Convenient Synthesis of 8-Substituted 9*H*-Dipyrido[3,2-*b*:3′,2′-*d*]pyrrole (6-Aza-δ-carbolines)

Eric Desarbre,[1] Jean-Yves Mérour*

Institut de Chimie Organique et Analytique, URA CNRS, BP 6759, Université d' Orléans, F-45067 Orléans Cedex, France

Fax +33(238)417078; E-mail: jmerour@univ-orléans.fr

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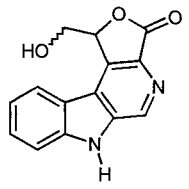
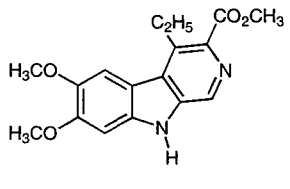
6-Aza-δ-carbolines have been readily obtained in three steps from 7-azaindolinone (1,2-dihydro-3*H*-pyrrolo[2,3-*b*]pyridin-3-one), by aldol condensation, inverse electron demand Diels–Alder reactions and treatment with hydroxylamine hydrochloride.

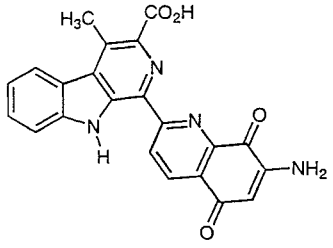
Carbolines play an important role in human biology. Some of them, like ZK 93426 or furo[3,4-*b*]-β-carboline have some affinities towards benzodiazepine receptors[1,2] and particularly the dimethoxy-β-carboline methyl ester (DMCM), which is a strong inverse agonist of the receptor ligands.[3] A second type of carboline structure offers some antitumor or antibiotic activities, e.g. lavendamycine[4] or grossularines 1 or 2.[5] Therefore, there is a great interest in synthesizing new derivatives of carbolines, and this paper describes the preparation of novel carbolines, the 6-azacarbolines. The replacement of indole nucleus by pyrrolopyridine framework in order to increase the pharmacological activity[6] or for modeling[7] some natural compounds has already been described.



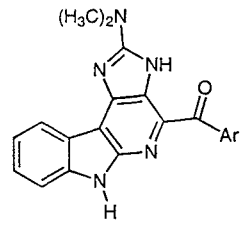
Furo[3,4-*b*]-β-carboline



DMCM



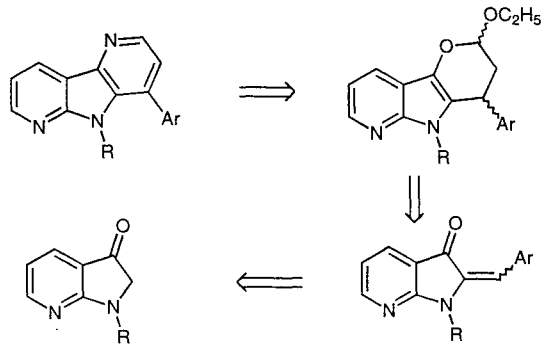
Lavendamycine



Grossularine 1 Ar = indol-3-yl
Grossularine 2 Ar = p-hydroxy phenyl

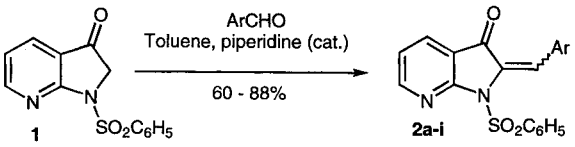
Many strategies[8] have been used to prepare carbolines. Quéguiner[9] has recently developed a method based on palladium cross-coupling reactions. 1-Acetyl-1*H*-indol-3(2*H*)-ones or indolinones have already been used to prepare δ-carbolines.[10] The strategy involves inverse electronic demand Diels–Alder reaction (IEDDA)[11,16–20] with 2-benzylidene indolinones as 1-oxabuta-1,3-diene to give pyrano compounds which were treated with hydroxylamine hydrochloride.

In this paper we have employed the same strategy using 1,2-dihydro-3*H*-pyrrolo[2,3-*b*]pyridin-3-one (7-azaindolinone) **1**[12] instead of indolinone as starting material to prepare 8-substituted 9*H*-dipyrido[3,2-*b*:3′,2′-*d*]pyrroles (6-aza-δ-carbolines) (Scheme 1). In the pyrrolo[2,3-*b*]pyridine series, few examples of azacarboline synthesis have been reported in the literature. They involve radical cyclization[13] or Bischler–Napieralski reaction.[14,15]



Scheme 1

We have already described[12] the synthesis of some α,β-ethylenic ketones **2** from 7-azaindolinone **1**. Compound **1** was treated with aromatic aldehydes in the presence of piperidine as catalyst in refluxing toluene to give a mixture of *E*/*Z*-**2a–i**. The *E*-isomers were generally predominant (Scheme 2, Table 1).

