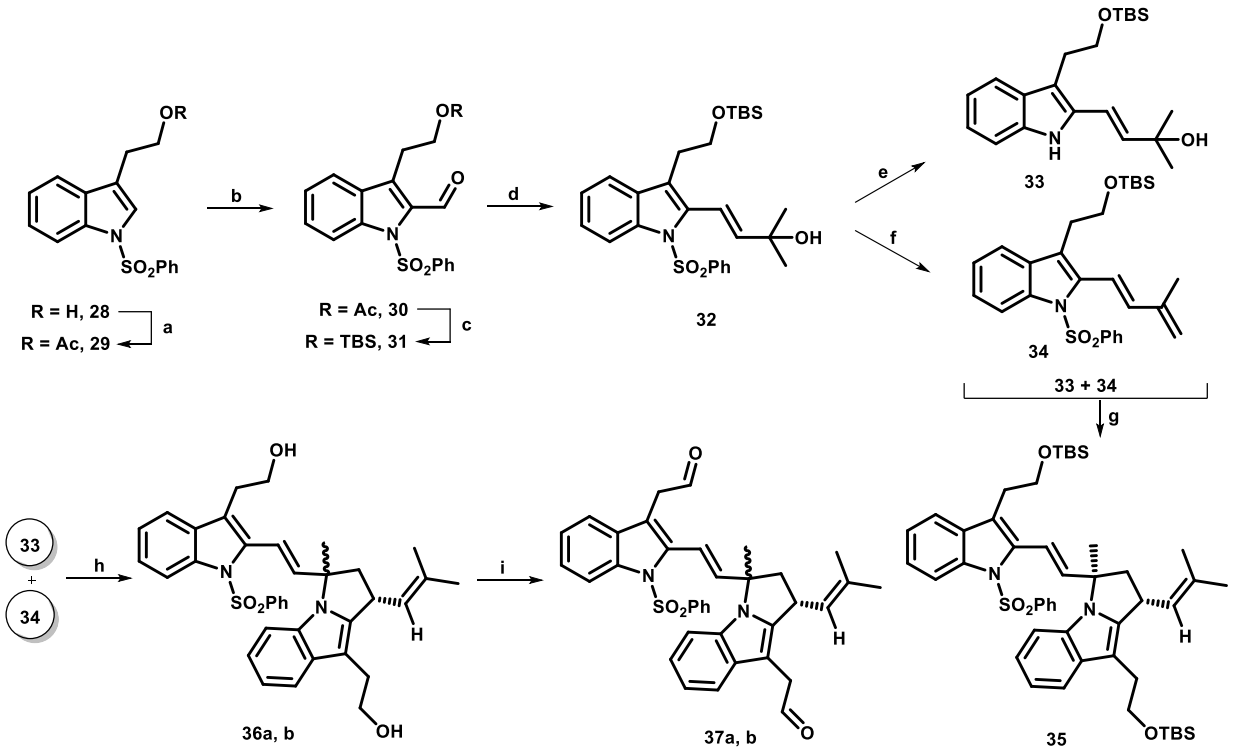


Scheme 7. *Reagents and conditions*: (a) i) MeOTf, CH_2Cl_2, 0 °C; ii) TFA, 0 °C-rt, 20 min (21% for **2**, 19% for **3**, 30% for **27**).

Dethe, D. H. *et al.* (2011)[7]

