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Application of 7-*endo-trig* Pictet–Spengler Cyclization to the Formation of the Benzazepine Ring: Synthesis of Benzazepinoindoles[‡]

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The preparation of benzazepinoindoles, fused heterocycles with a benzazepine moiety, was accomplished through an intramolecular 7-*endo-trig* Pictet–Spengler cyclization. The precursors comprising C-3- or C-2-linked *o*-aminobenzylindoles required for the cyclization were obtained either by treating 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. 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.

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 compounds were found to be a potent kinase inhibitor of several related cyclin-dependent kinases (CDKs),[4] and hymenialdisine also exhibits potent antiproliferative, antineurodegenerative, and anti-inflammatory activities in various cell lines and animal models (Figure 1).[5]

Recently, we reported a straightforward and easy synthetic route for annulated quinolines and quinoxalines by using a 6-*endo-trig* cyclization following our modified Pictet–Spengler strategy.[6] The methodology involved condensation of carbonyl-containing compounds to arylamine substrates linked to an activated heterocycle, which proceeded through the intramolecular attack of a π nucleophilic carbon atom from the activated heterocycle onto the carbon atom of the iminium ion. In contrast, examples for the formation of the corresponding seven-membered ring through a 7-*endo-trig* Pictet–Spengler cyclization are scarce,[7] probably because generation of such rings still remains a challenge in organic synthesis.[8] In this paper, we wish to apply a 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.

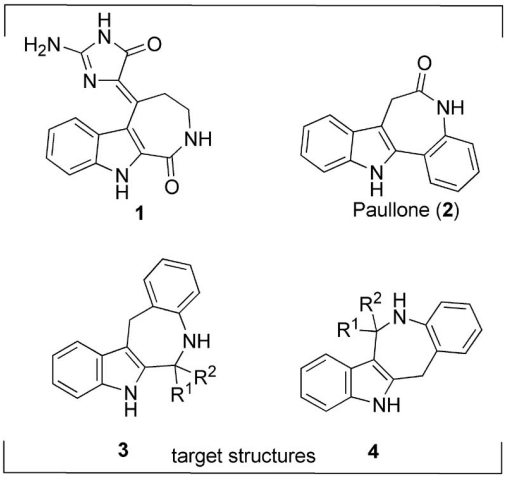

Figure 1. Polycyclic structures based on the azepinoindole template.

Results and Discussion

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

Thus, the key step in our strategy involves synthesis of substrates **5** and **6**, in which a benzylamine 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 by using a modified procedure published in the literature.[9] Resulting nitro intermediates **7a**,**b** were then reduced with Fe/HCl to give corresponding substrates **5a**,**b**.

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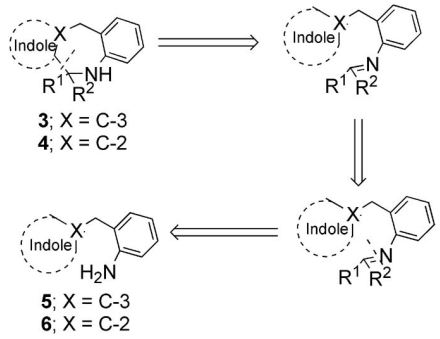
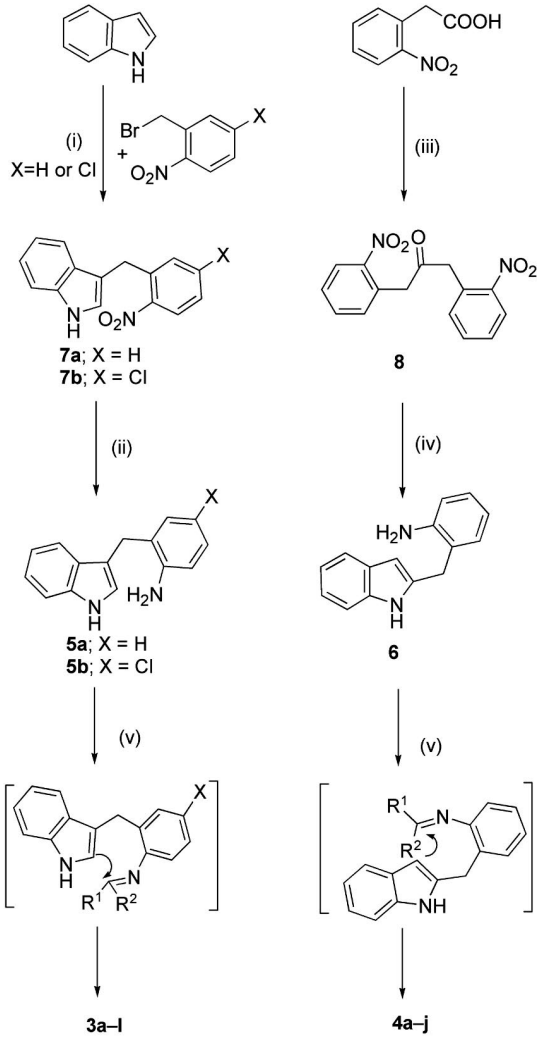


Scheme 1. Retrosynthetic route for benzazepinoindoles **3** and **4** by the 7-*endo-trig* Pictet–Spengler cyclization involving arylamine substrates **5** and **6** as precursors.