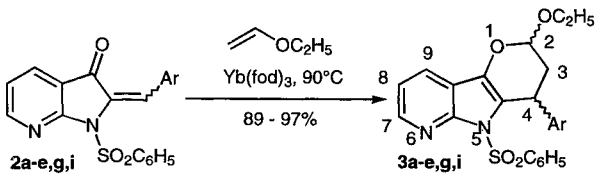


2	Ar	2	Ar
a	4-$MeOC_6H_4$	**f**	2-$O_2NC_6H_4$
b	4-ClC_6H_4	**g**	2-$MeO_2CC_6H_4$
c	4-$O_2NC_6H_4$	**h**	3-pyridyl
d	4-MeC_6H_4	**i**	2-methoxycarbonyl-1-methylindol-3-yl
e	Ph		

Scheme 2

The *E*/*Z*-isomeric mixture of compounds **2a–e,g,i** was stirred at 90 °C in ethyl vinyl ether with a catalytic amount of $Yb(fod)_3$ (10 %) in a sealed tube to give diastereomeric pyrano compounds **3a–e,g,i** in good yield (Scheme 3, Table 2), but apparently without any selectivity.[11,16] This is confirmed by the fact that pure *E*-**2b,e** gave a mixture

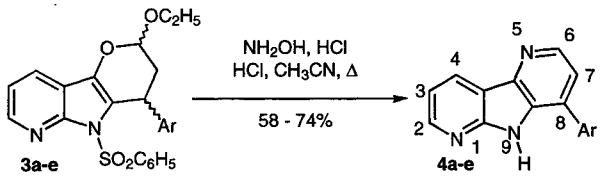
of *cis* / *trans* compounds **3**, where the *trans*-diastereomer is predominant (Table 2). Performing the cycloaddition on the pure *E*-**2e** at 50 °C instead of 90 °C slightly modified the diastereomeric ratio of compound **3e** (35:65 instead of 40:60), which reflected a decrease in the isomerization in favor of the *trans*-diastereomer. It has been discussed by Tietze[17] that isomerization of the 1-oxabuta-1,3-diene could occur during the cycloaddition reaction. This phenomenon could also be catalyzed by the Lewis acid Yb^{3+} during the hetero Diels–Alder process; thus four transition states (TS) have to be considered for compound **2** (*E* and *Z* configuration). The *trans*-isomer **3** would be formed via the *endo-E-trans* TS and the *cis*-isomer **3** would be the result of the *endo-Z-syn* TS, and vice versa for the *exo*-transition structures. One other possible explanation for the low diastereoselectivity is the fact that the *cis*-diastereomer is more stable (0.69 kcal/mol for **3a**)[21] than the *trans*-diastereomer.



Scheme 3

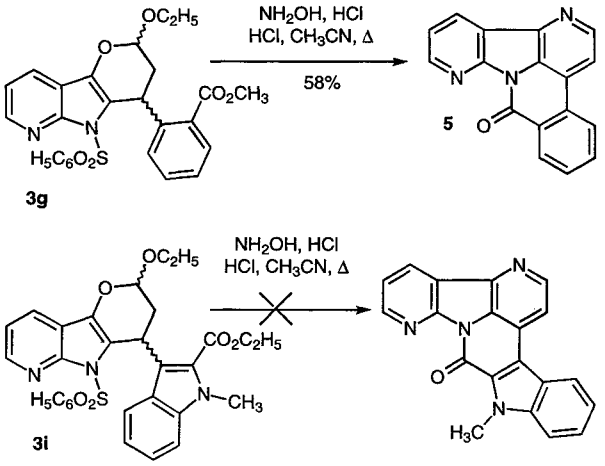
The *trans* or *cis* configuration has been tentatively determined on the basis of spectral data, especially ^{1}H NMR spectra, in comparison with similar structures,[16] but with some ambiguity. As in the indole series, the ^{1}H NMR spectrum of the supposed *cis*-diastereomer of **3e** exhibits a signal at $\delta = 5.30$ (dd, $J = 2.2$, 5.2 Hz) for the anomeric proton H-2, which occurs at $\delta = 5.21$ (dd, $J = 2.2$, 7.4 Hz) for the *trans*-diastereomer. The benzylic proton H-4 appeared as a doublet of doublets in each case, but at $\delta = 4.90$ for the *cis*-diastereomer and 4.92 for the *trans*-diastereomer. The difference between the pseudo axial and pseudo equatorial coupling constant of H-3 with H-4 for *trans*- and *cis*-diastereomers was not significant and 2D NMR studies failed to give conclusive evidence for determining the configuration of each diastereomer. In order to have more information, the *Z*-isomer of the ethylenic ketone *Z*-**2d** was desulfonylated to give *Z*-2-(4-methylbenzylidene)-1,2-dihydro-3*H*-pyrrolo[2,3-*b*]pyridin-3-one and was reacted with ethyl vinyl ether. The ^{1}H NMR spectrum of the corresponding desulfonylated cycloadduct (H-2, $\delta = 5.30$, dd, $J_{2,3a} = 8.5$ Hz, $J_{2,3e} = 1.8$ Hz; H-4, $\delta = 4.42$, dd, $J_{3e,4} = 6.6$ Hz, $J_{3a,4} = 9.7$ Hz; H-3*e*, $\delta = 2.52$, ddd, $J_{2,3e} = 1.8$ Hz, $J_{3e,4} = 6.6$ Hz, $J_{3e,3a} = 13.5$ Hz; H-3*a*, $\delta = 2.26$, m, $J_{2,3a} = 8.5$ Hz, $J_{3a,4} = 9.7$ Hz, $J_{3e,3a} = 13.5$ Hz) allowed us to assign without any doubt the *cis* configuration for it, which was also in agreement with NOE difference experiments (interaction of H-4 with H-3*e* and H-2). By comparison we were able to confirm the postulated *trans* configuration of the major diastereomer of **3a–e** which is in agreement with an *endo* process.

