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Diazonamide synthetic studies. Reactivity of *N*-unsubstituted benzofuro[2,3-*b*]indolines

Ilga Mutule[1], Toms Kalnins[1], Edwin Vedejs[1,2], Edgars Suna[1]*

[1] *Latvian Institute of Organic Synthesis, 21 Aizkraukles St., Riga LV-1006, Latvia; e-mail: edgars@osi.lv*

[2] *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, U. S. A.; e-mail: edved@umich.edu*

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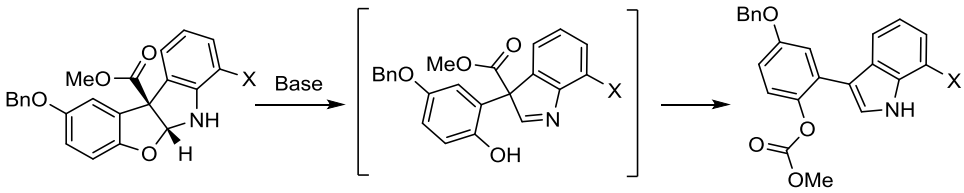


X = Me, Br, 2-MeC$_6$H$_4$

Benzofuro[2,3-*b*]indolines undergo ring opening in the presence of base to generate 3*H*-indolines. The latter can rearrange into 3-arylindoles through an intramolecular transfer of the methoxycarbonyl moiety from quaternary carbon to oxygen of phenol. The intermediate 3*H*-indolines can be isolated upon DMAP-catalyzed *O*-acylation of the phenol moiety with Boc_2O.

Keywords: diazonamide, DMAP, hemiaminal, indole, 3*H*-indoline.

Benzofuro[2,3-*b*]indoline is a core structure in a number of natural products such as the marine metabolite diazonamide A (**1**), azonazine (**2**), and voacalgine A (**3**), a representative of the pleiocarpamine family of alkaloids (Fig. 1). Among them, diazonamide A (**1**) is an especially important synthetic target[1] because it exerts nanomolar cytotoxicity against a broad panel of human tumor cell lines.[2] Not surprisingly, the development of methods for the assembly and further functionalization of benzofuro[2,3-*b*]indoline heterocyclic system has been a focus of research efforts.[3,4]

A majority of the natural products contains an *N*-substituted benzofuro[2,3-*b*]indoline scaffold and only diazonamide A (**1**) possesses the *N*-unsubstituted tetracyclic core. In the context of diazonamide A total synthesis, this structural feature imposes challenges associated with a potentially labile nature of the *N*-unsubstituted cyclic hemiaminal moiety. Thus, our group[5] and Moody[6] have observed fragmentation of the benzofuro[2,3-*b*]-indoline to indolic side products. For example, during attempted Suzuki cross coupling of the *N*-unsubstituted benzofuro[2,3-*b*]indoline **4a** with boronate **5a** in the presence of base, we obtained 3-arylindole **6a** as a major product (86% yield, Scheme 1, Conditions A). Installation of an *N*-MOM protecting group in the benzofuro[2,3-*b*]-indoline moiety helped to avoid the fragmentation of the cyclic hemiaminal in the Suzuki cross coupling and allowed for the desired biaryl **7a** to be isolated in 82% yield (Scheme 1, Conditions A).[7] The formation of the undesired 3-arylindole **6b** was encountered also in the Stille cross coupling involving the *N*-unsubstituted tetracyclic stannane **4b** under virtually neutral conditions

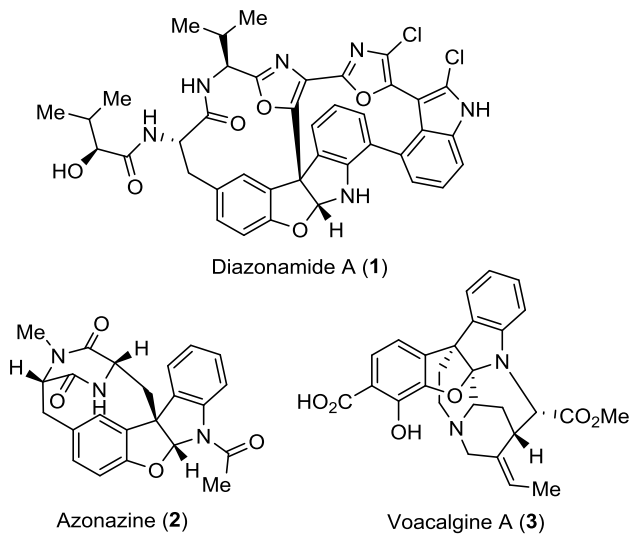
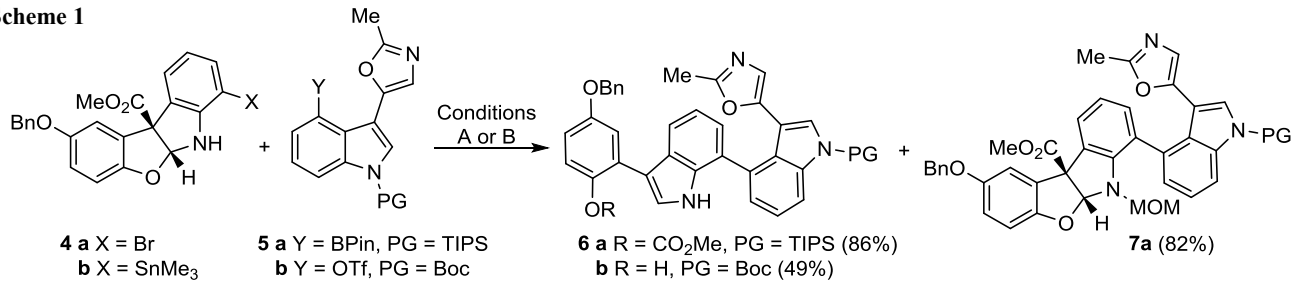


Figure 1. Benzofuro[2,3-*b*]indoline motif-containing representative natural products.