Synthesis of substrate **6** was carried out in two steps from 2-nitrophenyl acetic acid by a 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), substrate **5a** (X = H) was initially treated with 4-chlorobenzaldehyde under the traditional Pictet–Spengler protocols involving 2% TFA in DCM at both 0 °C and at room temperature. Interestingly, 7-*endo-trig* cyclization resulting in benzazepinoindole **3a** occurred under both sets of conditions, but the best results were obtained in 2% TFA in DCM at room temperature; the reaction was complete in 45 min (Table 1).

The crude product obtained after workup was purified by silica-gel column chromatography with the use of EtOAc/hexane as the eluent; it was isolated in 79% yield. The scope and limitation of our strategy with substrates **5a**,**b** was established by synthesizing benzazepinoindoles **3b**–**l**; a variety of aldehydes and ketones were tolerated (Table 2). For the Pictet–Spengler cyclization, 2% TFA/DCM at room temperature 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 (10–30 h) and afforded products in 20–72% yields (Table 2). Aldehydes with electron-donating groups had no adverse effect on the rate of cyclization. This is in contrast to the typical Pictet–Spengler reaction, where aldehydes with electron-withdrawing groups had favorable affects on *endo* cyclization, whereas 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 with the use of 2% TFA/DCM at room temperature. The progress of the reaction was monitored by TLC and HPLC. As expected, cyclization of substrate **6** to afford **4a** was found to be complete within 20 min. The scope and limitation of our strategy with substrate **6** was established by synthesizing benzazepinoindoles **4b**–**j**, substrates containing both aromatic and aliphatic aldehydes and ketones were tolerated (Table 2). In general, the rate of the π-cyclization reactions for both substrates with structurally diverse carbonyl groups varied from 10 min to 30 h and followed the order of reactivity aromatic aldehydes > aliphatic aldehydes > ketones.



Scheme 2. Synthesis of compounds **3** and **4**. Reagents and conditions: (i) Na_2CO_3, acetone/water (4:1), 70 °C, 36 h; (ii) Fe, HCl/EtOH (1:4), 100 °C, 1.5 h (iii) DCC/DMAP, dry THF, r.t., 3 h (iv) Fe–CH_3COOH/C_2H_5OH (1:1), 3 h; (v) R^1R^2CO, 2% TFA in DCM, r.t.

Table 1. Optimization of the reaction conditions for conversion of substrate **5a** into **3a**.

Entry	Reaction conditions	*T* [°C]	Time [h]	Yield of **3a** [%][a]
1	2% TFA in DCM	0	12	45
2	2% MSA/CH_3CN	r.t.	2	51
3	2% TFA in CH_3CN	r.t.	2	55
4	2% TFA in DCM	r.t.	0.75	79
5	$Yb(OTf)_3$ in DCM	r.t.	8	42

[a] Isolated yield.

Table 2. Physicochemical characteristics of compounds **3** and **4**.

Entry	Substrate	Product	R^1	R^2	Time	Isolated Yield [%]	MS (ES) $[M + H]^+$	Retention time[a] [min]
1	**5a**	**3a**	4-ClC_6H_4	H	45 min	79	345.2	22.175
2	**5a**	**3b**	4-$O_2NC_6H_4$	H	30 min	94	356.2	20.708
3	**5a**	**3c**	4-$CH_3C_6H_4$	H	35 min	72	325.2	20.855
4	**5a**	**3d**	4-$CH_3OC_6H_4$	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-$O_2NC_6H_4$	H	20 min	85	390.3	22.271
10	**5b**	**3j**	4-ClC_6H_4	H	25 min	79	379.2	23.770
11	**5b**	**3k**	3,4-$(CH_3O)_2C_6H_3$	H	30 min	73	405.1	21.688
12	**5b**	**3l**	4-NCC_6H_4	H	25 min	76	370.2	22.008s
13	**6**	**4a**	2-HOC_6H_4	H	20 min	76	327.2	17.628
14	**6**	**4b**	indol-3-yl	H	45 min	42	350.2	20.190
15	**6**	**4c**	4-NCC_6H_4	H	15 min	90	336.2	17.600
16	**6**	**4d**	4-$CH_3C_6H_4$	H	20 min	85	325.2	26.582
17	**6**	**4e**	3,4-$(CH_3O)_2C_6H_3$	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

[a] Retention time on HPLC (C18 reverse-phase column; 150 × 4.8 mm; 5 μm) with a linear gradient of 10–100% CH_3CN in water over 30 min, flow rate of 1.0 mL min^{-1}, and UV detection at 220/254 nm.

