Synthesis of New Pyrrolobenzazepines via Pictet–Spengler Cyclization

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Abstract: A new six-step divergent strategy was developed allowing access to pyrrolobenzazepine structures from pyrrole. This strategy was based on a regioselective Friedel–Crafts acylation followed by a Pictet–Spengler cyclization.

Key words: azepine, pyrrole, fused-ring systems, Pictet–Spengler reaction

The pyrrolo[2,3-*c*]azepine scaffold is an original structure found in various natural products such as stevensine, hymenin, or hymenialdisine (Figure 1). These alkaloids were extracted from marine sponges belonging to the genera *Axinella*, *Acanthella*, *Hymeniacidon,* and *Pseudoaxinyssa*. Their structures were elucidated preliminarily from spectral studies in comparison with biogenetically and structurally related sponge metabolites[1] and the X-ray crystal structure of hymenialdisine has already been reported.[2]

These compounds have shown significant biological activities. For example, hymenin possesses potent α-adrenoceptor blocking properties,[3] and hymenialdisine was found to be an inhibitor of mitogen-activated protein kinase-1 (MEK-1), cyclin-dependent kinases (CDK-1), or glycogen synthase kinase-3β (GSK-3β).[4]

The first total synthesis of hymenialdisine was described by Annoura et al.[5] It was synthesized via the preparation of a dihydropyrrolo[2,3,*c*]azepinedione intermediate (aldisine) obtained by the condensation of β-alanine methyl

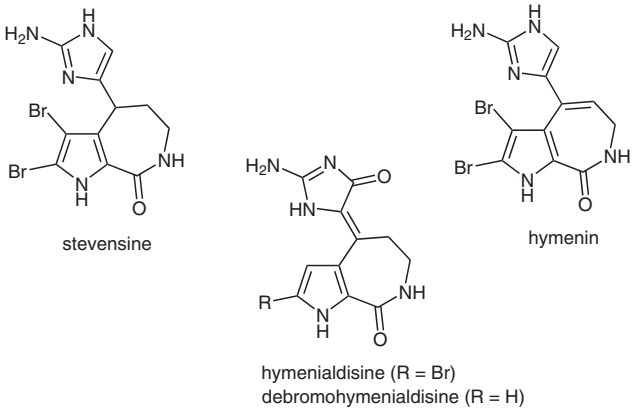
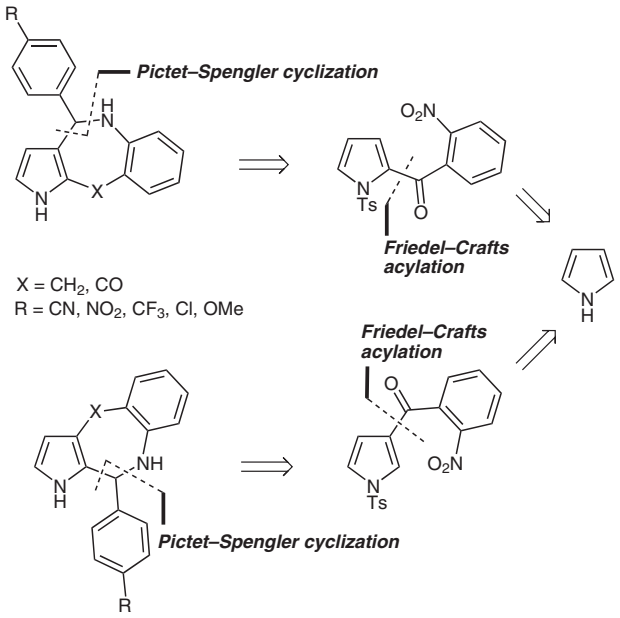


Figure 1 Stevensine, hymenin, and hymenialdisine structures



Scheme 1 Retrosynthetic pathway and strategic bond disconnections of pyrrolo[2,3-*c*]benzazepine and pyrrolo[3,2-*c*]benzazepine core

ester with pyrrole-2-carboxylic acid. Recently, Horne et al. described the synthesis of the pyrroloazepine moiety based on a four-step strategy starting from pyrrole.[6] While this product class was characterized by the presence of a caprolactam moiety, we were interested in the synthesis of amino and amino ketone analogues.