The diastereoisomerism is not relevant because the pyrano ring was cleaved to form the azacarboline compounds. When a diastereomeric mixture of compounds **3a–e** was treated with hydroxylamine hydrochloride and concentrated HCl in acetonitrile, we observed the formation of compounds **4a–e** (Scheme 4, Table 3). Without the addition of concentrated HCl, low yields were obtained. In each case, the hydrolytic cleavage of the phenylsulphonyl group has been observed.



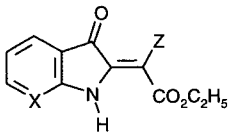
Scheme 4

Phenanthroline **5** was prepared in a one-pot reaction in 58% yield from compound **3g** by the same procedure. A complex mixture was obtained by reacting the compound **3i** with $NH_2OH \cdot HCl$ and concentrated HCl (Scheme 5).



Scheme 5

The azacarbolines **4** thus prepared are substituted by a phenyl group in 8-position owing to the structure of the starting material **2**. In this respect, we have unsuccessfully reacted compounds **6**,[22] **7**[23] and **8**[22] in order to obtain different substituted carbolines.



6 X = CH Z = H
7 X = CH Z = $CO_2C_2H_5$
8 X = N Z = $CO_2C_2H_5$

In summary we have presented a method to readily prepare 6-aza-δ-carbolines. But unfortunately, the α-and β-carbolines were not accessible via this IEDDA strategy.[24] Hence, we are currently investigating new synthetic procedures for β-azacarbolines.

