EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200364

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Special Collection

Synthesis of Diarylamines and Methylcarbazoles and Formal Total Synthesis of Alkaloids Ellipticine and Olivacine

Edson Barrera,[a] R. Israel Hernández-Benitez,[a] Carlos A. González-González,[b] Carlos H. Escalante,[a] Aydeé Fuentes-Benítes,[b] Carlos González-Romero,[b] Elvia Becerra-Martínez,[c] Francisco Delgado,[a] and Joaquín Tamariz*[a]

New and efficient strategies for the conversion of 4-oxazolin-2-ones into 1-methyl and 1,4-dimethyl 3-formylcarbazoles are herein described. Highly convergent cascade and one-pot processes afforded the corresponding diarylamines, as *in situ* formed synthetic intermediates or final products in high overall yields. Special attention was given to the synthesis of methylated carbazoles by reacting 4,5-dimethyl-4-oxazolin-2-ones with enones under microwave irradiation. The carbazole scaffold was provided by the palladium(II)-catalyzed double C–H activation to generate oxidative cyclization of diarylamines. This methodology allowed for formal total syntheses of four naturally occurring pyrido[4,3-*b*]carbazole alkaloids ellipticine, 9-methoxyellipticine, olivacine, and 9-methoxyolivacine.

Introduction

Carbazoles are a broad family of natural alkaloids that contain a tricyclic dibenzopyrrole scaffold.[1] These aza-heterocycles, isolated from leaves, stem bark and roots of higher plants, are mainly of the genera *Clausena*, *Glycosmis, Micromelum*, and *Murraya*, belonging to the family Rutaceae.[2] For example, oxygenated and methylated tricyclic carbazoles comprise a large group of alkaloids,[1–5] while tetracyclic pyrido[4,3-*b*]carbazoles pertain to a smaller series of natural products. Two representative members of the latter group are ellipticine (**1a**) and 9-methoxyellipticine (**1b**) (Figure 1). They were first isolated from leaves of *Ochrosia elliptica* Labill.,[6] *Ochrosia sandwicensis* A.DC., and *Bleekeria vitiensis* (Markgraf),[7] and other genera of the Apocynaceae family,[8] as well as from the Loganiaceae family.[9] Subsequently, pyrido[4,3-*b*]carbazole analogues 9-hydroxyellipticine (**1c**), 5-formylellipticine (also called 17-oxoellipticine, **1d**), and 12-hydroxyellipticine (also known as 18-oxoellipticine, **1e**) were isolated from the stem bark of *Strychnos dinklagei* Gilg.[10] Olivacine (**2a**), an isomer of **1a**, and its congener 9-methoxyolivacine (**2b**) (Figure 1) were isolated from *Aspidosperma olivaceum* Müll. Arg.,[11] *A. longipetiolatum*,[12] *A. vargasii* A.DC.,[13] and other Apocynaceae genera.[14]

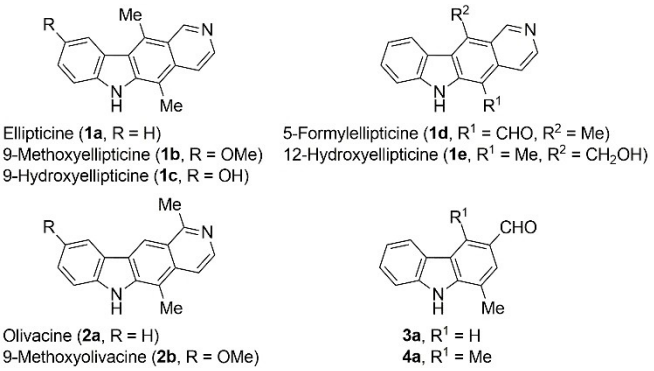


Figure 1. Naturally occurring pyrido[4,3-*b*]carbazoles **1a**-**e** and **2a**-**b**, and synthetic precursors **3a** and **4a**.