Scheme 1



4 a X = Br
b X = $SnMe_3$

5 a Y = BPin, PG = TIPS
b Y = OTf, PG = Boc

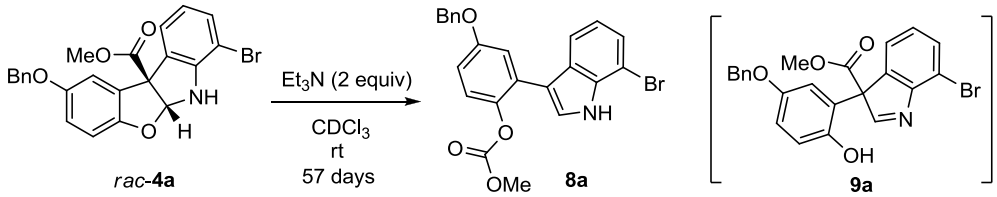
6 a R = CO_2Me, PG = TIPS (86%)
b R = H, PG = Boc (49%)

7a (82%)

Conditions A: $(Cy_3P)_2Pd(\eta^2\text{-}O_2)$ (20 mol %), K_3PO_4 (4 equiv), dioxane, 100°C
Conditions B: Pd_2dba_3, Ph_3As, LiCl, THF

Fragmentation of *N*-unsubstituted benzofuro[2,3-*b*]indolines **4a**,**b**

Scheme 2



rac-**4a**

8a

9a

Base-mediated fragmentation of hemiaminal *rac*-**4a**

(49%, Scheme 1, Conditions B).[5a] The observed fragmentation of the cyclic hemiaminals to 3-arylindoles under basic or neutral cross-coupling conditions prompted us to investigate stability and reactivity of the *N*-unsubstituted benzofuro[2,3-*b*]indoline **4a**.

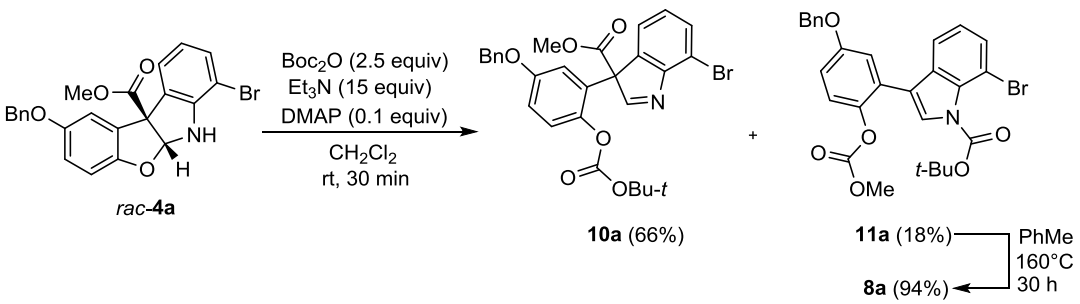
The hemiaminal *rac*-**4a** was found to be stable in $CDCl_3$ solution at room temperature, but addition of Et_3N (2 equiv) resulted in very slow formation of 3-arylindole **8a** (Scheme 2). After 24 h at room temperature only trace amounts (<5%) of compound **8a** were formed and complete conversion of the hemiaminal *rac*-**4a** to indole **8a** required 57 days at room temperature. We hypothesized that the formation of 3-arylindole **8a** would proceed through an initial formation of 3*H*-indoline intermediate **9a**.

Unfortunately, we could not observe the formation of ring-opening intermediates such as compound **9a** by NMR spectroscopy in the base-facilitated fragmentation of hemiaminal *rac*-**4a** to indole **8a**. Possibly, the lifetime of putative intermediate **9a** was too short on the timescale of the NMR experiment. Therefore, an electrophilic reagent was sought to trap the intermediate **9a**. Boc_2O was chosen as the trapping reagent because it did not react with the starting benzofuro[2,3-*b*]indoline *rac*-**4a** in the absence of base (Boc_2O in CH_2Cl_2, rt, 24 h or neat Boc_2O, rt, 24 h, or Boc_2O, $ZrCl_4$, MeCN, rt, 24 h). Disappointingly, addition of Boc_2O (2 equiv) to the hemiaminal *rac*-**4a** in the presence of Et_3N (2 equiv) in $CDCl_3$ returned no detectable amounts of *O*-Boc-protected phenol **9a** or any other intermediates derived from the ring opening of the hemiaminal *rac*-**4a**. The unreacted hemiaminal *rac*-**4a** (<5% conversion) was the only species observed after 24 h at rt. However, we were pleased to see that addition of catalytic amounts (10 mol %) of DMAP to the mixture of hemiaminal *rac*-**4a**, Boc_2O, and Et_3N brought about a rapid conversion of the starting hemiaminal *rac*-**4a** (>95% after 30 min at rt) and formation of *O*-Boc-phenol **10a** as a major product (66%) together with *N*-Boc-indole **11a*** (18%, Scheme 3).

Importantly, a control experiment without added Boc_2O (hemiaminal *rac*-**4a**, 5 equiv of Et_3N, and 0.5 equiv of DMAP in $CDCl_3$ at room temperature) showed only unreacted hemiaminal *rac*-**4a** after 24 h (<5% conversion).

* Isolated compound **11a** was converted to *N*-deprotected indole **8a** under thermal conditions (PhMe, 160°C, 30 min)[8] to confirm the structural assignment for compound **8a**, which was based on the NMR experiments.

Scheme 3

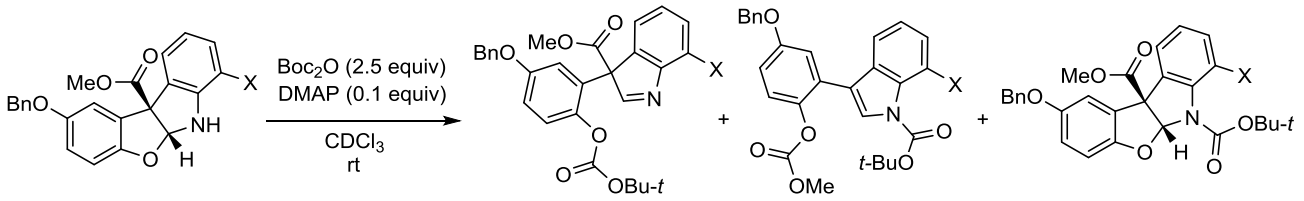


rac-**4a**

10a (66%)

Ring opening of the hemiaminal *rac*-**4a** in the presence of Boc_2O

Table 1. Influence of substituents on the fragmentation of hemiaminals *rac*-**4a**,**c**–**e**



rac-**4a,c–e** **10a,c–e** **11a,c–e** **12a,c–e**

Entry	Hemiaminal*	X	Reaction time, h	Product yield**, %		
				10a,**c**–**e**	**11a**,**c**–**e**	**12a**,**c**–**e**
1	**4a**	Br	1.5	85***	15***	–
2	**4c**	Me	72	91	–	–
3	**4d**	2-MeC_6H_4	72	81	–	–
4	**4e**	CN	20	–	–	98

* Racemic, diastereomerically pure hemiaminals **4a**,**c**–**e** were used.
** Isolated yields.
*** Yields established by ^{1}H NMR spectroscopy.

