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Application of 7-endo *trig* Pictet-Spengler cyclization to the formation of benzazepine ring: Synthesis of new benzazepinoindoles[$]

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Abstract— The preparation of benzazepinoindoles, a fused heterocycles with a benzazepine moiety was realised via an intramolecular 7-endo *trig* Pictet-Spengler cyclization. The precursors comprising C-3- or C-2-linked o-aminobenzyl indoles (**5** and **6**) required for the cyclization were obtained by treating either indoles with *o*-nitrobenzyl bromide followed by reduction of the nitro group or by treating 2-nitrophenylacetic acid with DCC/DMAP followed by reduction of the aryl nitro functionality. The resulting substrates **5** and **6** were then subjected to the 7-endo *trig* Pictet-Spengler reaction with a variety of aldehydes and ketones to furnish new polycyclic structures benzazepinoindoles.

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Introduction

The azepinoindole template has been found to be present in the marine sponge metabolite hymenialdisine[1] (**1**) and in paullone[2] (**2**), a synthetic benzazepinoindolone undergoing clinical trials[3] as an anticancer agent. Both the compounds were found to be a potent kinase inhibitor of several related CDKs[4] with hymenialdisine also exhibiting potent anti-proliferative, anti-neurodegenerative, and anti-inflammatory activities in various cell lines and animal models.[5]

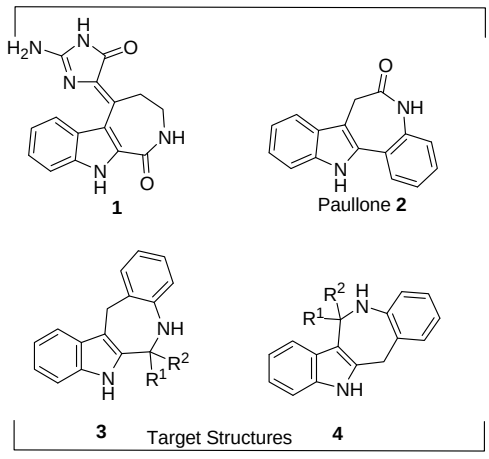
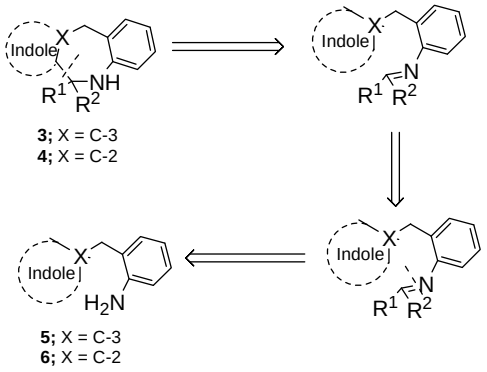


Figure 1. Polycyclic structures based on azepinoindole template

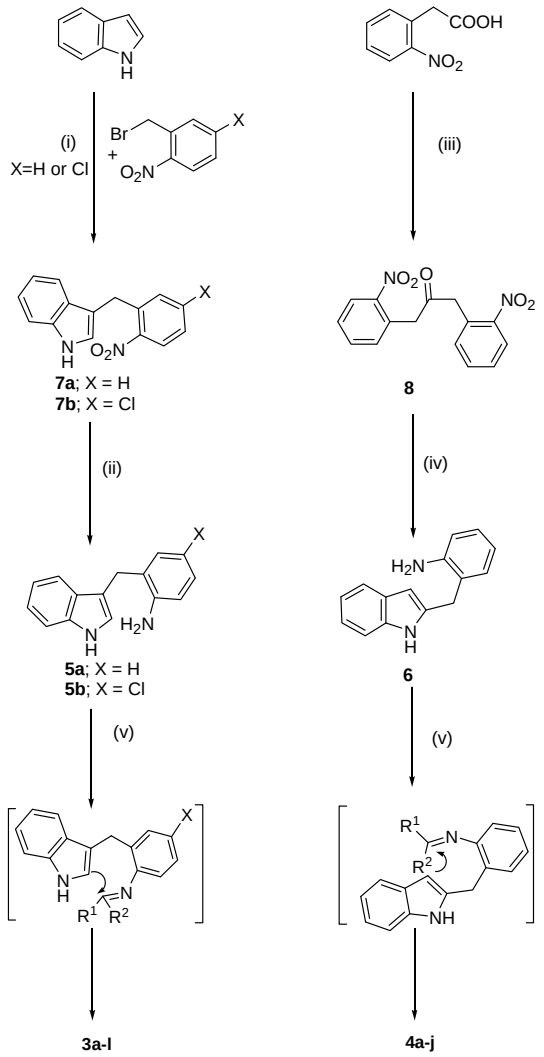
Recently we reported a straightforward and easy synthetic route for annulated quinolines and quinoxalines using 6-endo *trig* cyclization following our modified Pictet-Spengler strategy.[6] The methodology involved condensation of carbonyls to aryl amine substrates linked to an activated heterocycle which proceeds through the intramolecular attack of a π nucleophilic carbon from the activated heterocycle onto the carbon of the iminium ion. On the other hand, examples for the corresponding 7-membered ring formation through 7-endo *trig* Pictet-Spengler cyclization are scarce[7]probably because generation of such rings still remains a challenge for organic synthesis.[8] In the present paper, we wish to apply 7-endo *trig* cyclization based on our modified Pictet-Spengler methodology for the synthesis of benzazepinoindoles (**3** and **4**) and some derivatives thereof hitherto not reported in the literature.

