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Novel synthesis of naphtho[2,1-*b*]pyrano pyrrolizidines and indolizidines through intramolecular 1,3-dipolar cycloaddition reaction

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ABSTRACT

A facile synthesis of a series of naphtho[2,1-*b*]pyrano pyrrolizidines and indolizidines was accomplished in good yields in a one-pot reaction through intramolecular 1,3-dipolar cycloaddition of azomethine ylides with Baylis–Hillman adducts as dipolarophiles. The protocol is applicable to a wide variety of photochromic and biologically active napthopyrano products. The regio and stereochemical outcome of the cycloaddition reaction was ascertained by X-ray crystallographic study of some of the products.

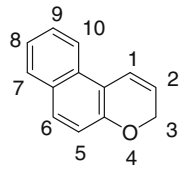
The 3*H*-naphtho[2,1-*b*]pyran and 3*H*-naphtho[2,1-*b*]pyran-7,10-dione ring systems form the core unit in a number of natural products.[1] Conocurvone which contains the skeleton 3*H*-naphtho [2,1-*b*]pyran-7,10-dione (Fig. 1) is a unique natural product and possesses remarkable anti-HIVactivity.[1a]

3*H*-Naphtho[2,1-*b*]pyrans are also known to exhibit photochromic properties and found to have wide applications in the manufacture of ophthalmic lenses, contact lenses, solar protection glasses, filters, camera optics, transmission devices, agrochem films, glazing, decorative objects, and information storage by optical inscription.[2]

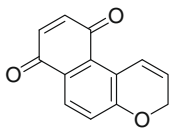
Indolizidine and pyrrolizidine alkaloids are naturally occurring *N*-heterocyclic metabolites which include a large number of compounds that display pronounced biological and pharmacological activities with therapeutic potential.[3] Swainsonine exhibits metastasis and tumor growth control besides immunomodulatory activity.[4] Stellettamide A, a recently discovered indolizidine alkaloid, has shown antifungal activity and cytotoxicity against K562 epithelium cells.[5] The increasing need of indolizidine and pyrrolizidine alkaloids for biological screening makes these heterocyclic compounds an attractive target in organic synthesis. As a consequence, new and practical methodologies leading to these classes of molecules are not only desirable but also necessary.

Intramolecular [3+2] cycloaddition of azomethine ylide has been used widely to construct complex cyclic systems from relatively simple precursors. This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms ring systems with regio and stereocontrol.[6]

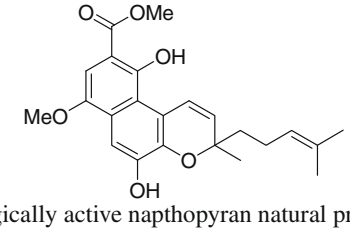
Although many methods are available for the synthesis of indolizidine and pyrrolizidines most of them require vigorous reaction conditions and use of an expensive catalyst. Recent synthesis of pyrrolizidine and indolizidine includes organolanthanide catalyzed intra and intermolecular tandem C–N and C–C bond forming process,[7] conjugate addition of β and γ-chloroamines to acetylenic sulfones,[8] and ring-closing metathesis reactions of L-pyroglutamic acid.[9]



3*H*-naptho[2,1-*b*]pyran



3*H*-naptho[2,1-*b*]pyran-7,10-dione



Biologically active napthopyran natural product

Figure 1.

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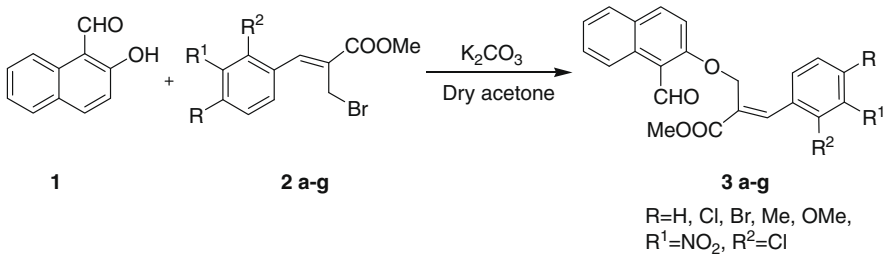
α-Methylene-β-hydroxy esters are easily accessible by Baylis–Hillman reaction,[10] and are well utilized as versatile building blocks for the stereoselective construction of natural products including alkaloids,[11] macrolides,[12] terpenoids,[13] and harmones.[14]