Since pyrido[4,3-*b*]carbazoles **1a**–**c** have exhibited potent antitumor activity, a great effort has been made to find related compounds with a better pharmacological profile.[15] As a consequence, various ellipticine-based derivatives have been synthesized and reported. While datelliptium, retelliptine and pazelliptine proved to be promising antitumor agents,[16] elliptinium acetate (celiptium®) and ditercalinium® were introduced as clinically efficient drugs in chemotherapy for the treatment of several types of cancer.[17] Olivacine (**2a**), **2b**, and related pyrido[4,3-*b*]carbazoles have also displayed a strong anticancer effect.[15d,18]

Given the importance of **1a** and **2a** and analogous pyrido[4,3-*b*]carbazoles, diverse synthetic approaches have been developed.[1c,2,8a,17c,19] A particularly attractive strategy is

[a] *E. Barrera, Dr. R. I. Hernández-Benitez, Dr. C. H. Escalante, Prof. Dr. F. Delgado, Prof. Dr. J. Tamariz*
Departamento de Química Orgánica
Escuela Nacional de Ciencias Biológicas
Instituto Politécnico Nacional
Prol. Carpio y Plan de Ayala S/N, 11340 Mexico City, Mexico
E-mail: jtamarizm@gmail.com
jtamarizm@ipn.mx
https://www.encb.ipn.mx
[b] *Dr. C. A. González-González, Prof. Dr. A. Fuentes-Benítes, Prof. Dr. C. González-Romero*
Departamento de Química Orgánica
Facultad de Química
Universidad Autónoma del Estado de México
Paseo Colón/Paseo Tollocan S/N, 50000 Toluca, Estado de México, Mexico
[c] *Dr. E. Becerra-Martínez*
Centro de Nanociencias y Micro y Nanotecnologías (CNMN)
Instituto Politécnico Nacional
Av. Luis Enrique Erro S/N, Unidad Profesional Adolfo López Mateos, Ciudad de México, Zacatenco, 07738 Mexico City, Mexico

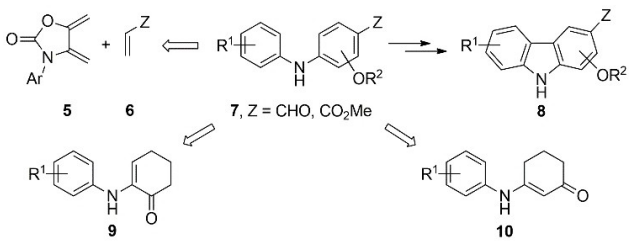
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200364

Special Collection *Part of the "Organic and Supramolecular Chemistry in Latin America" Special Collection.*

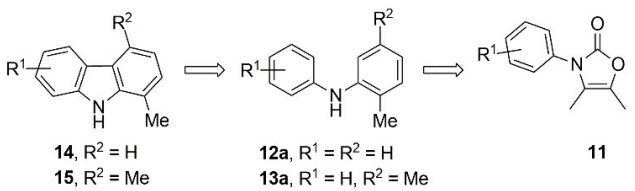
the conversion of 3-formylcarbazole **4a** (Figure 1) into **1a** by utilizing the Cranwell-Saxton methodology and its related optimized protocols.[20] It consists of a condensation of the formyl group of **4a** with 2,2-diethoxyethylamine to generate the imine, followed by hydrogenation, to produce the secondary amine. The latter undergoes an acid-catalyzed cyclization to form the dihydropyridine ring, and then palladium-catalyzed dehydrogenation to give the corresponding tetracyclic carbazole **1a**. Similar and non-selective routes have been reported for the elaboration of **2a** from **3a** and its *N*-benzyl derivative.[20c,21]