Results and Discussion

Our synthetic strategy involved regioselective linkage of a benzyl amine moiety to either position 2 or 3 of the indole followed by the 7-endo *trig* Pictet-Spengler cyclization with various carbonyl compounds (Scheme 1).



Scheme 1: Retrosynthetic route for benzazepinoinodoles **3** and **4** via 7-endo *trig* Pictet-Spengler cyclization involving aryl amine substrates **5** and **6** as precursors.



Scheme 2: Synthesis of compounds based on **3** and **4.** Reagents and conditions: (i) Na_2CO_3, Acetone:Water (4:1), 70 ^{0}C , 36h; (ii) Fe, HCl / EtOH (1:4), 100 ^{0}C, 1.5h (iii) DCC/DMAP, dry THF, rt, 3h (iv) Fe - CH_3COOH:C_2H_5OH (1:1), 3h; (v) R^1R^2CO, 2 % TFA in DCM, rt.

Thus, the key step in our strategy involves synthesis of substrates **5** and **6** in which a benzyl amine moiety is attached to C-3 and C-2 of the indole ring respectively (Scheme 2). Synthesis of substrate **5a-b** was carried out by treating indole with 2-nitrobenzyl bromide in the presence of Na_2CO_3 using the modified procedure published in the literature.[9] The resulting nitro intermediates **7a-b** were then reduced with Fe/HCl to give corresponding substrates **5a-b**. Synthesis of the substrate **6** was carried out in two steps from 2-nitrophenyl acetic acid by the protocol published in the literature.[10] Once we had substrates **5** and **6,** we next investigated their abilities to undergo 7-endo *trig* Pictet–Spengler cyclizations with structurally diverse aldehydes and ketones. For the Pictet–Spengler cyclization (Scheme 2), the substrate **5a** (X=H) was initially treated with 4-chlorobenzaldehyde under the traditional Pictet–Spengler protocols involving 2% TFA in DCM at both 0^{o}C and at room temperature. Interestingly, 7-endo *trig* cyclization resulting in benzazepinoindole **3a** occurred under both the conditions but the best results were obtained in 2% TFA in DCM at room temperature and it took 45 min for the completion of the reaction (Table 1). The crude product obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluent and was isolated in 79% yield. The scope and

Table 1: Optimization of the reaction conditions for conversion of substrate **5a** to **3a**

Entry	Reaction Conditions	Temp (^{o}C)	Time	Yield of **3a**$^{\#}$
1.	2 % TFA in DCM	0	12h	45
2.	2% MSA/CH_3CN	rt	2h	51
3.	2% TFA in CH_3CN	rt	2h	55
4.	2 % TFA in D CM	rt	45min	79
5.	$Yb(OTf)_3$ in DCM	rt	8h	42