Table 1. Compounds **2** Prepared

Product[a]	Reaction Time (h)	Yield (%)	Ratio of *E*/*Z*[b]	mp[c] (°C)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	1.5	84	55:45	172–174	1680	3.88 (s, 6H, $CH_{3E}+CH_{3Z}$), 6.98 (m, 4H, $2\times2H_{arom}$), 7.18 (m, 2H, $H_{5E}+H_{5Z}$), 7.28 (m, $2H_{arom}$), 7.39 (m, $2H_{arom}$), 7.44 (m, $1H_{arom}$), 7.53 (m, 2H, H_{arom} + *Z*-CH=), 7.61 (m, $2H_{arom}$), 7.84 (m, $2H_{arom}$), 7.88 (1H, H_{4Z}), 7.94 (m, 1H, H_{4E}), 8.01 (m, $2H_{arom}$), 8.08 (m, $2H_{arom}$), 8.10 (s, 1H, *E*-CH=), 8.68 (m, 2H, $H_{6E}+H_{6Z}$)
2b	1.5	70	*E*[d]	154–156	1700	7.19 (dd, 1H, H_5, J = 5.2, 7.4), 7.41 (d, $2H_{arom}$, J = 8.8), 7.44 (m, $2H_{arom}$), 7.57 (m, $1H_{arom}$), 7.86 (d, $2H_{arom}$, J = 8.8), 7.90–8.00 (m, $3H_{arom}+H_4$), 8.07 (s, 1H, =CH), 8.69 (m, 1H, H_6, J = 2.2, 5.2)
2c	1.25	88	75:25	208–210	1700, 1510, 1340	7.20–7.25 (m, 2H, $H_{5E}+H_{5Z}$), 7.30–7.70 (m, $6H_{arom}$), 7.85–8.10 (m, 7H, $4H_{arom}+H_{4E}+H_{4Z}$ + *Z*-CH=), 8.12 (s, 1H, *E*-CH=), 8.20–8.30 (m, $8H_{arom}$), 8.68 (dd, 1H, H_{6E}, J = 1.8, 5.2), 8.72 (dd, 1H, H_{6Z}, J = 1.8, 5.2)
2d	2	66	55:45	158–160	1690	2.31 (s, 6H, $CH_{3E}+CH_{3Z}$), 7.07 (m, 2H, $H_{5E}+H_{5Z}$), 7.10–7.21 (m, $6H_{arom}$), 7.25–7.35 (m, $3H_{arom}$), 7.43 (m, 2H, $1H_{arom}$ + *Z*-CH=), 7.51 (d, $2H_{arom}$, J = 7.4), 7.75–7.80 (m, $7H_{arom}$), 7.83 (dd, 1H, H_{4E}, J = 1.5, 8.1), 8.01 (s, 1H, *E*-CH=), 8.58 (m, 2H, $H_{6E}+H_{6Z}$)
2e	1.5	78	*E*[d]	140–142	1680	7.16 (dd, 1H, H_5, J = 5.2, 7.4), 7.35–7.65 (m, $8H_{arom}$), 7.85–7.98 (m, 3H, $2H_{arom}+H_4$), 8.13 (s, 1H, *E*-CH=), 8.68 (m, 1H, H_6, J = 1.5, 5.2)
2f	2	60	*E*[d]	202–204	1710, 1520, 1320	7.14 (dd, 1H, H_5, J = 5.2, 7.7), 7.50–7.70 (m, $6H_{arom}$), 7.87 (dd, 1H, H_4, J = 1.7, 7.7), 8.20–8.30 (m, $3H_{arom}$), 8.41 (s, 1H, *E*-CH=), 8.66 (dd, 1H, H_6, J = 1.7, 5.2)
2g	2.5	62	*E*[d]	172–174	1700	3.89 (s, 3H, CH_{3E}), 3.99 (s, 3H, CH_{3Z}), 7.13 (dd, 1H, H_{5E}, J = 4.4, 7.4), 7.23 (dd, 1H, H_{5Z}, J = 4.4, 7.4), 7.42–7.14 (m, $13H_{arom}$), 7.86 (dd, 1H, H_{4E}, J = 1.5, 7.4), 7.97 (dd, 1H, H_{4Z}, J = 1.5, 7.4), 8.12 (m, $2H_{arom}$), 8.21 (m, $4H_{arom}$), 8.60 (s, 1H, *E*-CH=), 8.65 (dd, 1H, H_{6E}, J = 1.5, 4.4), 8.73 (dd, 1H, H_{6Z}, J = 1.5, 4.4)
2h	1.5	84	*E*[d]	154–156	1740	7.18 (dd, 1H, H_5, J = 5.2, 8.1), 7.36 (dd, 1H, $H_{4'}$, J = 4.4, 8.1), 7.46 (m, $2H_{arom}$), 7.59 (m, $1H_{arom}$), 7.93–8.00 (m, 3H, $2H_{arom}$, $H_{5'}$), 8.07 (s, 1H, *E* CH=), 8.32 (d, 1H, H_4, J = 8.1), 8.62 (d, 1H, $H_{3'}$, J = 4.4), 8.68 (dd, 1H, H_6, J = 1.5, 5.2), 8.89 (s, 1H, $H_{1'}$)
2i	1.5	84	*E*[d]	104–106 (dec)	1700	3.85 (s, 3H, OCH_{3E}), 4.06 (s, 3H, OCH_{3Z}), 4.12 (s, $2\times3H$, NCH_3), 7.30–7.60 (m, $2\times8H_{arom}$), 7.85–8.10 (m, $6H_{arom}$), 8.26 (s, 1H, *Z*-CH=), 8.51 (s, 1H, *E*-CH=), 8.71 (m, 2H, $H_{4E}+H_{4Z}$)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.20, N ± 0.25. For Ar, see Scheme 2.
[b] Determined by ^1H NMR spectroscopy.
[c] Solvent: MeOH/H_2O.
[d] Amount of *E*-isomer > 95%.

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60 (230–400 mesh). ^1H NMR spectra were recorded on a Bruker AM 300 using TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer. Mass spectra were obtained on a Nermag R 10C spectrometer (chemical ionization with ammonia).

(*E*/*Z*)-2-Arylmethylene-1,2-dihydro-1-phenylsulfonyl-3*H*-pyrrolo-[2,3-*b*]pyridin-3-ones 2; General Procedure:
A mixture of **1** (274 mg, 1 mmol) and an aromatic aldehyde (1.2 mmol) in toluene (15 mL) containing piperidine as catalyst (3 drops) was refluxed for the time indicated in Table 1. Toluene was evaporated in vacuo and the residue was chromatographed using CH_2Cl_2 as eluent to give **2**. (Table 1).

(*trans*/*cis*)-8-Aryl-6-ethoxy-6,7-dihydro-9-phenylsulfonyl-8*H*-pyrano-pyridine[2,3-*b*:2′,3′-*b*]pyrroles 3; General Procedure:
In a sealed tube, compounds **2** (0.35 mmol) and Yb(fod)$_3$ (0.035 mmol) were mixed in ethyl vinyl ether (2 mL) and stirred at 90 °C for the time indicated in Table 2. The solvent was evaporated in vacuo and the residue was chromatographed using CH_2Cl_2 as eluent to give the products **3** (Table 2).

