Fluorous-tagged indolylboron for the diversity-oriented synthesis of biologically-attractive bisindole derivatives†

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The diversity-oriented synthesis of bisindole derivatives to construct concise libraries using consecutive cross-coupling reactions and prepare new sulfonamide type fluorous protecting groups is presented.

Horváth and Rábai effectively utilized the affinity between perfluorinated molecules and fluorous solvents for a new recycling system for transition metal catalysts in organic synthesis.[1] Curran *et al.* further substantiated the concept of "fluorous synthesis" by including a simplified purification using reactants introduced into the perfluoroalkyl chains as fluorous tags.[2] Fluorous-tagged molecules are easily separated from non-fluorous molecules by a fluorous liquid–liquid extraction (F-LLE) using fluorous solvents or a fluorous solid phase extraction (F-SPE) using perfluorinated silica gel. From the viewpoint of high throughput synthesis, fluorous and solid phase syntheses have been extensively investigated.[3] In connection to our recent studies on the solid phase synthesis of indole derivatives,[4] we have focused our efforts on the diversity-oriented preparation of indoles using a fluorous synthesis. Occasionally, difficulties have been encountered while optimizing our solid phase synthesis of bisindolylmaleimide (PKC inhibitor) using a Pd catalyzed cross-coupling reaction[4b] due to the limited monitoring of the solid phase reaction's progress.[5] However, fluorous molecules can be treated like typical soluble organic compounds, and conventional solution phase reactions are effective for optimizing the transformations.

Certain bisindole alkaloids have unique structures that possess a five- or six-membered central ring which is shared by the two indole units and show diverse biological activities. Bisindolylmaleimide and bisindolylbenzoquinone (antitumor[6a] and insulin receptor activator[6b]) are recent, representative skeletons of these natural compounds (Fig. 1). Moreover, it has been reported that one of the non-natural bisindole derivatives with a bisindolylpyridine skeleton exhibits potent cytotoxity.[7] Although many synthetic methods have been reported for each bisindole derivative,[8] a common synthetic method for bisindole alkaloids has yet to be reported. Thus, we planned a general synthetic route for diverse bisindole derivatives with various central rings.

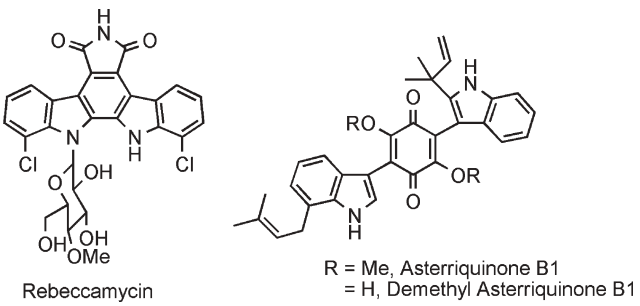
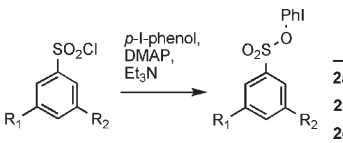


Fig. 1

In solid phase synthesis, resins with various linkers (PS–Ts–Cl, PS–DES, *etc.*) act as functional protecting groups and linkages to the polymer. Similarly, the use of fluorous protecting groups (functional group protection and fluorous tag introduction) has been investigated (F–Boc,[9a] F–CbzCl,[9b] *etc.*). However, sulfonamide type tags have yet to be explored in fluorous synthesis. In this paper, the fluorous synthesis of bisindole alkaloid skeletons using a sulfonamide type tag (Rf_8–Bs) and the concise construction of a diversity-oriented library containing natural and non-natural indole compounds are reported.