Isolated yield

limitation of our strategy with substrates based on **5a-b** was established by synthesizing 11 compounds based on benzazepinoindoles **3b-l** using a variety of aldehydes and ketones (Table 2). For the Pictet–Spengler cyclization 2% TFA–DCM at rt protocol was used and for the condensation involving aldehydes, in general, the cyclization was found to be complete within 45 min. On the contrary, condensation with ketones was found to be sluggish (10-30h) and afforded products in 20-72% yields (Table 2). Aldehydes with electron-donating group had no adverse effect on the rate of cyclization. This is in contrast to the typical Pictet–Spengler reaction where aldehydes with electron withdrawing group had favourable affects on endo cyclization while aldehydes with electron donating substituents failed to undergo π-cyclization.[11] After successfully establishing the Pictet-Spengler reaction on substrates **5a-b,** we shifted our attention to substrate **6.** The substrate was initially treated with salicyldehyde using 2% TFA–DCM at rt protocol. The progress of reactions was monitored by TLC and HPLC. As expected, cyclization in the substrate **6** resulting in **4a** was found to be complete within 20 min. The scope and limitation of our strategy with substrate **6** was established by synthesizing 9 compounds based on benzazepinoindoles **4b-j** using both aromatic/aliphatic aldehydes and ketones (Table 2). In general, rate of π-cyclization reactions for both the substrates with structurally diverse carbonyls varied from 10 min to 30 h and followed the order of reactivity aromatic aldehydes>aliphatic aldehydes>ketones.

Conclusion

In conclusion, we have described a efficient method for generating indole annulated benzazepine ring via 7-endo *trig* Pictet-Spengler cyclization. Our methodology allows rapid access to benzazepinoindoles with different substitution patterns and could be suitable for the preparation of a wide library of compounds. The indole linked aryl amine precursors used in the present investigation for the 7-endo trig cyclizations, are new additions to the repertoire of "second-generation substrates" for the Pictet-Spengler reaction reported earlier by us.

Experimental Section

Synthesis of key intermediate 5: General procedure

A solution of **7** (3.2 mmol) and Fe (9.52 mmol) in acidic ethanol (1:4 HCl:EtOH), was refluxed under nitrogen atmosphere for 1.5 h. The solution was allowed to cool down and then poured into ice, the pH is made slightly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. EtOAc (50 mL) was added to the mixture and filtered through a bed of Celite^R. The organic layer was finally washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under

reduced pressure. The crude product was purified on a silica gel column using hexane: ethyl acetate (9:1, v/v) as eluent to afford **5**.

Table 2: Physico-chemical characteristics of compounds based on **3** and **4**

Entry	Amine Substrates	Product	R^1	R^2	Time	Isolated Yield (%)	ESMS (M^++H)	Retention Time* (t_R=min)
1.	**5a**	**3a**	4-Cl-C_6H_4	H	45 min	79	345.2	22.175
2.	**5a**	**3b**	4-NO_2-C_6H_4	H	30 min	94	356.2	20.708
3.	**5a**	**3c**	4-CH_3-C_6H_4	H	35 min	72	325.2	20.855
4.	**5a**	**3d**	4-CH_3O-C_6H_4	H	40 min	62	341.2	19.697
5.	**5a**	**3e**	C_3H_5	H	50 min	75	263.1	18.108
6.	**5a**	**3f**	CH_3	CH_3	10 h	72	263.0	17.069
7.	**5a**	**3g**	C_6H_5	CH_3	30 h	46	325.1	14.540
8	**5a**	**3h**	R^1 and R^2 = C_6H_{10}		30 h	50	303.1	19.705
9	**5b**	**3i**	4-NO_2-C_6H_4	H	20 min	85	390.3	22.271
10	**5b**	**3j**	4-Cl-C_6H_4	H	25 min	79	379.2	23.770
11	**5b**	**3k**	3,4-di- (CH_3O)-C_6H_3	H	30 min	73	405.1	21.688
12.	**5b**	**3l**	4-CN-C_6H_4	H	25 min	76	370.2	22.008s
13.	**6**	**4a**	2-OH-C_6H_4	H	20 min	76	327.2	17.628
14.	**6**	**4b**	Indole-3-	H	45 min	42	350.2	20.190
15.	**6**	**4c**	4-CN-C_6H_4	H	15 min	90	336.2	17.600
16.	**6**	**4d**	4-CH_3-C_6H_4	H	20 min	85	325.2	26.582
17.	**6**	**4e**	3,4-di- (CH_3O)-C_6H_3	H	15 min	54	371.2	20.700
18.	**6**	**4f**	C_3H_5	H	25 min	75	263.1	16.996
19.	**6**	**4g**	$C_6H_5CH_2CH_2$	H	35 min	48	339.2	21.759
20.	**6**	**4h**	CH_3	CH_3	3 h	55	263.1	18.494
21.	**6**	**4i**	R^1 and R^2 =C_6H_{10}		30 h	20	303.2	27.291
22.	**6**	**4j**	C_6H_5	CH_3	30 h	30	325.1	19.519

* Retention time on HPLC (C18 reversed-phase column ; 150 X 4.8 mm ; 5μm) with a linear gradient of 10-100% CH_3CN in water over 30 min, flow rate of 1.0 mL/min, and UV detection at 220/254 nm.