Our synthetic strategy involved, starting from free pyrrole, two key steps: a regioselective Friedel–Crafts acylation of the N-protected pyrrole and a Pictet–Spengler cyclization with various aromatic aldehydes (Scheme 1). Such a strategy, in combination with the possibility of using a wide range of commercially available reagents (aryl aldehydes and aryl acids), should allow the functionalization of the aromatic rings and could be suitable for the preparation of a wide library of compounds.

The first key step of our synthetic approach is the regioselective acylation of the 1-(*p*-toluenesulfonyl)pyrrole (**1**) developed by Varvounis et al.[7] In fact, 1-(*p*-toluenesulfonyl)pyrrole (**1**), synthesized in phase-transfer conditions,[8] could be acylated at C-2 or C-3 position depending on the Lewis acid used during the reaction. Thus, the acylation of 1-(*p*-toluenesulfonyl)pyrrole (**1**) by *o*-nitrobenzoyl chloride in the presence of $SnCl_4$ as Lewis acid allowed to obtain the 2-acyl pyrrole derivative as the main product

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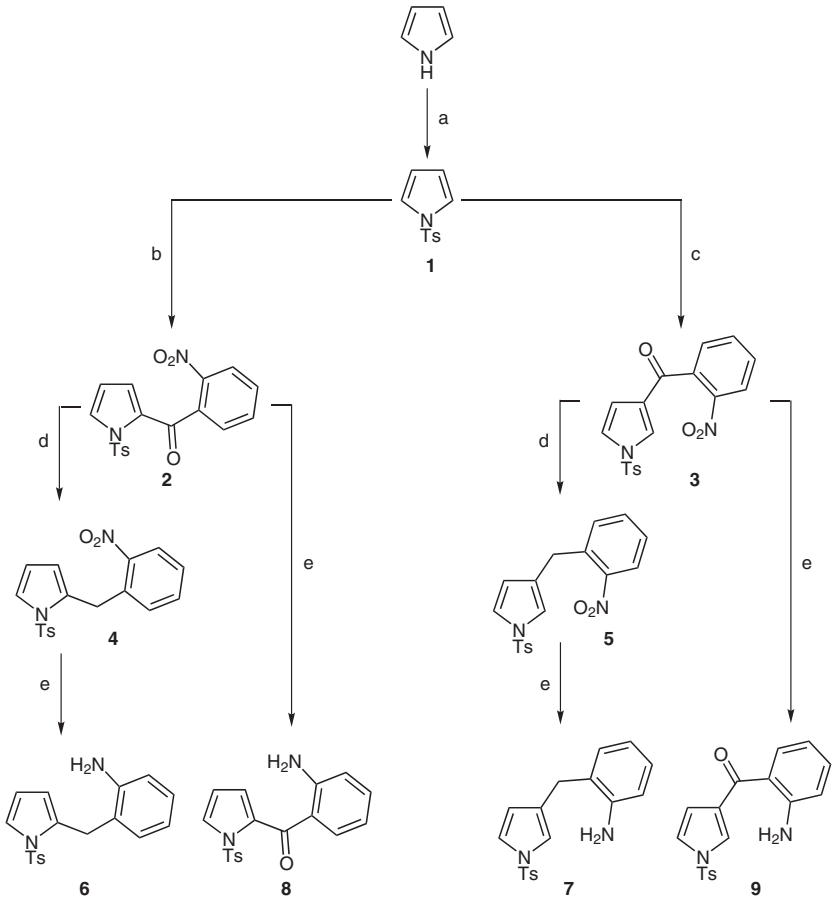


Scheme 2 *Reagents and conditions*: (a) TsCl (1.4 equiv), *n*-Bu_4NHSO_4 (0.1 equiv), NaOH, CH_2Cl_2, 0 °C to r.t., 15 h (96%); (b) $SnCl_4$ (1.5 equiv), *o*-nitrobenzoyl chloride (1.4 equiv), DCE, –10 °C, 2 h (78%); (c) $AlCl_3$ (1.5 equiv), *o*-nitrobenzoyl chloride (1.4 equiv), DCE, –10 °C, 2 h (62%); (d) *t*-$BuNH_2{\cdot}BH_3$ (6 equiv), $AlCl_3$ (3 equiv), CH_2Cl_2, 0 °C to r.t., 15 h (65–70%); (e) Pd/C 10% (0.1 equiv), CH_2Cl_2, r.t., 4 h (72–89%).