Evidently, DMAP-catalyzed trapping of the equilibrating ring-opened intermediate **9a** with Boc_2O to form *O*-Boc-phenol **10a** facilitates fragmentation of the benzofuro[2,3-*b*]-indoline *rac*-**4a** by shifting the equilibrium between compounds **4a** and **9a** toward the latter.

Surprisingly, DMAP-catalyzed transformation of the hemiaminal *rac*-**4a** to *O*-Boc-phenol **10a** and indole **11a** proceeded even without the added triethylamine. Thus, 10 mol % of DMAP effected the complete conversion of the benzofuro[2,3-*b*]indoline *rac*-**4a** within 1.5 h (Table 1, entry 1). Apparently, the facile formation of *O*-Boc-phenol **10a** is achieved by *tert*-butoxide, the strong base formed *in situ* in the reaction of DMAP with Boc_2O.* Notably, electron-releasing substituents at position 7 of the benzofuro[2,3-*b*]-indoline (*rac*-**4c** X = Me and *rac*-**4d** X = 2-MeC_6H_4) considerably slowed down the rearrangement of the corresponding hemiaminals (from 1.5 to 72 h; entries 2, 3). Furthermore, the formation of 3-arylindoles **11c**,**d** was not observed for these substrates and 3*H*-indoles **10c**,**d** were the only products. In sharp contrast, 7-cyanobenzofuro[2,3-*b*]-indoline *rac*-**4e** did not undergo ring opening under standard conditions (entry 4). Instead, *N*-Boc-protected hemiaminal **12e** was isolated in almost quantitative yield (98%).

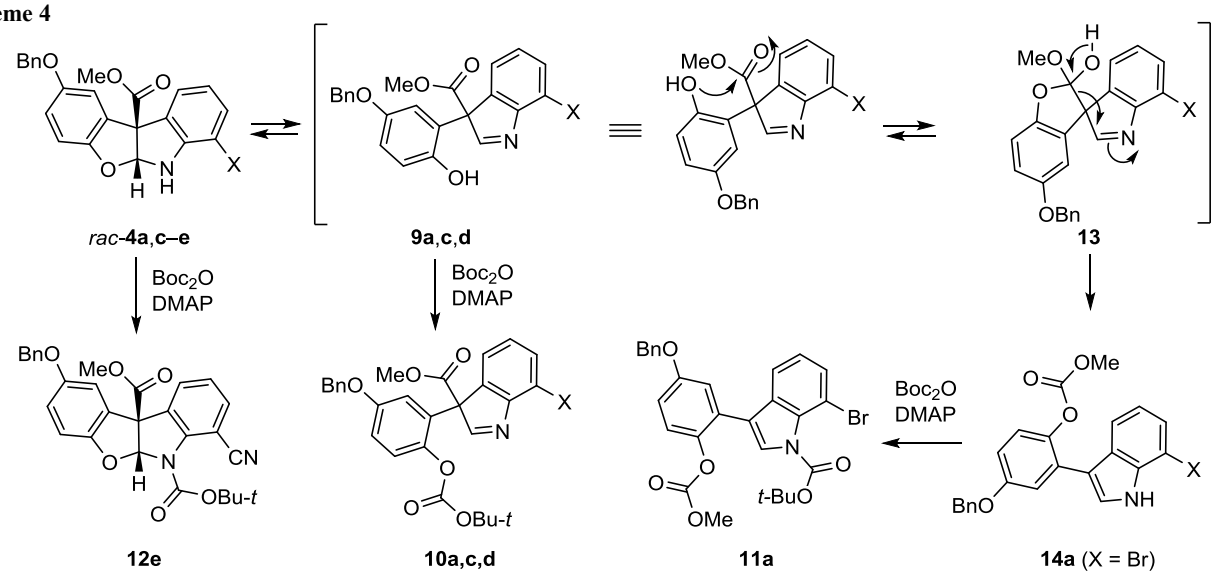
The isolation of *O*-Boc phenols **10a**,**c**,**d** provide evidence that the ring opening of the benzofuro[2,3-*b*]indolines **4a**,**c**–**e** is the first step of the multistep rearrangement process (Scheme 4). Presumably, electron-withdrawing substituents (X = CN) in the benzofuro[2,3-*b*]indoline *rac*-**4e** stabilize the tetracyclic system and prevent the ring opening to form compound **9e**. Hence, DMAP-catalyzed *N*-acylation of benzofuro[2,3-*b*]indoline *rac*-**4e** with Boc_2O affords the ring-closed *N*-Boc hemiaminal **12e**. Other benzofuro[2,3-*b*]indolines *rac*-**4a**,**c**,**d** apparently lack the stabilization by substituent and exist in the equilibrium with the corresponding phenols **9a**,**c**,**d**. For these substrates, *N*-acylation rates with Boc_2O are presumably slower compared to the competing *O*-acylation of the corresponding opened forms **9a**,**c**,**d**. Possibly, diminished *N*-acylation rates of the benzofuro[2,3-*b*]indolines *rac*-**4a**,**c**,**d** compared to *rac*-**4e** are the result of steric hindrance around the nitrogen atom introduced by *ortho* substituents X. Since a CN group is the smallest substituent in the series, increased steric hindrance imposed by other substituents (X = Me, 2-MeC_6H_4, Br) may account for reduced rates of the catalytic *N*-acylation of tetracycles *rac*-**4a**,**c**,**d** with Boc_2O. Hence, the competing DMAP-catalyzed *O*-acylation with Boc_2O facilitates the opening of the benzofuro[2,3-*b*]-indolines *rac*-**4a**,**c**,**d** to form 3*H*-indolines **10a**,**c**,**d**.

In the absence of external electrophile such as Boc_2O phenols **9** may undergo an intramolecular acyl transfer *via* tetrahedral intermediate **13** with indole acting as a good leaving group to form the *N*-unsubstituted indole **14**. Notably, for phenol **9a**, the intramolecular acyl transfer from carbon to oxygen to afford compound **14a** was a competing side reaction (yield 15%, Table 1, entry 1) to DMAP-catalyzed intermolecular *O*-acylation with the excess of Boc_2O (2 equiv). Possibly, the better leaving group ability of the 7-bromoindole moiety compared to 7-methyl- and 7-(2-methylphenyl)-substituted analogs ensures sufficiently rapid decomposition of the putative tetrahedral intermediate **13a** to form compound **14a** (Scheme 4). It should be noted that in the presence of DMAP/Boc_2O anionic versions of intermediates *rac*-**4a**,**c**–**e** and **9a**,**c**–**e** could also be involved,[9] but they are not illustrated in the Scheme 4 for simplicity.