8-Aryl-9*H*-dipyrido[3,2-*b*:3′,2′-*d*]pyrroles 4; General Procedure:
Compounds **3** (0.3 mmol), NH_2OH HCl (0.75 mmol) and conc. HCl (37%, 0.3 mmol) were added in MeCN (5 mL) and refluxed for the time indicated in Table 3. H_2O (15 mL) was added and the carboline was extracted with EtOAc (3 × 15 mL). After drying ($MgSO_4$), the solvent was evaporated in vacuo and the residue was chromatographed using CH_2Cl_2/MeOH (99.5:0.5, v/v) as eluent to give **4** (Table 3).

12-Oxopyrido[3′,2′:4,5]pyrrolo[3,2,1-*b*,*c*][1,3]phenanthroline (5):
Compound **5** was obtained from **3g** (492 mg, 1 mmol) as described for the preparation of **4**; yield 0.157 g (58%); mp 270–272 °C (EtOH).
IR (KBr): ν = 1670 (CO) cm^{-1}.
^1H NMR ($CDCl_3$): δ = 7.54 (dd, 1H, H_3, J = 5.2, 8.1 Hz), 7.77 (t, $1H_{arom}$, J = 7.4 Hz), 7.87 (t, $1H_{arom}$, J = 7.4 Hz), 8.00 (d, 1H, H_7, J = 5.2 Hz), 8.31 (d, $1H_{arom}$, J = 7.4 Hz), 8.67 (dd, 1H, H_4, J = 1.5, 8.1 Hz), 8.76 (d, $1H_{arom}$, J = 7.4 Hz), 8.82–8.85 (m, 2H, H_2, H_6).
MS SM (NH_3): m/z = 272 (M^+ + 1).