As part of our ongoing programme for the synthesis of novel heterocycles through cycloaddition reaction,[15] herein we report an expeditious and facile protocol for the synthesis of novel napthopyrano pyrrolizidines and indolizidines by intramolecular 1,3-dipolar cycloaddition of azomethine ylides generated from naptho-*O*-alkenyl aldehydes prepared from Baylis–Hillman adducts in a one-pot reaction.

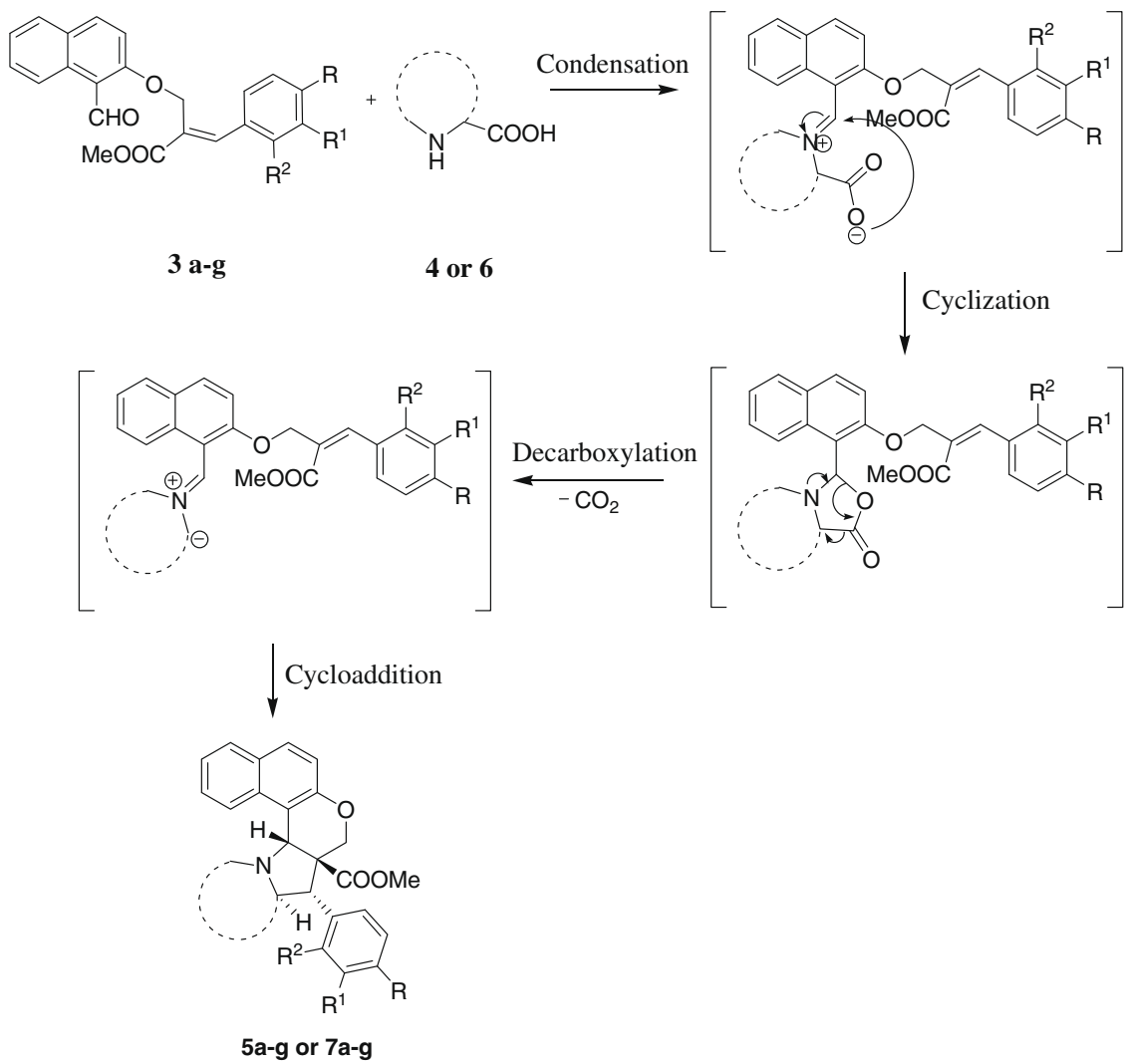
The required Baylis–Hillman adducts **3a–g** were prepared by the direct alkylation of the hydroxynapthaldehyde with Baylis–Hillman bromides in the presence of K_2CO_3 and dry acetone (94%) in 3 h (Scheme 1).