Among the diverse methods described for preparing the carbazole scaffold,[1,2] the palladium-catalyzed diarylamine intramolecular coupling has been an efficient and versatile procedure.[19d,22] Its broad usage included the synthesis of precursors of pyrido[4,3-*b*]carbazoles.[19d,g] Based on this strategy, our group previously developed a novel approach for the synthesis of diarylamines **7** through a regioselective Diels-Alder cycloaddition of 2-oxazolidinone-grafted exocyclic dienes **5**,[23] which were employed in the total synthesis of several natural carbazoles **8** (Scheme 1).[24] Other routes for obtaining the polysubstituted diarylamines **7** and converting them into naturally occurring 1- and 2-oxygenated carbazoles started from captodative enamines 2-anilinocyclohexenones **9**[25] and *push-pull* 3-anilinocyclohexene enaminones **10**.[26]

The preliminary results showed that 4-oxazolin-2-ones **11** are versatile building blocks for the construction of polycyclic structures such as diarylamines **12a** ($R^1 = H$) and **13a** ($R^1 = H$) (Scheme 2).[27] Owing to the synthetic potential of this finding and to gain insights into the scope of the strategy, the conditions were herein optimized. Moreover, new approaches are described for the straightforward preparation of methylated diarylamines, **12** and **13**, and their conversion into 1-methyl



Scheme 1. Previously reported syntheses of diarylamines **7** and their conversion into carbazoles **8**, starting from dienes **5**, captodative enamines **9**, and *push-pull* enaminones **10**.



Scheme 2. Synthesis of methylated diarylamines **12a** and **13a** from 4-oxazoline-2-ones **11**, and their conversion into 1-methyl (**14**) and 1,4-dimethyl (**15**) carbazoles.

(**14**) and 1,4-dimethyl (**15**) carbazoles, which are plausible precursors for the formal total synthesis of olivacine (**2a**) and ellipticine (**1a**), respectively, and some of their substituted analogues.

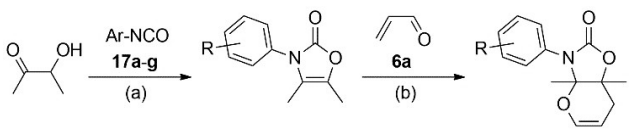
Results and Discussion

The preparation of 4-oxazolin-2-ones **11a–g** was carried out by a solvent-free condensation of acetoin (**16**) with the series of aryl isocyanates **17a–g** under microwave (MW) irradiation,[27] providing the expected products **11a–g** in high yields (Table 1). The latter compounds reacted with acrolein (**6a**) under MW irradiation to furnish the 3-aryl-3a,7a-dimethyl-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **18a–g** in good yields (Table 1). Based on DFT calculations,[28] this process appears to take place through a concerted hetero-Diels-Alder cycloaddition, which was highly efficient and regioselective regardless of the electronic effect of the functional group or its position in the aryl ring. This is probably due to the quasi-orthogonal conformation of the aromatic ring attached to the nitrogen atom with respect to the 4-oxazolidin-2-one ring (as established by X-ray diffraction of derivative **11c**[29] and analogous heterocycles[23a,29,30]), thus avoiding the perturbance of the electronic density of the endocyclic double bond.

The synthesis of bicyclic dienes **19a–g** was carried out by reacting 4-oxazolin-2-ones **11a–g** with acrolein (**6a**) in the presence of methyl iodide, under conventional heating or MW irradiation, as reported for **19a**.[27] The yields of compounds **19a–g** were rather modest with either energy source (Table 2).

According to the most recent report,[28] the first step of the reaction mechanism for this transformation involves the formation of the corresponding bicyclic tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **18**, followed by the opening of the hemiaminal moiety to provide intermediates **20**. The latter undergo cyclization to species **21** and then dehydration, resulting in the observed products **19** (Scheme 3). It is likely

Table 1. Synthesis of **11a–g** and their conversion into bicyclic tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **18a–g**.[a]