Table 2. Compounds **3** Prepared

Product[a]	Reaction Time (h)	Yield (%)	Ratio of *cis*/*trans*[b]	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a[c]	3.5	93	40:60	1590, 1370, 1170	*cis:* 1.12 (t, 3H, CH_3, J = 7.4), 2.16 (ddd, 1H, C*H*H, J = 5.2, 5.8, 14.0), 2.53 (ddd, 1H, CH*H*, J = 2.2, 7.4, 14.0), 3.55–3.65 (m, 1H, C*H*HCH$_3$), 3.79 (s, 3H, CH_3), 3.85–3.95 (m, 1H, CH*H*CH$_3$), 4.84 (dd, 1H, CH, J = 5.8, 7.4), 5.30 (dd, 1H, OCHO, J = 2.2, 5.2), 6.68 (d, 2H$_{arom}$, J = 8.8), 6.98 (d, 2H$_{arom}$, J = 8.8), 7.15–7.30 (m, 3H, 2H$_{arom}$ + H$_8$), 7.41 (m, 1H$_{arom}$), 7.57 (d, 2H$_{arom}$, J = 8.1), 7.84 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.44 (dd, 1H, H$_7$, J = 1.5, 4.4) *trans:* 1.24 (t, 3H, CH_3, J = 7.4), 2.07 (ddd, 1H, C*H*H, J = 2.2, 5.2, 13.3), 2.50 (ddd, 1H, CH*H*, J = 6.6, 6.6, 13.3), 3.60–3.70 (m, 1H, C*H*HCH$_3$), 3.81 (s, 3H, CH_3), 3.95–4.05 (m, 1H, CH*H*CH$_3$), 4.88 (dd, 1H, CH, J = 5.2, 6.6), 5.21 (dd, 1H, OCHO, J = 2.2, 6.6), 6.77 (d, 2H$_{arom}$, J = 8.8), 7.01 (d, 2H$_{arom}$, J = 8.8), 7.15–7.30 (m, 3H, 2H$_{arom}$ + H$_8$), 7.42 (m, 1H$_{arom}$), 7.61 (d, 2H$_{arom}$, J = 8.1), 7.83 (dd, 1H, H$_9$, J = 1.5, 7.4), 8.45 (dd, 1H, H$_7$, J = 1.5, 4.4)
3b[d]	3.0	97	30:70	1600, 1370, 1170	*cis:* 1.02 (t, 3H, CH_3, J = 7.4), 2.12 (ddd, 1H, C*H*H, J = 5.2, 5.2, 14.0), 2.48 (ddd, 1H, CH*H*, J = 2.2, 7.4, 14.0), 3.40–3.60 (m, 1H, C*H*HCH$_3$), 3.75–3.90 (m, 1H, CH*H*CH$_3$), 4.82 (dd, 1H, CH, J = 5.2, 7.4), 5.25 (dd, 1H, OCHO, J = 2.2, 5.2), 6.94 (d, 2H$_{arom}$, J = 8.8), 7.04 (d, 2H$_{arom}$, J = 8.8), 7.10–7.30 (m, 3H, 2H$_{arom}$ + H$_8$), 7.40 (m, 1H$_{arom}$), 7.54 (d, 2H$_{arom}$, J = 7.4), 7.80 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.42 (dd, 1H, H$_7$, J = 1.5, 5.2) *trans:* 1.18 (t, 3H, CH_3, J = 7.4), 1.96 (ddd, 1H, C*H*H, J = 2.2, 5.9, 14.0), 2.43 (ddd, 1H, CH*H*, J = 6.6, 6.6, 14.0), 3.50–3.65 (m, 1H, C*H*HCH$_3$), 3.85–4.00 (m, 1H, CH*H*CH$_3$), 4.82 (dd, 1H, CH, J = 5.9, 6.6), 5.15 (dd, 1H, OCHO, J = 2.2, 6.6), 6.98 (d, 2H$_{arom}$, J = 8.8), 7.10–7.30 (m, 5H, 4H$_{arom}$ + H$_8$), 7.39 (m, 1H$_{arom}$), 7.56 (d, 2H$_{arom}$, J = 8.1), 7.78 (dd, 1H, H$_9$, J = 1.5, 7.4), 8.41 (dd, 1H, H$_7$, J = 1.5, 4.4)
3c	3.5	96	35:65	1510, 1340, 1380, 1170	*cis:* 0.99 (t, 3H, CH_3, J = 7.4), 2.28 (ddd, 1H, C*H*H, J = 3.7, 3.7, 14.0), 2.58 (ddd, 1H, CH*H*, J = 2.2, 8.1, 14.0), 3.40–3.60 (m, 1H, C*H*HCH$_3$), 3.35–3.90 (m, 1H, CH*H*CH$_3$), 5.01 (dd, 1H, CH, J = 3.7, 8.1), 5.35 (dd, 1H, OCHO, J = 2.2, 3.7), 7.20–7.30 (m, 5H, 4H$_{arom}$ + H$_8$), 7.46 (m, 1H$_{arom}$), 7.67 (d, 2H$_{arom}$, J = 7.4), 7.88 (dd, 1H, H$_9$, J = 1.5, 7.4), 8.00 (d, 2H$_{arom}$, J = 8.1), 8.50 (dd, 1H, H$_7$, J = 1.5, 5.2) *trans:* 1.21 (t, 3H, CH_3, J = 7.4), 1.99 (ddd, 1H, C*H*H, J = 2.2, 7.4, 14.0), 2.53 (ddd, 1H, CH*H*, J = 6.6, 7.4, 14.0), 3.58–3.72 (m, 1H, C*H*HCH$_3$), 3.85–4.00 (m 1H, CH*H*CH$_3$), 4.96 (dd, 1H, CH, J = 6.6, 7.4), 5.24 (dd, 1H, OCHO, J = 2.2, 7.4), 6.98–7.34 (m, 5H, 4H$_{arom}$ + H$_8$), 7.44 (m, 1H$_{arom}$), 7.66 (d, 2H$_{arom}$, J = 8.1), 7.82 (dd, 1H, H$_9$, J = 1.5, 7.4), 8.09 (d, 2H$_{arom}$, J = 8.8), 8.46 (dd, 1H, H$_7$, J = 1.5, 5.2)