In summary, the fragmentation reaction of benzofuro-[2,3-*b*]indolines *rac*-**4a**,**c**–**e** has been studied. They undergo ring opening to the corresponding phenols **9a**,**c**,**d** in the presence of a base such as Et_3N or DMAP/Boc_2O.[9] The intermediate phenols **9a**,**c**,**d** can be isolated upon DMAP-catalyzed *O*-acylation with Boc_2O. Without the added

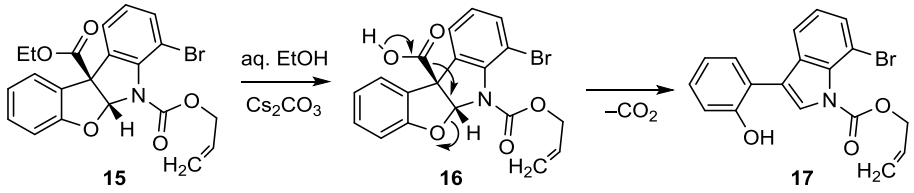
* As has been demonstrated by Hassner,[9] the reaction of DMAP with Boc_2O produces ion pair: *N*-Boc-pyridinium *tert*-butoxycarboxylate. The *tert*-butoxycarboxylate decomposes to CO_2 and the strong base *tert*-butoxide.

Scheme 4



Working mechanism for DMAP-catalyzed fragmentation of benzofuro[2,3-b]indolines *rac*-**4a**,**c**–**e**

Scheme 5



Mechanism suggested by Moody

Boc_2O, phenols **9** undergo an intramolecular transfer of the methoxycarbonyl group *via* the tetrahedral intermediate **13** with indole acting as a good leaving group to form *O*-methoxycarbonyl phenols **14**. The proposed mechanism differs from an alternative base-mediated pathway suggested by Moody for *N*-substituted benzofuro[2,3-*b*]-indolines,[6] which would involve an initial hydrolysis of ester **15** by aqueous base, followed by decarboxylation of the intermediate carboxylic acid **16** with concomitant formation of *N*-substituted aromatic indole **17** (Scheme 5).

According to the mechanism proposed by Moody, phenolate acts as a good leaving group resulting in the formation of *O*-unsubstituted *N*-protected phenol **17** as the fragmentation product. It should be noted, that we observed the formation of *N*-unsubstituted *O*-methoxycarbonyl-phenols **6a** and **14a** with the methoxycarbonyl moiety originating from the ester moiety at the quaternary carbon in the starting benzofuro[2,3-*b*]indolines, hence suggesting that our mechanism differs from that of Moody. Therefore, benzofuro[2,3-*b*]indolines may undergo fragmentation to 3-arylindoles by two alternative mechanisms, depending on the reaction conditions.

Experimental

IR spectra were recorded on a Shimadzu IR Prestige21 FTIR spectrometer in thin film. ^1H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury NMR spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as internal standard. High-resolution mass spectra (ESI) were obtained on a Waters Tof Synapt GSi mass spectrometer. Preparative HPLC was performed on a Waters SunFire^{TM} Prep Silica OBD^{TM} 5μm, 30 × 100 mm, mobile phase 10% EtOAc in petroleum ether, flow rate 35 ml/min. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates (Merck).

Unless otherwise noted, all chemicals were used as obtained from commercial sources and all reactions were performed under argon atmosphere in an oven-dried (120°C) glassware. Toluene was distilled from sodium/benzophenone prior the use. Anhydrous 1,4-dioxane (Acros), N,N-dimethylacetamide (Acros), and toluene were degassed by multiple freeze-pump-thaw cycles, and handled using Schlenk technique. Anhydrous CH_2Cl_2 was obtained by passing commercially available solvent through activated alumina columns. Commercially available anhydrous K_3PO_4 was heated at 250°C for 3 h and stored in a glove box under argon atmosphere.

Methyl 2-(benzyloxy)-7-methyl-6,10b-dihydro-5a*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (4c). *N*-MOM-protected hemiaminal *rac*-**4a**[7] (25 mg, 0.055 mmol) and $PdCl_2$(dppf) (2.1 mg, 0.0025 mmol) were placed into a 5 ml pressure vial and suspended in anhydrous dioxane (1.0 ml) under nitrogen atmosphere. Then dimethylzinc (1.2 M

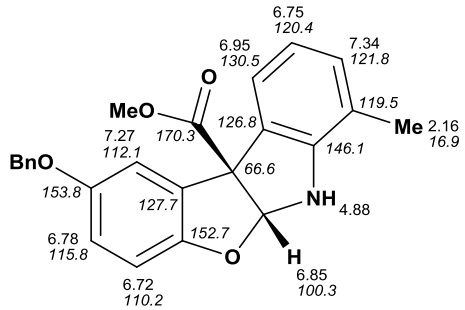


Figure 2. ^{1}H and ^{13}C NMR assignment for compound **4c**.

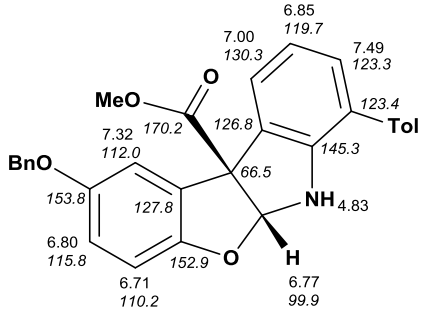


Figure 3. ^{1}H and ^{13}C NMR assignment for compound **4d**.