The reaction of secondary amino acids with the aldehydes **3a–g** generates azomethine ylide, which underwent neat 1,3-dipolar cycloaddition intramolecularly with *N*-tethered alkenes to give pyrrolizidines and indolizidines in a one-pot reaction (Scheme 2).

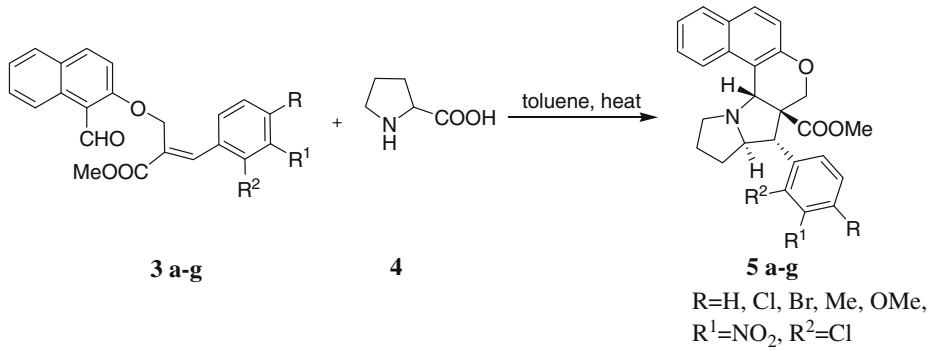
The aldehydes **3a–g** derived from Baylis–Hillman bromides were also condensed with L-proline **4** to generate azomethine ylides in refluxing toluene under Dean–Stark conditions, which



Scheme 1. Synthesis of *O*-alkenyl aldehydes.

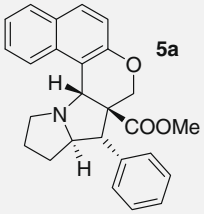
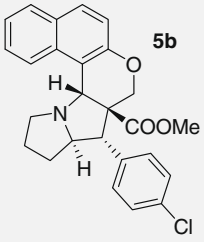
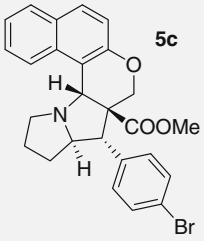
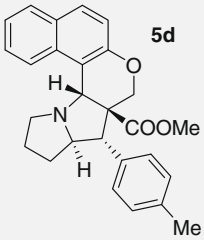
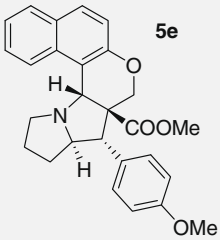


Scheme 2. Mechanism for the generation of azomethine ylide and intramolecular 1,3-dipolar cycloaddition reaction.



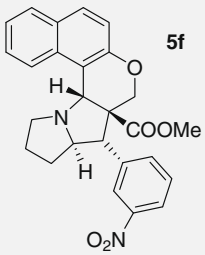
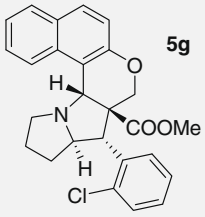
Scheme 3. Synthesis of naptho pyrano pyrrolizidine.