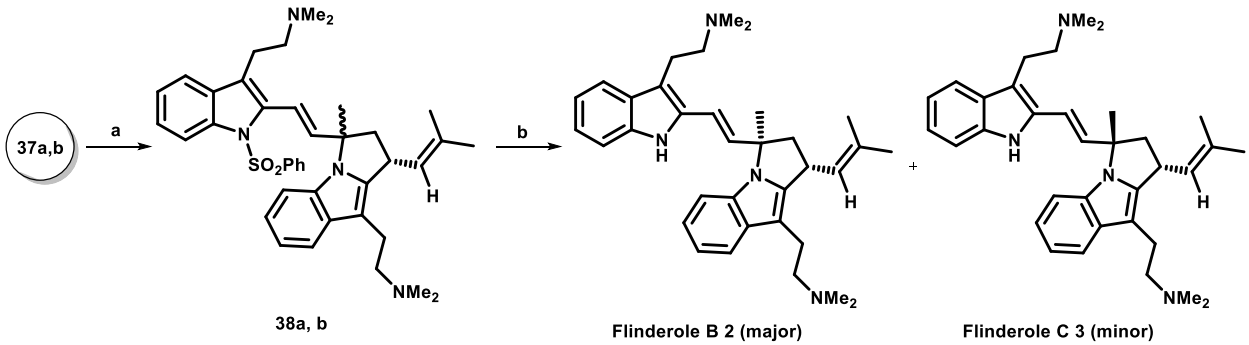
D. H. Dethe and co-workers in first report described the synthesis of isomeric flinderole B **2** and flinderole C **3** starting from readily protected tryptophol **28** as starting material (Scheme 8). The hydroxyl group of tryptophol **28** was acylated with acetic anhydride to synthesize compound **29** which on

subsequent formylation with dichloromethyl methyl ether and $SnCl_4$ afforded the aldehyde derivative **32** in 80% yield.



Scheme 8. *Reagents and conditions*: (a) Ac_2O, DMAP, pyridine, DCM, rt, 6 h, 91%; (b) dichloromethyl methyl ether, $SnCl_4$, DCM, -78 to -10 ^oC, 1 h, 80%; (c) i) LiOH, THF, H_2O, room temp., 3 h; ii) tert-Butyldiphenylsilyl chloride, imidazole, DCM, 0 ^oC to room temp., 6 h, 81%; (d) i) wittig reagent, DCM, room temp., 6 h, 91%; ii) Methyl Iodide, Mg turnings, I_2 (cat. amount), Et_2O, 0 ^oC to room temp., 2 h, 89%; (e) Na/Hg, Na_2HPO_4, CH_3OH, rt, 1 h, 97%; (f) Mesyl chloride, Et_3N, THF, 0 ^oC to reflux, 2 h, 81%; (g) $Cu(OTf)_2$, DCM, rt, 30 min, 62%; (h) $BF_3.OEt_2$, DCM, rt, 30 min, 78%; (i) IBX, ethyl acetate, reflux, 1 h, 84%.

The compound **31** on hydrolysis of acetate group and *O*-TBS protection furnished the compound **32** in 81% yield. The aldehyde **31** on 2C Wittig olefination and subsequent Grignard reaction with methylmagnesium iodide afforded the alcohol derivative **32** in good yield. The deprotection of phenylsulphonyl group of compound **32** with Na/Mg gave the alcohol intermediate **33** in 97% yield. The alcohol **32** was transformed into its mesylate using MsCl followed by elimination reaction to afford the olefin **34**. The treatment of compound **33** and **34** with $Cu(OTf)_2$ afforded the TBS protected adduct **35**, whereas intermediate **33** and **34** on BF_3. OEt_2 mediated cyclization furnished the alcohol **36a** and **36b**.



Scheme 9. *Reagents and conditions*: (a) $NHMe_2$, $NaCNBH_3$, Acetic acid, CH_3OH, rt, 12 h, 91%; (b) Na/Hg, Na_2HPO_4, CH_3OH, rt, 1 h, 62% for **12**, 15% for **13**.

The mixture of alcohol **36a** and **36b** on oxidation with IBX furnished the aldehyde **37a,b** in 4:1 diastereomeric ratio, which on reductive amination with dimethylamine afforded the mixture of amine **38a** and amine **38b** in 91% combined yield (Scheme 9). Finally, phenylsulphonyl group deprotection of **38a** and **38b** furnished the flinderole B **2** and flinderole C **3** in 62% and 15% yield, respectively.

Conclusion:

A general and highly efficient synthetic approaches for the total synthesis of pyrrolo[1,2-α]indoles framework and its application to the total syntheses of flinderoles A-C (**1-3**) and desmethylflinderole C **4** were discussed employing ring opening of cyclopropane by indoline, acid-mediated dimerization reactions as the key steps.

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