The tagging reagents, arylsulfonyl chlorides **1a–c**, were easily synthesized by coupling perfluoroalkyl iodide with halobenzenes in the presence of Cu powder and subsequent chlorosulfonylation.[10] Sulfonates **2a–c**, which had different F-contents, were readily separated using perfluoroalkylated silica gel TLC by selecting a suitable developing solvent (Scheme 1). Scheme 2 describes the synthesis of the bisindolylbenzoquinone skeleton. Protection and fluorous tag introduction of 3-iodoindole using **1b**, followed by Pd-catalyzed borylation,[11] gave key fluorous boronate **3**. The cross-coupling between **3** and dihalo central ring **4** proceeded smoothly. Employing Tl_2CO_3[12] as the base gave the best result for the cross-coupling. From the previous structure–activity relationship study, the dissymmetric structure (mono-functionalization of indole N atom as an example) was suggested to strengthen biological activities.[13] Thus, our synthetic route should have



1a R_1= H, R_2 = C_4F_9
1b R_1= H, R_2 = C_8F_{17} (Rf_8BsCl)
1c R_1= C_8F_{17}, R_2 = C_8F_{17}

	MeOH/H_2O = 80/20[a]	MeCN[a]	$CF_3C_6F_{10}$/Et_2O = 90/10[b]
2a	Rf = 0.3	0.8	0
2b	0	0.7	0
2c	0	0	0.3

a) Perfluorinated Silica gel TLC, b) Silica gel TLC

Scheme 1

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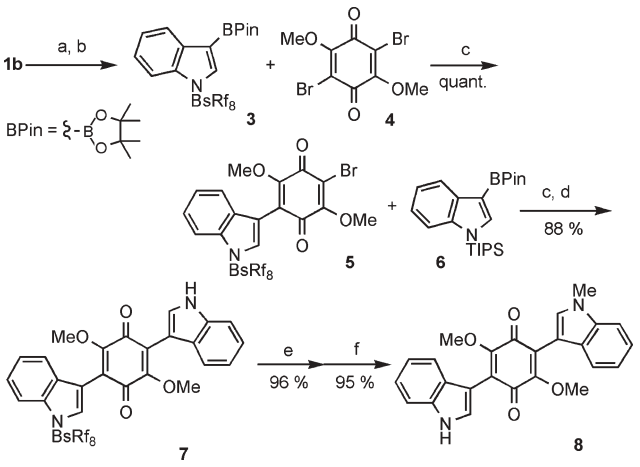
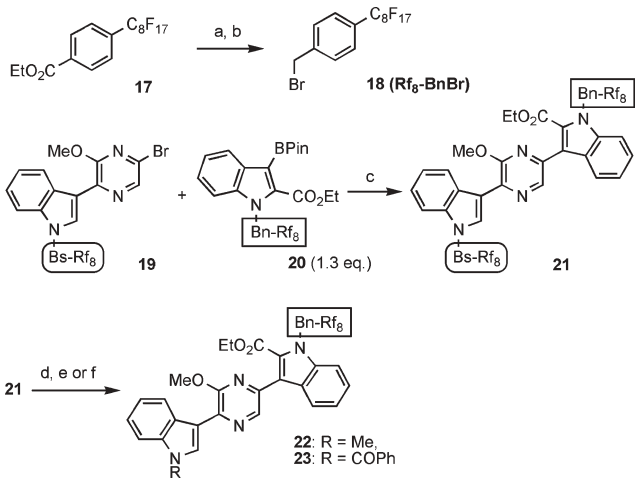
† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for synthesized compounds. See DOI: 10.1039/b516487g



Scheme 2 *Reagents and conditions*: (a) 3-Iodoindole, DMAP, Et_3N, CH_2Cl_2, rt, 12 h, 88%; (b) $PdCl_2(dppf)_2$, HBpin, Et_3N, dioxane, 80 °C, 4 h, 88%; (c) $Pd(PPh_3)_4$, Tl_2CO_3, benzene, 80 °C, 24 h; (d) CsF, THF/MeOH (1 : 1), rt, 30 min; (e) MeI, Cs_2CO_3, DMF, rt, 1.5 h; (f) Mg, NH_4Cl, THF/MeOH (1 : 1), rt, 2 h.