Table 1
Synthesis of naptho[2,1-*b*]pyrano pyrrolizidine derivatives

Entry	Substrate	R	R^1	R^2	Product[a]	Time (h)	Yield[b] (%)
1	**3a**	H	H	H	**5a** 	12	90
2	**3b**	Cl	H	H	**5b** 	12	85
3	**3c**	Br	H	H	**5c** 	13	80
4	**3d**	Me	H	H	**5d** 	12	72
5	**3e**	OMe	H	H	**5e** 	14	70

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	R	R^1	R^2	Product[a]	Time (h)	Yield[b] (%)
6	**3f**	**H**	NO_2	H	**5f** 	11	92
7	**3g**	H	H	Cl	**5g** 	11	81

[a] Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, and mass, spectral analysis.
[b] Yields refer to pure isolated products after purification by silica gel column chromatography.

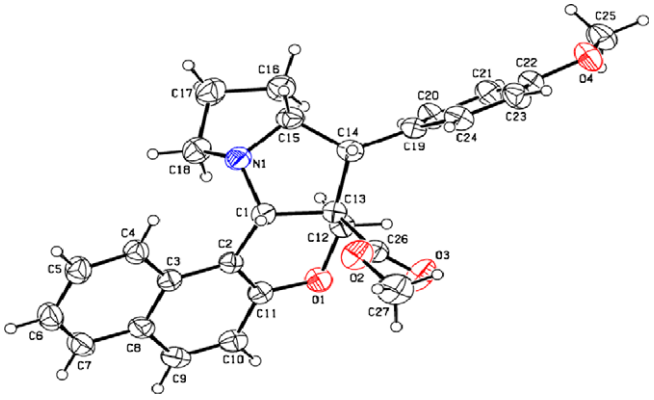


Figure 2. ORTEP diagram of compound **5e**.

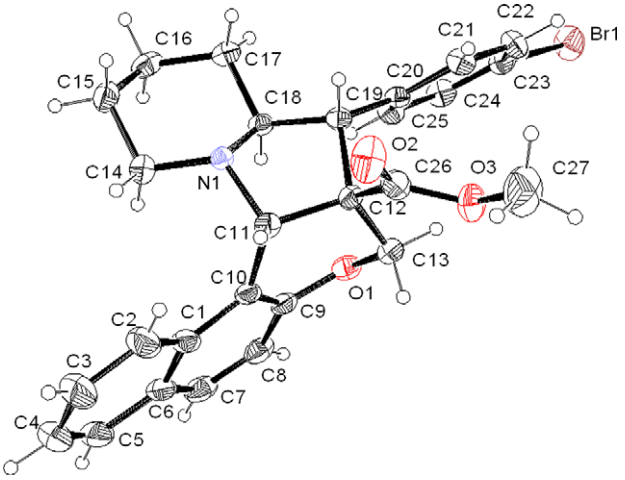
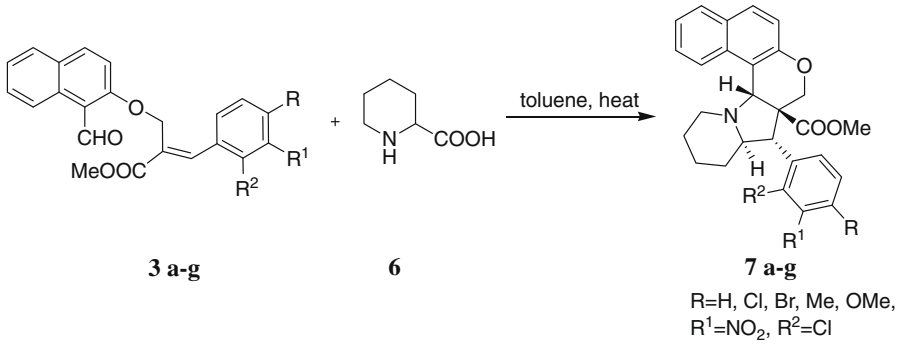


Figure 3. ORTEP diagram of compound **7c**.

underwent intramolecular cycloaddition to give naphthopyrano pyrrolizidines **5a–g** in good yield (Scheme 3, Table 1, entries 1–8).