whereas the use of $AlCl_3$ led mainly to the formation of 3-acyl pyrroles via reaction of organoaluminum intermediate as recently reported by Huffman (Scheme 2).[9]

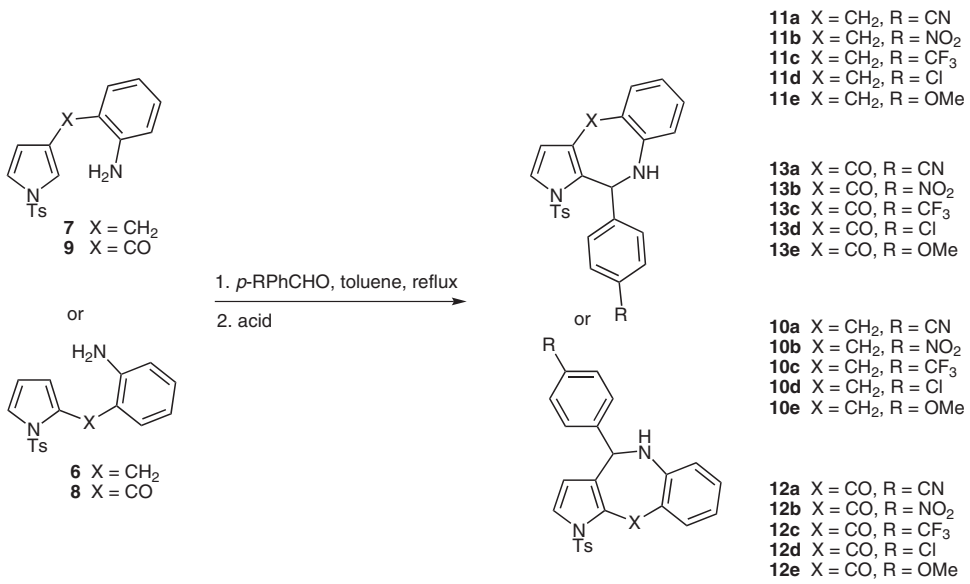
The two regioisomers **2** and **3** were next selectively reduced to **4** and **5** by reductive deoxygenation of the aryl ketone using *tert*-butylamine borane complex and $AlCl_3$ as described by Lau et al.[10] The anilines **6**, **7** and **8**, **9** were then obtained starting, respectively, from the nitro or from the keto compounds by catalytic hydrogenation under atmospheric pressure at room temperature. This straightforward pathway allowed us to synthesize amines **6–9** on gram scale, starting from free pyrrole, in overall yields between 37% and 66% (Scheme 2).

The Pictet–Spengler reaction generally refers to condensation of tryptamines or tryptophans with aldehydes or ketones to give the corresponding β-carboline derivatives.[11] This reaction is also a powerful method for the preparation of tetrahydroisoquinoline having been applied to the racemic or diastereoselective synthesis of aryl and heteroaryl tetraisoquinolines.[12] This methodology has also been used in our laboratory to fuse benzazepine ring with benzo[*b*]thiophene.[13] Recently, Pictet–Spengler reaction was applied to electron-rich heteroaromatic rings. Thus, heteroaromatics such as imidazole, thiazole or pyrazole were investigated as substrates for the Pictet–Spengler cyclization.[14] These condensations led either to azepine or pyridine rings fused with the heteroaromatic moiety. To the best of our knowledge, only a few examples described the use of the Pictet–Spengler for the condensation of an amine onto a pyrrole ring to synthesize a pyridine fused ring.[15] Moreover, no example of synthesis of azepine fused with pyrrole ring using Pictet–Spengler reaction has been described.

With amines **6–9**, we investigated whether these compounds could undergo a Pictet–Spengler-type cyclization in the presence of an aryl aldehyde (Scheme 3).

First, we studied the cyclization of compound **7** in the presence of *p*-cyanobenzaldehyde. In this case, cyclization may occur either at the C-2 position or at the C-4 position of the pyrrole ring. A similar case was studied by Dodd et al.[16] for the condensation of methyl-2-amino-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate with formaldehyde to form tetrahydro-6-azaindole. The authors only observed the formation of the product resulting from the condensation at the C-2 position of the pyrrole ring.