solution in toluene, 83 μl, 0.10 mmol) was added and the resulting clear yellow solution was heated in an oil bath at 100°C for 1 h. The off-white precipitate was filtered through a pad of Celite and the pad was washed with EtOAc (25 ml). The filtrate was washed with water (10 ml) and the layers were separated. The aqueous layer was back-extracted with EtOAc (2×10 ml) and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated (rotary evaporator). The residue was purified on silica gel column using gradient elution from 2% EtOAc in petroleum ether to 25% EtOAc in petroleum ether to afford colorless oil (15 mg) comprising a mixture of MOM-protected and MOM-deprotected products. To achieve complete cleavage of the *N*-MOM protecting group in the product, the isolated mixture of products was dissolved in MeOH (2 ml) and aqueous concentrated HCl (50 μl) was added. The colorless solution was stirred at room temperature for 5 h, basified with aqueous sat. $NaHCO_3$ solution to pH 7 and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated (rotary evaporator). Column chromatography on silica gel using gradient elution from 2% EtOAc in petroleum ether to 25% EtOAc in petroleum ether afforded the product as colorless oil (9 mg, 47%, Fig. 2). R_f 0.43 (petroleum ether – EtOAc, 5:4). IR spectrum, ν, cm^{-1}: 3395 (NH), 1736 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.45–7.30 (6H, m); 7.27 (1H, dd, *J* = 2.7, *J* = 0.4); 6.95 (1H, ddd, *J* = 7.5, *J* = 1.2, *J* = 0.7); 6.86 (1H, d, *J* = 3.5); 6.78 (1H, dd, *J* = 8.7, *J* = 2.7); 6.75 (1H, t, *J* = 7.5); 6.72 (1H, dd, *J* = 8.7, *J* = 0.4); 5.00 (2H, s); 4.88 (1H, d, *J* = 3.5); 3.80 (3H, s); 2.16 (3H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 170.3; 153.8; 152.7; 146.1; 137.3; 130.5; 128.7; 128.1; 127.8; 127.7; 126.8; 121.8; 120.4; 119.5; 115.8; 112.1; 110.2; 100.3; 71.3; 66.6; 53.2; 16.9. Found, *m*/*z*: 388.1542 [M+H]$^+$. $C_{24}H_{22}NO_4$. Calculated, *m*/*z*: 388.1549.

Methyl 2-(benzyloxy)-7-(*ortho*-tolyl)-6,10b-dihydro-5a*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (4d). *N*-MOM -protected *rac*-**4a**[7] (50 mg, 0.11 mmol), *ortho*-tolylboronic acid pinacolyl ester (26 mg, 0.12 mmol), $(PCy_3)_2Pd(\eta^2\text{-}O_2)$[7] (14 mg, 20 mol %), and oven-dried K_3PO_4 (85 mg, 0.44 mmol) were weighed into a 5 ml pressure vial in a glove box (argon atmosphere). Anhydrous degassed toluene (2.5 ml) was added, and the reaction mixture was heated in an oil bath at 110°C for 18 h, then diluted with EtOAc (15 ml) and washed with water (15 ml). The aqueous layer was back-extracted with EtOAc (15 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). Column chromatography on silica gel using gradient elution from 2% EtOAc in petroleum ether to 25% EtOAc in petroleum ether afforded product as yellow oil (38 mg) comprising a mixture of MOM-protected and MOM-deprotected products according to ^{1}H NMR. To achieve complete cleavage of *N*-MOM protecting group in the product, the mixture of products was dissolved in MeOH (3 ml) and aqueous concentrated HCl (100 μl) was added. The reaction mixture was stirred at room temperature for 20 h, then basified to pH 7 using aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated (rotary evaporator). Purification of the residue on the silica gel column using gradient elution from 2% EtOAc in petroleum ether to 25% EtOAc in petroleum ether afforded the biaryl **4d** as colorless oil (17 mg, 33%, Fig. 3). R_f 0.53 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 3394 (N–H), 1733 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.49 (1H, d, *J* = 7.6); 7.47–7.33 (5H, m); 7.32 (1H, d, *J* = 2.7); 7.28–7.20 (4H, m); 7.00 (1H, dd, *J* = 7.6, *J* = 1.1); 6.85 (1H, t, *J* = 7.6); 6.80 (1H, dd, *J* = 8.7, *J* = 2.7); 6.77 (1H, d, *J* = 2.7); 6.71 (1H, d, *J* = 8.7); 5.03 (2H, s); 4.83 (1H, s); 3.84 (3H, s); 2.18 (3H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 170.2; 153.8; 152.9; 145.3; 137.6; 137.3; 136.6 (br. s); 130.6; 130.3; 129.9 (br. s); 128.7; 128.1; 128.0; 127.8; 126.7 (br. s); 126.2; 123.4 (br. s); 123.3; 119.7; 115.8; 112.0; 110.2; 99.9; 71.3; 66.5; 53.3; 20.1. Found, *m*/*z*: 464.1861 [M+H]$^+$. $C_{30}H_{26}NO_4$. Calculated, *m*/*z*: 464.1862.

Methyl 2-(benzyloxy)-7-cyano-6,10b-dihydro-5a*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (4e). *N*-MOM-protected *rac*-**4a**[7] (100 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.005 mmol), dppf (11.1 mg, 0.10 mmol), and $Zn(CN)_2$ (16.6 mg, 0.14 mmol) were weighed into a 5 ml pressure vial and anhydrous degassed DMA (2.5 ml) was added under nitrogen. The suspension was stirred at 110°C for 2 h, filtered through a pad of Celite, and the pad was washed with EtOAc (30 ml). The filtrate was washed with water (2 × 15 ml), brine, dried over Na_2SO_4, and concentrated (rotary evaporator). Purification of a brown oily residue on silica gel column using gradient elution from 7% EtOAc in petroleum ether to 56% EtOAc in petroleum ether was followed by additional purification on preparative TLC using 25% acetone in petroleum ether and afforded **methyl 2-(benzyloxy)-7-cyano-6-(methoxymethyl)-**

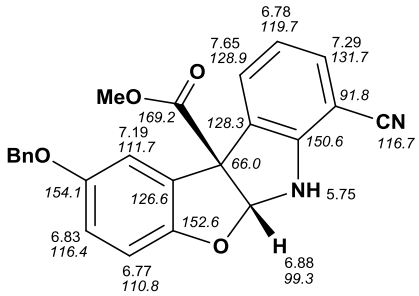


Figure 4. ^{1}H and ^{13}C NMR assignment for compound **4e**.

6,10b-dihydro-5a*H*-benzofuro[2,3-*b*]indole-10b-carboxylate as a brownish oil (46 mg, 53%). R_f 0.37 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 2222 (C≡N), 1738 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.69 (1H, ddd, *J* = 7.5, *J* = 1.2, *J* = 0.5); 7.43–7.30 (6H, m); 7.17 (1H, d, *J* = 2.6); 6.86–6.76 (4H, m); 5.39 (1H, d, *J* = 10.9); 5.04 (1H, d, *J* = 10.9); 5.00 (2H, s); 3.82 (3H, s); 3.47 (3H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 169.0; 154.2; 152.3; 147.9; 137.0; 134.0; 130.3; 128.9; 128.7; 128.2; 127.7; 126.8; 120.2; 117.7; 116.5; 111.9; 110.9; 103.1; 92.1; 77.1; 71.3; 63.6; 55.3; 53.6. Found, *m*/*z*: 411.1344 [M–CH$_3$O]$^+$. $C_{25}H_{19}N_2O_4$. Calculated, *m*/*z*: 411.1345.