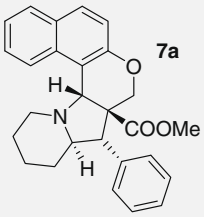
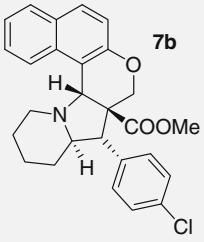
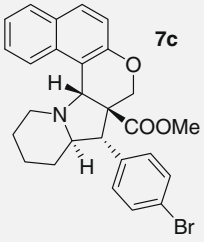
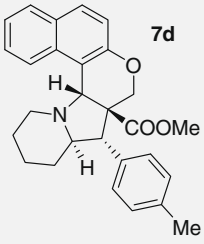
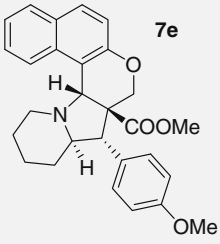
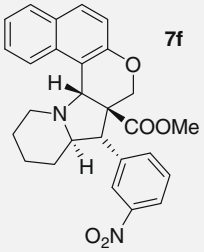
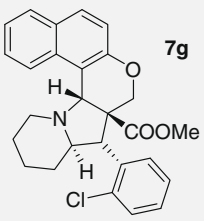
The formation of the cycloadducts was confirmed through spectral analysis.[16] Thus the IR spectrum of **5a** showed a sharp peak at 1745 cm^{-1} for the ester carbonyl group. The ^{1}H NMR spectrum of the **5a** exhibited a singlet at δ 3.45 for methyl protons of the ester. The benzylic proton exhibited a doublet at δ 6.98 (J = 9.0 Hz) and the ring junction proton appeared as a singlet at δ 5.18. The $-OCH_2$ protons appeared as two doublets at δ 4.20 and 4.79. Finally, the structure of **5a** was confirmed by mass spectrometry, which showed a peak at m/z 398.83 [M^+]. Further, the X-ray structure[17] of **5e** confirmed the cis stereochemistry at the ring junction (Fig. 2).

To establish the generality of this cycloaddition reaction we extended the method for the synthesis of naptho[2,1-*b*]pyranoindolizidine derivatives using similar reaction conditions. Thus



Scheme 4. Synthesis of naptho pyrano indolizidine.

Table 2
Synthesis of naptho[2,1-*b*]pyrano indolizidine derivatives

Entry	Substrate	R	R^1	R^2	Product[a]	Time (h)	Yield[b] (%)
1	**3a**	H	H	H	 **7a**	12	88
2	**3b**	Cl	H	H	 **7b**	12	86
3	**3c**	Br	H	H	 **7c**	13	83
4	**3d**	Me	H	H	 **7d**	12	78
5	**3e**	*O*Me	H	H	 **7e**	14	72
6	**3f**	H	NO_2	H	 **7f**	11	94
7	**3g**	H	H	Cl	 **7g**	11	85

[a] Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, and mass, spectral analysis.
[b] Yields refer to pure isolated products after purification by silica gel column chromatography.

azomethine ylide generated by the condensation of DL-pipecolinic acid **6** with naphtho-*O*-alkenyl aldehydes **3a–g** underwent smooth intramolecular cycloaddition reaction in refluxing toluene to afford the indolizidine derivatives **7a–g** in good yield (Scheme 4).

The structures and regiochemistry of the cycloadducts **7a–g** were confirmed by the spectroscopic data, and also by X-ray crystallographic analysis (Fig. 3).[18] The reactions were found to be highly regioselective leading to the formation of only one product in which ring junction protons were found to be cis. It was observed that the azomethine ylide generated from the alkenyl aldehyde with an electron-withdrawing group in the phenyl ring was found to be more reactive (Table 2, entry 6) than those which possess electron-donating group (Table 2, entries 4 and 5). However the yield of the cycloadducts was found to be moderate to good in all cases irrespective of the nature of the substituent present in the phenyl ring (Table 2).

In conclusion, we have developed a new method for the synthesis of a variety of naphthopyranoindolizidines and pyrrolizidines by intramolecular 1,3-dipolar cycloaddition using the Baylis–Hillman adducts as internal dipolarophiles.