The amine **7** was condensed with *p*-cyanobenzaldehyde in refluxing toluene to give intermediate imine with total conversion (followed by ^1H NMR). The formation of the



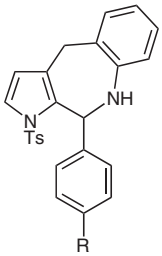
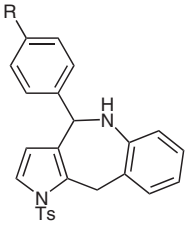
Scheme 3 Pictet–Spengler cyclization of pyrrole derivatives **6–9**

imine was relatively fast (60 min) due to the electron-withdrawing effect of the cyano group. Treatment of the resulting imine under the conditions described by Kundu et al.[14b] [i.e., PTSA (0.1 equiv), toluene, reflux] did not give any cyclized adduct. However, using Ohwada's procedure,[17] with five equivalents of TFA in toluene at room temperature, only one product was observed after one hour of reaction. The structure of the azepine **11a** was elucidated by ^{1}H NMR. In fact, the observation in the ^{1}H NMR spectrum, of two doublets at δ = 6.28 and 7.30 ppm with a coupling constant of 3.4 Hz indicated the presence of two vinylic protons onto the pyrrole ring. So, as expected, the cyclization occurred only at the C-2 position of the pyrrole ring. Moreover, the regioselectivity of the Pictet–Spengler condensation was unambiguously confirmed by X-ray crystallography of a single crystal of the azepine **11a**.[18]

This methodology was extended to the preparation of pyrrolobenzazepines **10a–e** and **11b–e**.[19] As already reported by our group for the synthesis of benzothienobenzazepines,[13] reaction times for the formation of imines were relatively short with electron-poor benzaldehyde derivatives (R = CN, NO_2, CF_3) at room temperature in toluene whereas the use of electron-rich benzaldehydes (R = OMe) required longer reaction times in refluxing toluene. Treatment of the imine with TFA in the conditions described by Ohwada[17] allowed us to isolate pyrrolo[3,2-*c*]benzazepines **10a–e** and pyrrolo[2,3-*c*]benzazepines **11a**,**b** (Table 1).

As can be seen in Table 1, the yields were generally good to excellent. We only obtained poor yields when *p*-methoxybenzaldehyde or *p*-chlorobenzaldehyde were used (entries 5, 9, and 10). We assumed that the electronic enrichment of the iminium intermediate, due to the electron-donating group onto the benzaldehyde, penalized the Pictet–Spengler cyclization which occurred via a SE-type mechanism.

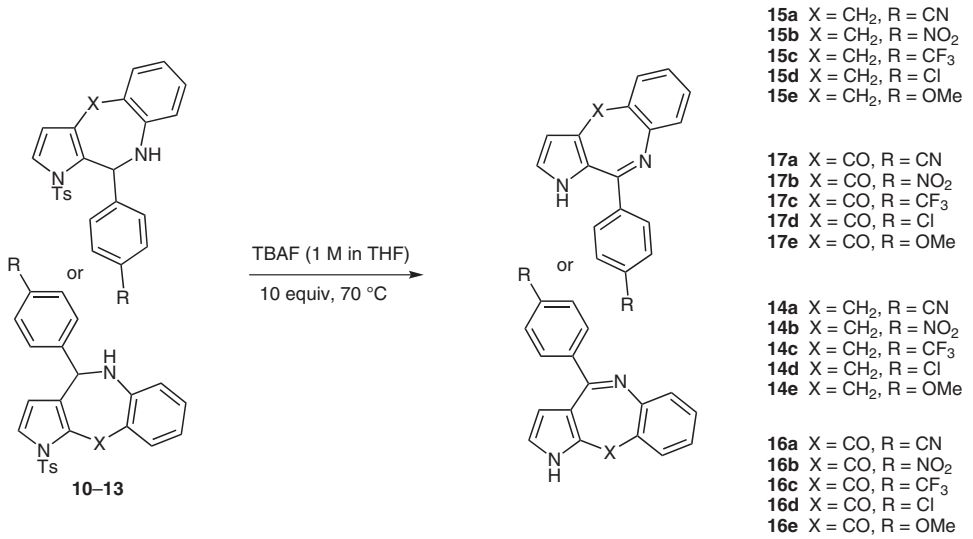
Table 1 Pictet–Spengler Cyclization with Amines **6** and **7**[19]