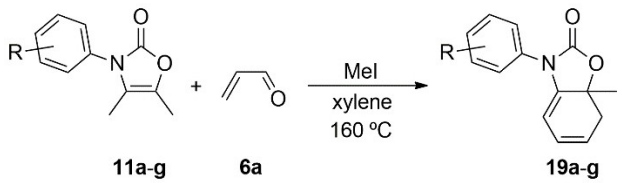


Entry	17	R	Product	Yield [%][b]	Product	Yield [%][b]
1	**17a**	H	**11a**	95[c]	**18a**	93
2	**17b**	3-Me	**11b**	94[d]	**18b**	88
3	**17c**	4-Me	**11c**	88[d]	**18c**	93
4	**17d**	3-OMe	**11d**	95[d]	**18d**	89
5	**17e**	4-OMe	**11e**	92[d]	**18e**	92
6	**17f**	3,4-$(OMe)_2$	**11f**	76[d]	**18f**	87
7	**17g**	4-Cl	**11g**	84[d]	**18g**	56

[a] Standard conditions: Step (a): **17a–g** (1.1–1.5 mol equiv); Method A: 130–140 °C, 24–48 h; Method B: MW (100–150 W), 120–150 °C, 1.5-4.0 h. Step (b): **6a** (2.0 mol equiv), MW (100 W), 80 °C, 5 h. [b] Isolated yields. [c] Methods A and B. [d] Method B.

Research Article
doi.org/10.1002/ejoc.202200364

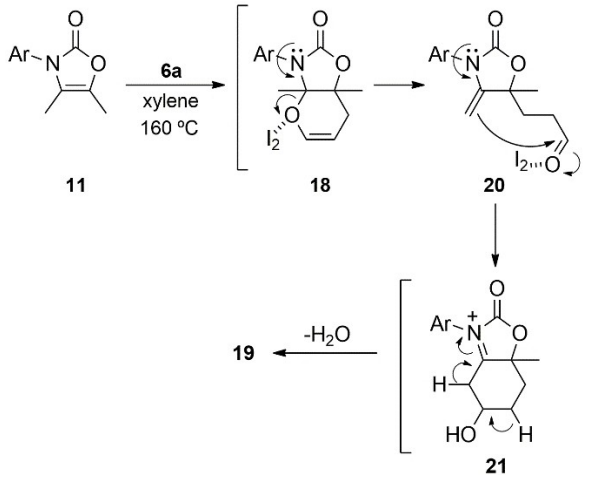
Table 2. Synthesis of **19a–g** by an MeI-promoted thermal reaction of **11a–g** with **6a**.[a]



11a-g **6a** **19a-g**

Entry	11	R	Method	Product	Yield [%][b]
1	**11a**	H	A	**19a**	43
2	**11a**	H	B	**19a**	53
3	**11b**	3-Me	B	**19b**	46
4	**11c**	4-Me	A	**19c**	45
5	**11c**	4-Me	B	**19c**	61
6	**11d**	3-OMe	B	**19d**	52
7	**11e**	4-OMe	B	**19e**	51
8	**11f**	3,4-$(OMe)_2$	B	**19f**	63
9	**11g**	4-Cl	A	**19g**	40
10	**11g**	4-Cl	B	**19g**	40

[a] Method A: **6a** (5.0 mol equiv) and MeI (2.0 mol equiv), in xylene, 160 °C, 48 h. Method B: **6a** (5.0 mol equiv) and MeI (2.0 mol equiv), in xylene, MW (200 W), 160 °C, 3 h. [b] Isolated yields.



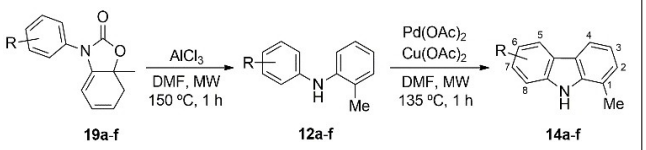
Scheme 3. Reaction mechanism for the transformation of compounds **11** into dienes **19**.

that the generation of iodine species (from methyl iodide) promotes the last steps.[27]

The cyclic carbamate moiety of dienes **19a–f** was efficiently hydrolyzed and aromatized by subjecting $AlCl_3$ in anhydrous DMF to MW irradiation at 150 °C for 1 h, affording diarylamines **12a–f** in quantitative yields (Table 3, step a). These compounds were cyclized to the corresponding 1-methylcarbazoles **14a–f** by a palladium(II)-catalyzed coupling through a double C–H activation under the previously described conditions.[26b] The latter series was obtained in good yields (Table 3, step b).