Scheme 3 *Reagents and conditions*: (a) $LiAlH_4$, THF, rt, 1 h, 87%; (b) PBr_3, CH_2Cl_2, rt, 2 h, 54%; (c) $Pd(PPh_3)_4$, Tl_2CO_3, 80 °C, benzene, 24 h, 98%; (d) TBAF, THF, rt, 1 h, 98%; (e) MeI, Cs_2CO_3, DMF, rt, 1.5 h, 97%; (f) PhCOCl, DMAP, Et_3N, CH_2Cl_2, rt, 2 h, 92%.

excellent flexibility for attaching dissymmetric indole units. Cross-coupling to introduce the second indole ring, followed by N-functionalization and cleavage from the fluorous tag, quantitatively gave **8**. Introducing the tag into the functionalization step allows each step to be purified by F-SPE. To the best of our knowledge, a precedent example of bisindolylbenzoquinone synthesis by Pd-catalyzed cross-coupling has yet to be reported.

By developing a concise synthetic route to bisindole compounds, we planned to construct natural and non-natural indole libraries (Fig. 2). Consecutive cross-coupling reactions and functionalization were adopted as our common synthetic route.

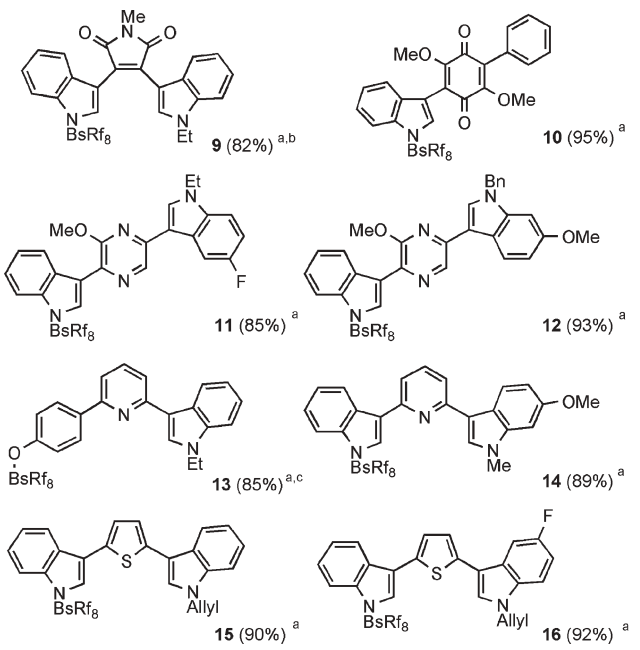


Fig. 2 a: Overall yield from boron ester; b: *N*-Lithioindole was used to introduce the second indole; c: Fluorous-tagged phenyl boronic acid pinacol ester was used.

Bisindolylpyrazine (**11**, **12**) and bisindolylpyridine (**14**) skeletons showed cytotoxic activity.[7] The coupling reaction with the fluorous-tagged phenyl boronate instead of **3** also proceeded in high yield (**13**).

Scheme 1 indicates that the light and heavy fluorous-tagged molecules are easily separated. Thus, we planned a fluorous synthesis *via* doubly-tagged molecules. The right coupling unit **20** was synthesized using novel fluorous Rf_8-BnBr (**18**) (Scheme 3).[14] The cross-coupling reaction between the fluorous-tagged **19** and **20** was purified by F-SPE. The MeCN eluent contained a trace amount of unreacted **19** and excess **20**. However, the subsequent THF eluent exclusively contained coupling product **21**. Selective mono deprotection and functionalization gave **22** and **23**. Hence, the partial detagging–functionalization of a doubly fluorous-tagged molecule is an effective method to construct a library of diverse bisindole systems.

In summary, the bisindolylbenzoquinone skeleton was easily assembled using fluorous-tagged indolylboron and dihaloaromatics *via* a palladium-catalyzed coupling reaction. This flexible synthetic route is suitable to construct a bisindole library. In addition, double fluorous tagging has potential for diverse functionalization. Further applications of this fluorous indole synthesis are currently under way.

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