2-(1*H*-indol-3-ylmethyl)aniline (5a): Yield = 64 %; white solid; mp 110-112^{0}C; R_f = 0.40 (1:9 EtOAc:Hexane); IR (KBr) ν_{max} 3020 2920, 2846 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.95 (brs, 1H, NH), 7.57 (d *J* = 7.8 Hz,, 1H, ArH), 7.33 (d, *J* = 8.0 Hz, 1H, ArH), 7.23-7.05 (m, 4H, ArH), 6.82-6.78 (m, 2H, ArH), 6.74 (d, *J* = 8.1 Hz, 1H, ArH), 4.00 (s, 2H, CH_2), 3.50 (brs, 2H, NH_2) ppm; mass (ES+) m/z 223.0 (M^+ + 1); Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60; found: C, 81.16; H, 6.43; N, 12.41.

Synthesis of key intermediates 6:

The synthesis was carried out by the procedure reported in the literature.[10]

2-(1*H*-indol-2-ylmethyl)aniline (6):Yield = 72 %; white solid; mp 110-112^{0}C [Lit[10] 110-112 ^{o}C]; R_f = 0.40 (1:4 EtOAc:Hexane); IR (KBr) ν_{max} 3380, 3312, 2905, 2841, 1619, cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.8 (brs, 1H, NH), 7.40 (d, *J* = 7.6 Hz, 1H, ArH), 7.27 (d, *J* = 7.6 Hz, 1H, ArH), 6.99-6.85 (m, 4H, ArH), 6.64 (dd, J_1 = 7.0 Hz, J_2 = 0.9, Hz, 1H, ArH), 6.50-6.49 (m, 1H, ArH), 6.16 (s, 1H, ArH), 4.87 (brs, 2H, NH_2), 3.89 (s, 2H, CH_2) ppm; mass (ES+) m/z 223.0 (M^+ + 1); Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60; found: C, 81.12; H, 6.27; N, 12.61.

General Procedure for 7-endo *trig* cyclization

The Synthesis of tetrahydroindolo[2,3-*c*][1]benzazepine (3) and tetrahydroindolo[3,2-*c*][1]benzazepine (4) derivatives:

A mixture of **5** or **6** (0.45 mmol) and benzaldehyde/ketone (0.49 mmol) in DCM (2 mL) was treated with 2% TFA in DCM and the progress of reaction was monitored by TLC. The reaction mixture, on completion, was evaporated, and the residue so obtained was triturated with aq.$NaHCO_3$ (10 mL). The suspension was then extracted with EtOAc (20 mL), washed with brine (10 mL), and dried over Na_2CO_3. The organic layer was concentrated to dryness under reduced pressure and the crude obtained was purified by column chromatography hexane: ethyl acetate (9:1, v/v) to afford **3** or **4**.

6-(4-chlorophenyl)-5,6,7,12-tetrahydroindolo[2,3-*c*][1]benzazepine (3a):

Yield = 79 %; white solid; mp 176-178^{o}C; R_f = 0.50 (1:3 EtOAc:Hexane); IR (KBr) ν_{max} 3422, 2927, 2848, 1637, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69-7.66 (m, 1H, ArH), 7.30-7.27 (m, 3H, ArH), 7.23-7.16 (m, 2H, ArH), 7.13-7.00 (m, 4H, ArH), 6.98-6.96 (m, 1H, ArH), 6.70 (d, *J* = 7.5 Hz, 1H, ArH), 5.46 (s, 1H, CH), 4.29 (d, *J* = 15.5 Hz, 1H, CH_2), 4.08 (d, *J* = 15.5 Hz, 1H, CH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 146.3, 142.3, 136.8, 135.4, 134.6, 131.6, 129.8, 128.1, 127.8, 126.9, 126.5, 123.4, 122.0, 120.7, 118.2, 117.6, 110.7, 109.0, 59.5, 28.1 ppm; mass (ES^+) m/z 345.2 (M^+ + 1); Anal. Calcd for $C_{22}H_{17}ClN_2$: C, 76.63; H, 4.97; N, 8.12; found: C, 76.58; H, 4.99; N, 8.15.