Acknowledgments

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16. *Synthesis of naphtho[2,1-b]pyrano pyrrolizidine* (**5a**): *Typical procedure*: A solution of **3a** (1 mmol) and L-proline **4** (1.5 mmol) was heated under reflux in toluene in a Dean–Stark apparatus. After completion of the reaction as evidenced by TLC the solvent was removed under reduced pressure. The crude product was purified by short column chromatography on silica gel (hexane/ethyl acetate, 95:5) to provide the product in 94% yield as white solid. Mp 68–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06–1.24 (m, 4H); 2.60–2.77 (m, 1H); 2.78–3.03 (m, 1H); 3.45 (s, 3H); 4.18 (s, 2H); 4.20 (d, J = 10.8 Hz, 1H); 4.79 (d, J = 10.8 Hz, 1H); 5.18 (s, 1H); 6.98–8.23 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 31.13, 49.83, 51.33, 54.68, 58.94, 63.34, 67.48, 110.44, 117.22, 122.69, 122.83, 126.04, 126.13, 127.12, 127.28, 127.89, 128.12, 128.63, 132.49, 135.32, 150.94, 172.30. m/z 398.83 [M$^+$]. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.19; H, 6.26; N, 3.50. Found: C, 78.30; H, 6.19; N, 3.58.
Naphtho[2,1-b]pyrano pyrrolizidine (**5c**): white solid. Mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.71–1.81 (m, 2H); 2.65–2.70 (m, 1H); 2.84–2.93 (m, 1H); 3.54 (s, 3H); 3.60 (s, 1H); 4.19–4.28 (s, 3H); 4.26 (d, J = 10.8 Hz, 1H); 4.81 (d, J = 10.8 Hz, 1H); 5.24 (s, 1H); 7.06–8.30 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 26.52, 31.96, 51.17, 54.25, 55.12, 59.86, 63.45, 68.37, 111.48, 118.26, 133.54, 123.83, 127.15, 128.23, 129.78, 131.44, 131.66, 135.46, 151.98, 173.19, m/z 477.12 [M$^+$]. Anal. Calcd for $C_{26}H_{24}NO_3Br$: C, 65.27; H, 5.02; N, 2.92. Found: C, 65.33; H, 4.99; N, 2.99.
Naptho[2,1-b]pyrano indolizidine (**7a**): Colorless solid, Mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.82–2.86 (m, 1H); 2.95–2.99 (m, 1H); 3.09–3.14 (m, 1H); 3.29–3.35 (m, 1H); 3.58 (s, 3H); 3.82 (d, J = 5.4 Hz, 1H); 4.00–4.12 (m, 3H); 4.28–4.37 (m, 1H); 4.49–4.53 (m, 1H); 4.61–4.72 (m, 2H); 5.12 (s, 1H); 7.04–8.33 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 39.85, 52.54, 53.67, 57.46, 58.22, 64.99, 71.81, 111.48, 118.77, 121.94, 123.39, 123.78, 127.01, 127.31, 127.56, 127.94, 128.52, 128.62, 128.74, 129.15, 130.18, 133.55, 133.83, 133.62, 135.70, 152.53, 172.05. m/z 412.73 [M$^+$]. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 70.45; H, 6.53; N, 3.38. Found: C, 70.55; H, 6.47; N, 3.46.
Naptho[2,1-b]pyrano indolizidine (**7c**): Colorless solid, Mp 172–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01–1.16 (m, 4H); 1.26–1.42 (m, 3H); 1.51–1.53 (m, 1H); 2.865–2.88 (m, 1H); 2.99–3.05 (m, 1H); 3.67 (d, J = 12.0 Hz, 1H); 3.75 (s, 3H); 4.02 (d, J = 11.7 Hz, 1H); 5.75 (s, 1H); 7.15 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 22.72, 25.31, 30.32, 49.05, 52.61, 57.85, 59.47, 63.52, 69.96, 116.51, 118.56, 121.31, 122.75, 123.84, 126.37, 128.88, 129.13, 129.68, 131.53, 131.81, 133.91, 135.93, 156.39, 174.43, m/z 467.14 [M$^+$]. Anal. Calcd for $C_{25}H_{26}NO_3Br$: C, 71.77; H, 5.55; N, 2.99. Found: C, 71.89; H, 5.49; N, 3.06.
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