3d	3.0	96	40:60	1610, 1370, 1170	*cis:* 1.14 (t, 3H, CH_3, J = 7.4), 2.16 (ddd, 1H, C*H*H, J = 5.9, 5.9, 14.0), 2.33 (s, 3H, CH_3), 2.55 (ddd, 1H, CH*H*, J = 2.2, 7.4, 14.0), 3.54–3.68 (m, 1H, C*H*HCH$_3$), 3.87–4.00 (m, 1H, CH*H*CH$_3$), 4.85 (dd, 1H, CH, J = 5.9, 7.4), 5.30 (dd, 1H, OCHO, J = 2.2, 5.9), 6.96 (m, 4H$_{arom}$), 7.15–7.25 (m, 3H, 2H$_{arom}$ + H$_8$), 7.41 (m, 1H$_{arom}$), 7.54 (d, 2H$_{arom}$, J = 7.4), 7.85 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.45 (dd, 1H, H$_7$, J = 1.5, 5.2) *trans:* 1.23 (t, 3H, CH_3, J = 7.4), 2.08 (ddd, 1H, C*H*H, J = 2.2, 5.9, 14.0), 2.35 (s, 3H, CH_3), 2.48 (ddd, 1H, CH*H*, J = 6.6, 7.4, 14.0), 3.55–3.69 (m, 1H, C*H*HCH$_3$), 3.92–4.05 (m 1H, CH*H*CH$_3$), 4.89 (dd, 1H, CH, J = 5.9, 6.6), 5.21 (dd, 1H, OCHO, J = 2.2, 7.4), 6.98 (m, 2H$_{arom}$), 7.04 (m, 2H$_{arom}$), 7.15–7.25 (m, 3H, 2H$_{arom}$ + H$_8$), 7.41 (m, 1H$_{arom}$), 7.58 (d, 2H$_{arom}$, J = 7.4), 7.82 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.45 (dd, 1H, H$_7$, J = 1.5, 5.2)
3e	2.0	94	40:60	1610, 1370, 1170	*cis:* 1.10 (t, 3H, CH_3, J = 7.4), 2.19 (ddd, 1H, C*H*H, J = 5.2, 5.9, 14.0), 2.55 (ddd, 1H, CH*H*, J = 2.2, 7.4, 14.0), 3.51–3.64 (m, 1H, C*H*HCH$_3$), 3.85–3.99 (m, 1H, CH*H*CH$_3$), 4.90 (dd, 1H, CH, J = 5.9, 7.4), 5.30 (dd, 1H, OCHO, J = 2.2, 5.2), 7.05–7.25 (m, 8H$_{arom}$), 7.40 (m, 1H$_{arom}$), 7.53 (d, 2H$_{arom}$, J = 7.4), 7.84 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.44 (dd, 1H, H$_7$, J = 1.5, 5.2) *trans:* 1.22 (t, 3H, CH_3, J = 7.4), 2.09 (ddd, 1H, C*H*H, J = 2.2, 5.2, 14.0), 2.49 (ddd, 1H, CH*H*, J = 6.6, 7.4, 14.0), 3.56–3.68 (m, 1H, C*H*HCH$_3$), 3.91–4.04 (m, 1H, CH*H*CH$_3$), 4.92 (dd, 1H, CH, J = 5.2, 6.6), 5.21 (dd, 1H, OCHO, J = 2.2, 7.4), 7.07–7.26 (m, 8H$_{arom}$), 7.40 (m, 1H$_{arom}$), 7.56 (d, 2H$_{arom}$, J = 8.1), 7.82 (dd, 1H, H$_9$, J = 1.5, 8.1), 8.44 (dd, 1H, H$_7$, J = 1.5, 5.2)
3g	14.0	91	50:50	1710	*cis:* 1.10 (t, 3H, CH_3, J = 7.4), 2.27 (ddd, 1H, C*H*H, J = 5.2, 5.2, 14.0), 2.77 (m, 1H, CH*H*), 3.50–3.65 (m, 1H, C*H*HCH$_3$), 3.85–4.00 (m, 1H, CH*H*CH$_3$), 4.00 (s, 3H, OCH_3), 5.32 (m, 1H, C*H*), 5.81 (m, 1H, OC*H*O), 6.91 (d, 1H$_{arom}$, J = 7.4), 7.08 (t, 1H$_{arom}$, J = 7.4), 7.15–7.30 (m, 4H$_{arom}$), 7.42 (m, 1H$_{arom}$), 7.61 (d, 2H$_{arom}$, J = 7.4), 7.85 (d, 1H, H$_9$, J = 8.1), 8.01 (d, 1H$_{arom}$, J = 7.4), 8.44 (m, 1H, H$_7$) *trans:* 1.20 (t, 3H, CH_3, J = 7.4), 2.15 (ddd, 1H, C*H*H, J = 1.5, 5.2, 14.0), 2.66 (ddd, 1H, CH*H*, J = 6.6, 7.4, 14.0), 3.55–3.70 (m, 1H, C*H*HCH$_3$), 3.85–4.00