2-(5,6,11,12-tetrahydroindolo[3,2-*c*][1]benzazepin-12-yl)phenol (4a):

Yield = 76 %; white solid; mp 167-169^{o}C; R_f = 0.53 (1:3 EtOAc:Hexane); IR (KBr) ν_{max} 3463, 2926, 2842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 (brs, 1H, OH), 7.45 (dd, J_1 = 5.9 Hz, J_2 = 1.6, Hz, 1H, ArH), 7.22-7.17 (m, 3H, ArH), 7.14-7.11 (m, 1H, ArH), 7.07-6.95 (m, 3H, ArH), 6.93-6.81 (m, 4H, ArH), 5.65 (s, 1H, CH), 4.68 (d, *J* = 15.9 Hz, 1H, CH_2) 3.70 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.1, 135.4, 131.9, 129.7, 129.5, 128.4, 128.1, 127.6, 125.7, 124.7, 123.8, 122.8, 121.6, 120.0, 119.6, 118.8, 117.5, 112.2, 110.7, 61.8, 33.0 ppm; mass (ES^+) m/z 327.2 (M^+ + 1); Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58; found: C, 80.78; H, 5.65; N, 8.52;

Acknowledgments

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[1] G. Cimino, S. De Rosa, D. De Stefano, L. Mazzarella, R. Puliti, G. Sodano, *Tetrahedron Lett.* **1982**, *23.* 767–768.

[2] C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer, C. Kunick, *J. Med. Chem.* **1999**, *42*, 2909–2919.

[3] J. K. Buolamwini, *Curr. Pharm. Des.* **2000,** *6*, 379–392.

[4] Y. Wan, W. Hur, C. Y. Cho, Y. Liu, F. J. Adrian, O. Lozach, S. Bach, T. Mayer, D. Fabbro, L. Meijer, N. S. Gray, *Chem. Biol.* **2004**, *11*, 247–259.

[5] (a) Y. Wan, W. Hur, C. Y. Cho, Y. Liu, F. J. Adrian, O. Lozach, S. Bach, T. Mayer, D. Fabbro, L. Meijer, N. S. Gray, *Chem. Biol.* **2004**, *11*. 247–259 (b) J. J. Breton, M. C. Chabot-Fletcher, *J. Pharmacol. Exp. Ther.* **1997**, *282*, 459–466. (c) L. Meijer, A.-M. W. H. Thunnissen, A. W. White, M. Garnier, M. Nikolic, L.-H. Tsai, J. Walter, K.E. Cleverley, P.C. Salinas, Y.Z. Wu, J. Biernat, E.M. Mandelkow, S.-H. Kim, G. R. Pettit, *Chem. Biol*. **2000**, *7*, 51–63. (d) D. Tasdemir, R. Mallon, M. Greenstein, L. R. Feldberg, S. C. Kim, K. Collins, D. Wojciechowicz, G. C. Mangalindan, G. P. Concepción, M. K. Harper, C. M. Ireland, *J. Med. Chem.* **2002**, *45*. 529–532.(e) V. Sharma, T. A. Lansdell, G. Jin, J. J. Tepe, *J. Med. Chem.* **2004**, *47*, 3700-3703.

[6] (a) B. Kundu, D. Sawant, R. Chhabra, *J. Comb. Chem.* **2005**, *7*, 317-321. (c) S. Duggineni, D. Sawant, B. Saha, B. Kundu, *Tetrahedron* **2006**, *62*, 3228-3241. (d) S. Sharma, B. Saha, D. Sawant, B. Kundu, *J. Comb. Chem.* **2007**, *9*, 783-792.

[7] (a) B. Kundu, D. Sawant, P. Partani, A. P. Kesarwani, *J. Org. Chem.* **2005**, *70*, 4889-4892. (b) S. Gracia, J. Schulz, S. Pellet-Rostaing, M. Lemaire, *Synlett* **2008**, 1852-1856. (c) Kraxner, J.; Hubner, H.; Gmeiner, P. *Arch. Pharm.* **2000**, *333*, 287-292.

[8] U. Nubbemeyer *Topics in Current Chemistry* **2001,** *216*, 125-196.

[9] M. Westermaier, H. Mayr, *Org. Lett***. 2006,** *8,* 4791-4794

[10] T.-L. Ho, D.-G. Jou, *Helv Chim Acta* **2002**, *85*, 3823-3827.

[11] E. D. Cox, J. Cook, *Chem. Rev.* **1995**, *95*, 1797-1842.