The *N*-MOM-protected hemiaminal from above (40 mg, 0.09 mmol) was dissolved in MeOH (2 ml), aqueous concentrated HCl (300 µl) was added, and the reaction mixture was stirred at room temperature for 36 h, then basified with aqueous saturated $NaHCO_3$ to pH 7 and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated (rotary evaporator). The residue was purified on silica gel column using gradient elution from 7% EtOAc in petroleum ether to 60% EtOAc in petroleum ether to afford compound **4e** as a colorless solid (18 mg, 56%, Fig. 4). R_f 0.38 (petroleum ether – EtOAc, 5:4). IR spectrum, ν, cm^{-1}: 3335 (N–H), 2224 (C≡N), 1728 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.65 (1H, d, *J* = 7.5); 7.44–7.31 (5H, m); 7.29 (1H, dd, *J* = 7.9, *J* = 1.1); 7.19 (1H, d, *J* = 2.6); 6.88 (1H, d, *J* = 2.2); 6.83 (1H, dd, *J* = 8.8, *J* = 2.6); 6.78 (1H, t, *J* = 7.7); 6.77 (1H, d, *J* = 8.8); 5.75 (1H, s); 5.01 (2H, s); 3.83 (3H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 169.2; 154.1; 152. 6; 150.6; 137.0; 131.7; 128. 9; 128.7; 128.3; 128.2; 127.7; 126.6; 119.7; 116.7; 116.4; 111.7; 110.8; 99.3; 91.8; 71.3; 66.0; 53.6. Found, *m*/*z*: 399.1326 [M+H]$^+$. $C_{24}H_{19}N_2O_4$. Calculated, *m*/*z*: 399.1345.

4-(Benzyloxy)-2-[3-(2-methyloxazol-5-yl)-1-(triisopropylsilyl)-1*H*,1'*H*-[4,7'-biindol]-3'-yl]phenyl methyl carbonate (**6a**). A hemiaminal *rac*-**4a**[7] (100 mg, 0.22 mmol), *N*-TIPS indolyl boronate **5a**[7] (106 mg, 0.22 mmol), $(PCy_3)_2Pd(\eta^2\text{-}O_2)$[7] (30 mg, 20 mol %), and an oven-dried K_3PO_4 (188 mg, 0.88 mmol) were weighed into an oven-dried pressure vial in a glove box (argon atmosphere). Anhydrous degassed dioxane (4 ml) was added, and the reaction mixture was heated in an oil bath at 100°C for 20 h, then diluted with EtOAc (25 ml) and washed with water (25 ml). The aqueous layer was back-extracted with EtOAc (25 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). Column chromatography on silica gel using gradient elution from 5% acetone in hexanes to 25% acetone in hexanes afforded the product **6a** as off-white foam (130 mg, 86%, Fig. 5). R_f 0.19 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 3421 (N–H), 1763 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.16 (1H, d, *J* = 1.5); 7.60 (1H, dd, *J* = 6.6, *J* = 2.7); 7.56 (1H, dd, *J* = 7.5, *J* = 1.5); 7.49–7.38 (5H, m); 7.38–7.29 (5H, m); 7.16 (1H, d, *J* = 8.9); 7.06–6.98 (2H, m); 6.90 (1H, dd, *J* = 8.9, *J* = 3.1); 6.16 (1H, s); 5.12 (2H, s); 3.70 (3H, s); 1.80 (3H, s); 1.75 (3H, septet, *J* = 7.5); 1.20 (18H, d, *J* = 7.5). ^{13}C{^{1}H}NMR spectrum, δ, ppm: 159.9; 156.7; 154.4; 145.7; 142.1; 142.0; 136.9; 135.0; 132.2; 131.0; 129.1; 128.7; 128.0; 127.4; 127.1; 125.6; 125.0; 123.7; 123.2; 122.9; 122.5; 122.3; 120.0; 118.5; 116.3; 113.8; 113.3; 111.8; 107.2; 70.4; 55.3; 18.2; 13.0; 12.8. Found, *m*/*z*: 726.3351 [M+H]$^+$. $C_{44}H_{48}N_3O_5Si$. Calculated, *m*/*z*: 726.3363.

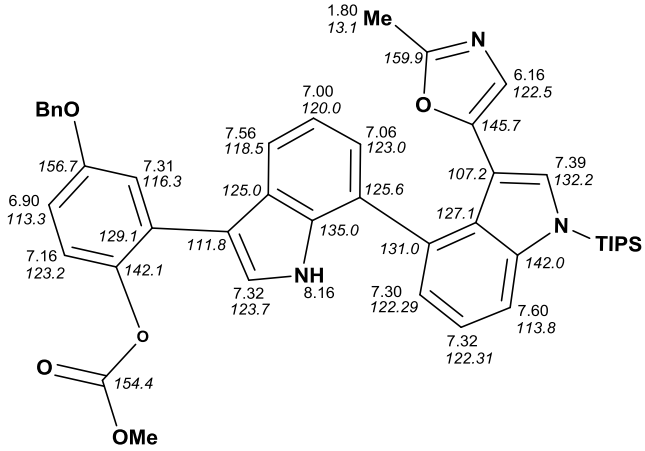


Figure 5. ^{1}H and ^{13}C NMR assignment for compound **6a**.

4-(Benzyloxy)-2-(7-bromo-1*H*-indol-3-yl)phenyl methyl carbonate (**8a**). A solution of hemiaminal *rac*-**4a**[7] (10 mg, 0.022 mmol) in $CDCl_3$ (0.7 ml) was placed in NMR tube and Et_3N (6 µl, 0.044 mmol) was added. The solution was kept at room temperature and progress of the reaction was monitored by ^{1}H NMR. Full conversion to the starting hemiaminal bromide *rac*-**4a** was observed after 57 days.