Table 2. (continued)

Product[a]	Reaction Time (h)	Yield (%)	Ratio of *cis*/*trans*[b]	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
					(m, 1 H, CH*H*CH_3), 3.98 (s, 3 H, OCH_3), 5.23 (dd, 1 H, CH, J = 1.5, 7.4), 5.80 (dd, 1 H, OCHO, J = 5.2, 6.6), 6.89 (d, 1 H_{arom}, J = 8.1), 7.15–7.35 (m, 5 H_{arom}), 7.40 (m, 1 H_{arom}), 7.61 (m, 2 H_{arom}), 7.81 (dd, 1 H, H_9, J = 1.5, 8.1), 8.03 (d, 1 H_{arom}, J = 8.1), 8.42 (dd, 1 H, H_7, J = 1.5, 5.2)
3i	24.0	89	50:50	1700	*cis:* 1.15 (t, 3 H, CH_3, J = 6.9), 2.35 (ddd, 1 H, C*H*H, J = 7.7, 8.6, 14.0), 2.63 (ddd, 1 H, CH*H*, J = 2.6, 7.7, 14.0), 3.60–3.75 (m, 1 H, C*H*HCH_3), 3.93 (s, 3 H, NCH_3), 4.06 (s, 3 H, OCH_3), 3.95–4.10 (m, 1 H, CH*H*CH_3), 5.38 (dd, 1 H, CH, J = 2.6, 7.7), 5.72 (dd, 1 H, OCHO, J = 7.7, 8.6), 6.40–6.60 (m, 2 H_{arom}), 6.85–7.40 (m, 8 H_{arom}), 7.93 (dd, 1 H, H_9, J = 1.7, 7.7), 8.43 (dd, 1 H, H_7, J = 1.7, 5.1) *trans* + *cis*: 1.10–1.26 (m, 6 H, 2 × CH_3), 2.20–2.40 (m, 2 H, 2 × C*H*H), 2.45–2.65 (m, 2 H, 2 × C*H*H), 3.55–3.75 (m, 2 H, 2 × C*H*HCH_3), 3.35–4.10 (m, 2 H, 2 × C*H*HCH_3), 3.93 (d, 3 H, NCH_3), 4.00 (s, 3 H, NCH_3), 4.06 (s, 6 H, 2 × OCH_3), 5.30–5.40 (m, 2 H, 2 × CH) 5.65–5.75 (m, 2 H, 2 × OCHO), 6.40–6.60 (m, 4 H_{arom}), 6.85–7.45 (m, 2 × 8 H_{arom}), 7.85–7.95 (m, 2 H, 2 × H_9), 8.40–8.45 (dd, 2 H, 2 × H_7, J = 1.7, 5.1)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.20, N ± 0.25. All compounds were oily products. For Ar in **a–i**, see Scheme 2.
[b] Determined by ^1H NMR spectroscopy.
[c] *cis*-Isomer: MS (CI, NH_3): m/z = 465 ($M^+ + 1$),
[d] *cis*-Isomer: MS (CI, NH_3): m/z = 468 ($M^+ + 1$), 470 ($M^+ + 3$).

Table 3. Compounds **4** Prepared

Product[a]	Reaction Time (h)	Yield (%)	mp[b] (°C)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (CI, NH_3) m/z
4a	1.0	58	264–266	3440–3400	3.87 (s, 3 H, CH_3), 7.11 (d, 2 H_{arom}, J = 8.6), 7.29 (dd, 1 H, H_3, J = 5.2, 6.9), 7.44 (d, 1 H, H_7, J = 5.2), 7.74 (d, 2 H_{arom}, J = 8.6), 8.50–8.60 (m, 3 H, H_6, H_2, H_4), 11.93 (s, 1 H, NH)	276 ($M^+ + 1$)
4b	1.5	58	231–233	3300–3260	7.25 (dd, 1 H, H_3, J = 5.2, 8.1), 7.41 (d, 1 H, H_7, J = 5.2), 7.54 (m, 2 H_{arom}), 7.70 (m, 2 H_{arom}), 8.04 (d, 1 H, H_2, J = 5.2), 8.67 (d, 1 H, H_6, J = 5.2), 8.71 (dd, 1 H, H_4, J = 1.5, 8.1)	280 ($M^+ + 1$)
4c	1.5	67	232–234	3400–3360, 1510, 1340	7.35 (dd, 1 H, H_3, J = 5.2, 7.7), 7.59 (d, 1 H, H_7, J = 5.2), 8.08 (d, 2 H_{arom}, J = 8.6), 8.41 (d, 2 H_{arom}, J = 8.6), 8.57–8.67 (m, 3 H, H_6, H_2, H_4), 12.18 (s, 1 H, NH)	291 ($M^+ + 1$)
4d	1.5	59	210–212	3460–3400	2.49 (s, 3 H, CH_3), 7.25 (dd, 1 H, H_3, J = 5.2, 8.1), 7.40 (d, 2 H_{arom}, J = 8.1), 7.45 (d, 1 H,. H_7, J = 5.2), 7.66 (d, 2 H_{arom}, J = 8.1), 8.19 (d, 1 H, H_2, J = 5.2), 8.67 (d, 1 H, H_6, J = 5.2), 8.72 (dd, 1 H, H_4, J = 1.5, 8.1)	260 ($M^+ + 1$)
4e	1.5	74	206–208	3380–3320	7.20 (dd, 1 H, H_3 J = 5.2, 8.1), 7.50 (d, 1 H, H_7, J = 5.2), 7.53–7.63 (m, 3 H_{arom}), 7.74–7.88 (m, 3 H, 2 H_{arom}, H_2), 8.71 (d, 1 H, H_6, J = 5.2), 8.76 (dd, 1 H, H_4, J = 1.5, 8.1)	246 ($M^+ + 1$)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.20, N ± 0.25. For Ar in **a–e**, see Scheme 2.
[b] Solvent: MeOH/H_2O.
[c] Solvent for ^1H NMR; for **4a, c**: DMSO-d_6; for **4b, d, e**: $CDCl_3$ + D_2O.

(1) Present address: Department of Organic Chemistry, CNT, NOVUM Research Park S-141 57 Huddinge, Sweden
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