Entry	Product		R	Temp (°C)	Yield (%)[a]
1		**11a**	CN	20	98
2		**11b**	NO_2	20	83
3		**11c**	CF_3	20	87
4		**11d**	Cl	20	82
5		**11e**	OMe	70	38[b]
6		**10a**	CN	20	83
7		**10b**	NO_2	20	76
8		**10c**	CF_3	20	75
9		**10d**	Cl	20	35
10		**10e**	OMe	70	23[b]

[a] 1 M in toluene, addition of TFA (5 equiv).
[b] 1 M in toluene, addition of TFA (10 equiv).

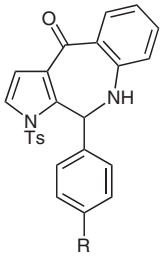
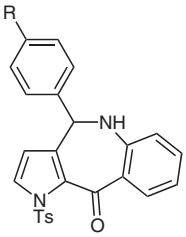
With keto analogues **8** and **9** (Scheme 3), the imine formation was not complete. Likewise, the cyclization was more difficult to complete and required heating (70 °C). Addition of a desiccant to favor the imine formation ($MgSO_4$) allowed to increase the yields in cyclized product of about 30% (Table 2).

Although the deprotection of sulfonyl groups could be achieved by basic hydrolysis with KOH or NaOH[20] or by reduction[21] in the presence of Na(Hg) or Na_2HPO_4, relatively drastic conditions are generally required. Yasuhara



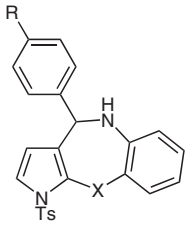
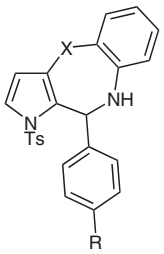
Scheme 4 Deprotection of compounds **10–13**

Table 2 Pictet–Spengler Cyclization with Amines **8** and **9**[13]

Entry	Product		R	Temp (°C)	Yield (%)[a]
1		**13a**	CN	70	47 (15)[c]
2		**13b**	NO_2	70	63 (23)[c]
3		**13c**	CF_3	70	43 (41)[c]
4		**13d**	Cl	70	53 (5)[c]
5		**13e**	OMe	70	15 (–)[b,c]
6		**12a**	CN	70	43 (20)[c]
7		**12b**	NO_2	70	41 (29)[c]
8		**12c**	CF_3	70	51 (6)[c]
9		**12d**	Cl	70	31 (16)[c]
10		**12e**	OMe	70	62 (–)[b,c]

[a] 1 M in toluene, addition of TFA (5 equiv).
[b] 1 M in toluene, addition of TFA (10 equiv).
[c] Values in parentheses are yields without using $MgSO_4$.

Table 3 Deprotection of Azepine **10–13**[24]

Entry	Azepine	Product	X	R	Yield (%)[a]
1		**14a**	CH_2	CN	77
2		**14b**	CH_2	NO_2	52
3		**14c**	CH_2	CF_3	74
4		**14d**	CH_2	Cl	73
5		**14e**	CH_2	OMe	24
6		**16a**	CO	CN	86
7		**16b**	CO	NO_2	56
8		**16c**	CO	CF_3	85
9		**16d**	CO	Cl	97
10	**10–12**	**16e**	CO	OMe	60
11		**15a**	CH_2	CN	88
12		**15b**	CH_2	NO_2	70
13		**15c**	CH_2	CF_3	46
14		**15d**	CH_2	Cl	21
15		**15e**	CH_2	OMe	56
16		**17a**	CO	CN	91
17		**17b**	CO	NO_2	84
18		**17c**	CO	CF_3	50
19		**17d**	CO	Cl	84
20	**11–13**	**17e**	CO	OMe	69

[a] 1 M TBAF in THF (10 equiv), reflux.

and Sakamoto[22] described the use of 1 M TBAF in refluxing THF (10 equiv) to deprotect *N*-tosyl nitrogen heteroaromatic compounds. We chose this mild and neutral method to deprotect all of our compounds. In fact, in our case, basic hydrolysis is not compatible with base-sensitive functions such as cyano group. Deprotected azepines **14–17** were obtained in good yields (Scheme 4, Table 3).