For structure assignment and compound characterization purposes, the indole **8a** was synthesized from *N*-Boc-indole **11a**. Accordingly, a solution of *N*-Boc-indole **11a** (30 mg, 0.054 mmol) in toluene (2.0 ml) was heated at 160°C in a closed 5 ml pressure vial for 30 h, then the solvent was evaporated and the brownish solid residue was purified on silica gel column using gradient elution from 7% EtOAc in petroleum ether to 60% EtOAc in petroleum ether. Indole **8a** was obtained as colorless foam (23 mg, 94%, Fig. 6). R_f 0.38 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 3422 (N–H), 1761 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.48 (1H, s); 7.55 (1H, d, *J* = 8.0); 7.47–7.32 (7H, m); 7.22 (1H, d, *J* = 3.0); 7.19 (1H, d, *J* = 8.9); 7.01 (1H, t, *J* = 7.8); 6.95 (1H, dd, *J* = 8.9, *J* = 3.0); 5.12 (2H, s); 3.70 (3H, s). ^{13}C {^{1}H} NMR spectrum, δ, ppm: 156.9; 154.4; 142.3; 137.0; 135.9; 128.8; 128.5; 128.2; 127.6; 127.5; 124.9; 124.3; 123.4; 121.7; 119.4; 116.7; 114.0; 113.6; 105.0;

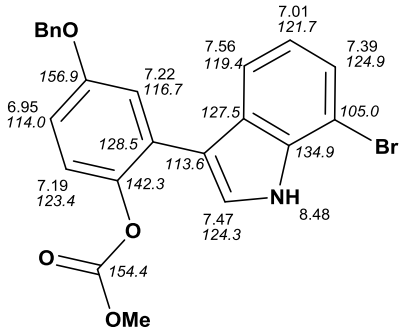


Figure 6. ^{1}H and ^{13}C NMR assignment for compound **8a**.

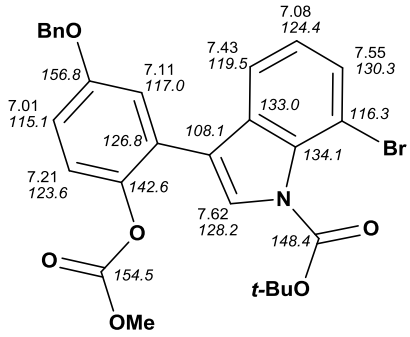


Figure 8. ^{1}H and ^{13}C NMR assignment for compound **11a**.

70.6; 55.5. Found, *m*/*z*: 452.0479 $[M+H]^+$. $C_{23}H_{19}BrNO_4$. Calculated, *m*/*z*: 452.0497.

Ring opening of the hemiaminal *rac*-4a in the presence of Boc_2O. The hemiaminal *rac*-**4a**[7] (880 mg, 1.64 mmol) was dissolved in anhydrous CH_2Cl_2 (70 ml) under nitrogen atmosphere, and the resulting solution was cooled to 0°C. Then, Et_3N (3.4 ml, 24.6 mmol) was added dropwise, followed by Boc_2O (892 mg, 4.10 mmol) and DMAP (50 mg, 0.40 mmol). The colorless solution was stirred at room temperature for 30 min, then the solvent was evaporated and the residue was purified on silica gel column (80 ml SiO_2, mobile phase 30% EtOAc in petroleum ether) to afford a mixture of *O*-Boc-phenol **10a** and *N*-Boc-indole **11a.** These two products were separated on the preparative HPLC.

Methyl 3-{5-(benzyloxy)-7-bromo-2-[(*tert*-butoxycarbonyl)oxy]phenyl}-3*H*-indole-3-carboxylate (10a) was obtained as a colorless foam (597 mg, 66%, Fig. 7). R_f 0.47 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 1761 (C=O), 1743 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.27 (1H, s); 7.62 (1H, d, *J* = 8.0); 7.45 (1H, d, *J* = 7.5); 7.34–7.17 (7H, m); 6.93 (1H, dd, *J* = 9.0, *J* = 3.0); 6.32 (1H, d, *J* = 3.0); 4.87 (1H, ABq, J_{AB} = 12.0); 4.86 (1H, ABq, J_{AB} = 12.0); 3.70 (3H, s); 1.55 (9H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 170.3; 168.6; 156.3; 154.1; 151.2; 143.5; 136.7; 136.1; 133.1; 128.5; 128.0; 127.3; 126.1; 123.9; 115.5; 115.1; 113.9; 84.0; 71.5; 70.3; 53.0; 27.6. Found, *m*/*z*: 574.0834 $[M+Na]^+$. $C_{28}H_{26}BrNNaO_6$. Calculated, *m*/*z*: 574.0841.

***tert*-Butyl 3-{5-(benzyloxy)-7-bromo-2-[(methoxycarbonyl)oxy]phenyl}-1*H*-indole-1-carboxylate (11a)** was obtained as a colorless oil (167 mg, 18%, Fig. 8). R_f 0.53 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 1763 (C=O), 1738 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.62 (1H, s); 7.55 (1H, dd, *J* = 7.8, *J* = 1.0); 7.46–7.32 (6H, m); 7.21 (1H, d, *J* = 8.9); 7.11 (1H, d, *J* = 3.0); 7.08 (1H, t, *J* = 7.8); 7.01 (1H, dd, *J* = 8.9, *J* = 3.0); 5.11 (2H, s); 3.71 (3H, s); 1.67 (9H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 156.8; 154.5; 148.4; 142.6; 136.8; 134.1; 133.0; 130.3; 128.9; 128.2 (2 peaks overlapping); 127.6; 126.8; 124.4; 123.6; 119.5; 117.0; 116.3; 115.1; 108.1; 84.7; 70.6; 55.5; 28.1. Found, *m*/*z*: 452.0484 $[M–(CH_3)_3COC(O)+2H]^+$. $C_{23}H_{19}BrNO_4$. Calculated, *m*/*z*: 452.0497.

Methyl 3-{5-(benzyloxy)-2-[(*tert*-butoxycarbonyl)oxy]-phenyl}-7-methyl-3*H*-indole-3-carboxylate (10c). A solution of hemiaminal **4c** (20 mg, 0.052 mmol, Fig. 9) in $CDCl_3$ (0.7 ml) was placed in NMR tube and DMAP (0.64 mg, 0.0052 mmol) was added, followed with Boc_2O (28 mg, 0.130 mmol). The clear colorless solution was kept at room temperature and progress of the reaction was monitored by ^{1}H NMR. Complete conversion of the starting hemiaminal **4c** was observed after 72 h. The solution was poured onto the silica gel column and purified using CH_2Cl_2 as a mobile phase to afford product **10c** (23 mg, 91%) as a yellowish oil. R_f 0.45 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 1761 (C=O), 1733 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20 (1H, s); 7.35 (1H, dd, *J* = 7.2, *J* = 1.0); 7.34–7.22 (7H, m); 7.22 (1H, d, *J* = 9.0); 6.92 (1H, dd, *J* = 9.0, *J* = 3.0); 6.37 (1H, d, *J* = 3.0); 4.86 (2H, s); 3.70 (3H, s); 2.61 (3H, s); 1.58 (9H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 169.6; 168.4; 156.5; 154.5; 151.6; 144.0; 134.5; 134.9; 131.8; 131.3; 128.7; 128.2; 127.7; 127.4; 127.2; 123.9; 122.5; 115.0; 114.2; 84.0; 70.5; 70.3; 53.1; 27.9; 17.0. Found, *m*/*z*: 510.1886 $[M+Na]^+$. $C_{29}H_{29}NNaO_6$. Calculated, *m*/*z*: 510.1892.