Conclusions

In conclusion, we have described an efficient method for generating the indole-annulated benzazepine ring through a 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 arylamine 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

General Procedure for the Synthesis of Key Intermediate 5: A solution of **7** (3.2 mmol) and Fe (9.52 mmol) in acidic ethanol (HCl/EtOH, 1:4) was heated at reflux under a nitrogen atmosphere for 1.5 h. The solution was cooled down and then poured into ice; the pH was made slightly basic (pH 8) by the addition of 5% aqueous $NaHCO_3$. EtOAc (50 mL) was added to the mixture, and the mixture was filtered through a bed of Celite. The organic layer was finally washed with water (50 mL) and brine (50 mL) and dried with anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The crude product was purified on a silica gel column (hexane/ ethyl acetate, 9:1) to afford **5**.

2-(1*H*-Indol-3-ylmethyl)aniline (5a): Yield: 64%; white solid; m.p. 110–112 °C; R_f = 0.40 (EtOAc/hexane, 1:9). IR (KBr): $\tilde{\nu}$ = 3020, 2920, 2846 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (br. s, 1 H, NH), 7.57 (d, J = 7.8 Hz, 1 H, ArH), 7.33 (d, J = 8.0 Hz, 1 H, ArH), 7.23–7.05 (m, 4 H, ArH), 6.82–6.78 (m, 2 H, ArH), 6.74 (d, J = 8.1 Hz, 1 H, ArH), 4.00 (s, 2 H, CH_2), 3.50 (br. s, 2 H, NH_2) ppm. MS (ES+): m/z = 223.0 $[M + 1]^+$. $C_{15}H_{14}N_2$ (222.29): calcd. C 81.05, H 6.35, N 12.60; found C 81.16, H 6.43, N 12.41.

2-(1*H*-Indol-2-ylmethyl)aniline (6): Prepared by the procedure reported in ref.[10] Yield: 72%; white solid; m.p. 110–112 °C [ref.[10] 110–112 °C]; R_f = 0.40 (EtOAc/hexane, 1:4). IR (KBr): $\tilde{\nu}$ = 3380, 3312, 2905, 2841, 1619 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.8 (br. s, 1 H, NH), 7.40 (d, J = 7.6 Hz, 1 H, ArH), 7.27 (d, J = 7.6 Hz, 1 H, ArH), 6.99–6.85 (m, 4 H, ArH), 6.64 (dd, J = 7.0 Hz, J = 0.9, Hz, 1 H, ArH), 6.50–6.49 (m, 1 H, ArH), 6.16 (s, 1 H, ArH), 4.87 (br. s, 2 H, NH_2), 3.89 (s, 2 H, CH_2) ppm. MS (ES+): m/z = 223.0 $[M + 1]^+$. $C_{15}H_{14}N_2$ (222.29): calcd. C 81.05, H 6.35, N 12.60; found C 81.12, H 6.27, N 12.61.

General Procedure for the 7-*endo-trig* Cyclization: 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 the reaction was monitored by TLC. The reaction mixture, upon completion, was concentrated, and the residue so obtained was triturated with aqueous $NaHCO_3$ (10 mL). The suspension was then extracted with EtOAc (20 mL), washed with brine (10 mL), and dried with anhydrous Na_2SO_4. The organic layer was concentrated to dryness under reduced pressure, and the crude material obtained was purified by column chromatography (hexane/ethyl acetate, 9:1) to afford **3** or **4**.

6-(4-Chlorophenyl)-5,6,7,12-tetrahydroindolo[2,3-*c*][1]benzazepine (3a): Yield: 79%; white solid; m.p. 176–178 °C; R_f = 0.50 (EtOAc/hexane, 1:3). IR (KBr): $\tilde{\nu}$ = 3422, 2927, 2848, 1637, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 1 H, ArH), 7.30–7.27 (m, 3 H, ArH), 7.23–7.16 (m, 2 H, ArH), 7.13–7.00 (m, 4 H, ArH), 6.98–6.96 (m, 1 H, ArH), 6.70 (d, J = 7.5 Hz, 1 H, ArH), 5.46 (s, 1 H, CH), 4.29 (d, J = 15.5 Hz, 1 H, CH_2), 4.08 (d, J = 15.5 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): 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. MS (ES+): m/z = 345.2 $[M + 1]^+$. $C_{22}H_{17}ClN_2$ (344.84): calcd. 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; m.p. 167–169 °C; R_f = 0.53 (EtOAc/hex-

ane, 1:3). IR (KBr): $\tilde{\nu}$ = 3463, 2926, 2842 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (br. s, 1 H, OH), 7.45 (dd, J = 5.9 Hz, J = 1.6, Hz, 1 H, ArH), 7.22–7.17 (m, 3 H, ArH), 7.14–7.11 (m, 1 H, ArH), 7.07–6.95 (m, 3 H, ArH), 6.93–6.81 (m, 4 H, ArH), 5.65 (s, 1 H, CH), 4.68 (d, J = 15.9 Hz, 1 H, CH_2) 3.70 (d, J = 16.0 Hz, 1 H, 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. MS (ES+): m/z = 327.2 $[M + 1]^+$. $C_{22}H_{18}N_2O$ (326.40): calcd. C 80.96, H 5.56, N 8.58; found C 80.78, H 5.65, N 8.52.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and characterization data for all compounds studied.

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