However, the absence in the ^1H NMR spectrum of the benzylic proton on the deprotected azepine revealed that we did not obtain the expected azepine but the corresponding imine (Scheme 4). Furthermore, no intermediary product was detected by TLC during the course of the deprotection. As far as we know, only one example of this 'oxidative desulfonation' of nitrogen heterocycles in the presence of TBAF was already reported by Bianchi and Kaufman for the synthesis of a tricyclic lactone.[23]

A new six-step, highly divergent strategy was developed allowing access to hymenialdisine analogues starting from pyrrole. Based on a regioselective Friedel–Crafts acylation followed by a Pictet–Spengler cyclization, pyrrolobenzazepines **14**, **15** and the corresponding pyrrolobenzazepinones **16**, **17** were obtained.

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(18) The X-ray crystal structure has been filed with the Cambridge Crystallographic Centre with deposition number CCDC 640594.
(19) **General Procedure for Preparation of Compounds 10–13**
To a stirred 1 M solution of amine **6**, **7**, **8**, or **9** in anhyd toluene was added the *para*-substituted benzaldehyde derivative (1.1 equiv), under argon atmosphere (in the case of amines **8** and **9**, 4 equiv of $MgSO_4$ were added). The mixture was heated at reflux until total conversion of the amine into the intermediary imine (followed by ^{1}H NMR). Then, the mixture was cooled to r.t. to add TFA (5 or 10 equiv). The resulting mixture was left at specified temperature (r.t. or 70 °C) until completion of the reaction. Residual TFA was neutralized at 0 °C with an aq sat. $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were successively washed with H_2O and brine, dried over $MgSO_4$, filtered, and solvents removed under reduced pressure. The crude product was purified by flash chromatography.
Analytical Data of Compound 11a
Pale yellow solid obtained in 98% yield after flash chromatography (cyclohexane–EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.63 (d, *J* = 16.2 Hz, 1 H), 3.73 (br s, 1 H), 4.14 (d, 16.2 Hz, 1 H), 6.06 (m, 1 H), 6.08 (dd, *J* = 1.3, 7.3 Hz, 1 H), 6.28 (d, *J* = 3.4 Hz, 1 H), 6.73 (d, *J* = 8.3 Hz, 2 H), 6.85 (m, 2 H), 6.97 (d, *J* = 8.3 Hz, 2 H), 7.04 (d, *J* = 8.3 Hz, 2 H), 7.11 (dd, *J* = 1.3, 7.1 Hz, 1 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 3.4 Hz, 1 H). HRMS: *m/z* = 439.5326.
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(24) **General Procedure for Preparation of Compounds 14–17**
A mixture of the azepine **10a–e**, **11a–e**, **12a–e**, or **13a–e** (1 equiv) and TBAF 1 M solution in THF (10 equiv) was heated at 70 °C for 10 h. The mixture was washed with H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and solvents removed under reduced pressure. The crude product was purified by flash chromatography.
Analytical Data of Compound 15a
Yellow solid obtained in 88% yield after flash chromatography (heptane–EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 2 H), 6.21 (t, *J* = 2.6 Hz, 1 H), 6.93 (t, *J* = 2.6 Hz, 1 H), 7.2 (dd, *J* = 1.7, 6.6 Hz, 1 H), 7.22 (td, *J* = 1.7, 6.6 Hz, 1 H), 7.29 (td, *J* = 1.7, 6.6 Hz, 1 H), 7.48 (dd, *J* = 1.7, 7.2 Hz, 1 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 8.0 (d, *J* = 8.3 Hz, 2 H), 8.24 (br s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 32.6, 108.7, 114.1, 118.9, 123.3, 123.5, 126.9, 127.8, 128.2, 128.7, 130.5, 132.0, 132.8, 133.4, 144.2, 147.0, 155.0. HRMS: *m/z* = 437.5148.