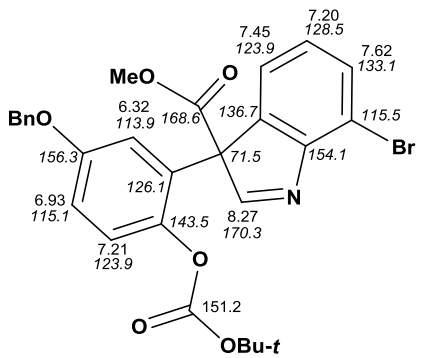


Figure 7. ^{1}H and ^{13}C NMR assignment for compound **10a**.

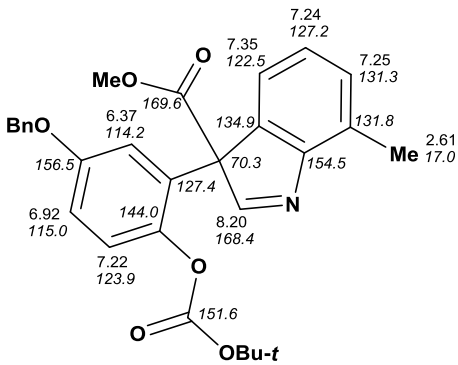


Figure 9. ^{1}H and ^{13}C NMR assignment for compound **10c**.

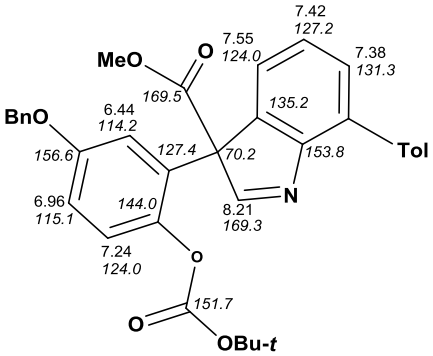


Figure 10. ^{1}H and ^{13}C NMR assignment for compound **10d**.

Methyl 3-{5-(benzyloxy)-2-[(*tert*-butoxycarbonyl)oxy]-phenyl}-7-(*ortho*-tolyl)-3*H*-indole-3-carboxylate (10d). To a solution of hemiaminal **4d** (30 mg, 0.065 mmol) in anhydrous CH_2Cl_2 (4 ml) under nitrogen atmosphere, DMAP (0.8 mg, 0.0065 mmol) and Boc_2O (36 mg, 0.16 mmol) were added. The clear colorless solution was stirred at room temperature for 72 h. The solvent was evaporated and the residue was purified on silica gel column using gradient elution from 2% EtOAc in petroleum ether to 25% EtOAc in petroleum ether to afford the product **10d** as yellow oil (30 mg, 82%, Fig. 10). R_f 0.49 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 1760 (C=O), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, s); 7.55 (1H, dd, *J* = 6.4, *J* = 2.3); 7.43–7.27 (11H, m); 7.24 (1H, d, *J* = 9.0); 6.96 (1H, dd, *J* = 9.0, *J* = 3.0); 6.44 (1H, d, *J* = 3.0); 4.90, 4.88 (2H, ABq, *J* = 12.0); 3.73 (3H, s); 2.19 (3H, s); 1.57 (9H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 169.5; 169.3; 156.6; 154.3; 153.8; 151.7; 144.0; 138.1; 136.5; 136.4; 135.7; 135.2; 131.3; 130.3; 128.8; 128.3; 128.0; 127.7; 127.4; 127.2; 125.7; 124.0; 124.0; 115.1; 114.2; 70.6; 70.2; 53.1; 27.9; 20.6. Found, *m*/*z*: 586.2222 $[M+Na]^+$. $C_{35}H_{33}NO_6Na$. Calculated, *m*/*z*: 586.2206.

6-*tert*-Butyl 10b-methyl 2-(benzyloxy)-7-cyano-6*H*-[1]benzofuro[2,3-*b*]indole-6,10b(5a*H*)-dicarboxylate (*rac*-12e). A solution of hemiaminal *rac*-**4e** (15 mg, 0.038 mmol) in $CDCl_3$ (0.7 ml) was placed in NMR tube and DMAP (0.46 mg, 0.0038 mmol) was added, followed with Boc_2O (21 mg, 0.094 mmol). The clear colorless solution was kept at room temperature and progress of the reaction was monitored by ^{1}H NMR spectroscopy. Complete conversion of the starting hemiaminal **4e** was observed after 20 h. The solution was poured onto the silica gel column and purified using CH_2Cl_2 as a mobile phase to afford *rac*-**12e** as a yellowish oil (16 mg, 83%, Fig. 11). R_f 0.38 (petroleum ether – EtOAc, 5:2). IR spectrum, ν, cm^{-1}: 2231 (C≡N), 1811 (C=O), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.72 (1H, d, *J* = 7.7); 7.55 (1H, d, *J* = 7.8); 7.44–7.30 (5H, m); 7.22 (1H, d, *J* = 2.5); 7.14 (1H, dd, *J* = 7.7, *J* = 7.8); 7.13 (1H, s); 6.82 (1H, dd, *J* = 8.8, *J* = 2.5); 6.77 (1H, d, *J* = 8.8); 5.01 (2H, s); 3.84 (3H, s); 1.67 (9H, s). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 168.5; 154.2; 152.4; 151.3; 142.2; 136.9; 134.6; 133.1; 129.1; 128.8; 128.2; 127.7; 126.1; 124.9; 116.9; 116.4; 111.7; 110.7; 102.4; 100.2; 85.1; 71.3; 63.7; 53.8; 28.2. Found, *m*/*z*: 499.1850 $[M+H]^+$. $C_{29}H_{27}N_2O_6Na$. Calculated, *m*/*z*: 499.1869.

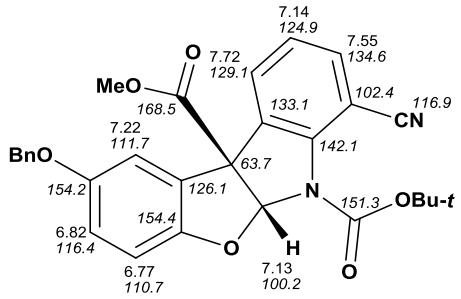


Figure 11. ^{1}H and ^{13}C NMR assignment for compound **12e**.

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