Considering the need to introduce a formyl group in the C-3 position of the carbazole precursors **3a** and **4b**, bicyclic dienes **19a**, **19c–e**, and **19g** were submitted to Vilsmeier-Haack conditions, which led to 6-formyl-7a-methyl-7,7a-dihydrobenzo[*d*]oxazol-2-(3*H*)-ones **22a**, **22c–e**, and **22g** in high yields (Table 4).

Table 3. Synthesis of **12a–f** and their conversion into 1-methylcarbazoles **14a–f**.[a]



19a-f **12a-f** **14a-f**

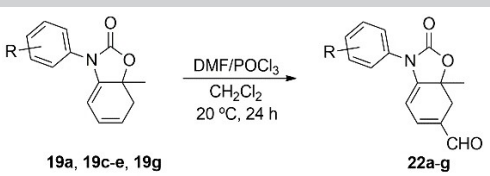
Entry	19	R	Product	Yield [%][b]	Product	Yield [%][b]
1	**19a**	H	**12a**	98	**14a**	72
2	**19b**	3-Me	**12b**	98	**14b**	74
3	**19c**	4-Me	**12c**	98	**14c**	76
4	**19d**	3-OMe	**12d**	98	**14d**	80
5	**19e**	4-OMe	**12e**	98	**14e**	66
6	**19f**	3,4-$(OMe)_2$	**12f**	97	**14f**	96

[a] Standard conditions: Step (a): $AlCl_3$ (1.5 mol equiv), DMF, MW (100 W), 150 °C, 1 h. Step (b): $Pd(OAc)_2$ (0.3 mol equiv), $Cu(OAc)_2$ (2.5 mol equiv), DMF, MW (100 W), 135 °C, 1 h. [b] Isolated yields.

Despite these satisfactory results, the synthesis of dienes **19a–g** gave only modest yields. Hence, the direct conversion of bicyclic tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **18a–g** into the corresponding formylated dienes **22a–g** was explored through a cascade process, which may involve the *in situ* formation of the respective dienes **19** before formylation takes place (Table 5). The overall yields of the two steps (starting from **11a–g**) were better with the inclusion of pyrans **18a–g** (48–82%) than with dienes **19** (32–49%).

Following the same methodology utilized for preparing diarylamines **12a–f** and 1-methylcarbazoles **14a–f** (Table 3), diene **22a** can be transformed to diarylamine **23a**. Thus, the use of $AlCl_3$ in anhydrous DMF under MW irradiation at 130–160 °C for 30–60 min was also an efficient method for generating **23a** in moderate to good yields (48–80%). However, the procedure was not reproducible when applying it to the other dienes **22**. Hence, decarboxylation/aromatization was attempted through a basic hydrolysis of the cyclic carbamate moiety.[23b] Accordingly, the treatment of **22a** with NaOH in a mixture of MeOH/H_2O (5:1) at a range of 80–120 °C furnished

Table 4. Synthesis of **22a–g** starting from **19a**, **19c–e** and **19g** under Vilsmeier-Haack conditions.[a]

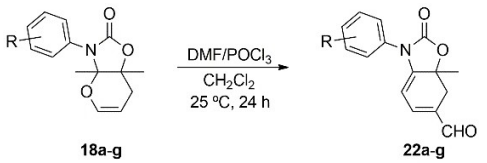


19a, **19c-e**, **19g** **22a-g**

Entry	Substrate	R	Product	Yield [%][b]
1	**19a**	H	**22a**	60
2	**19c**	4-Me	**22c**	71
3	**19d**	3-OMe	**22d**	95
4	**19e**	4-OMe	**22e**	83
5	**19g**	4-Cl	**22g**	97

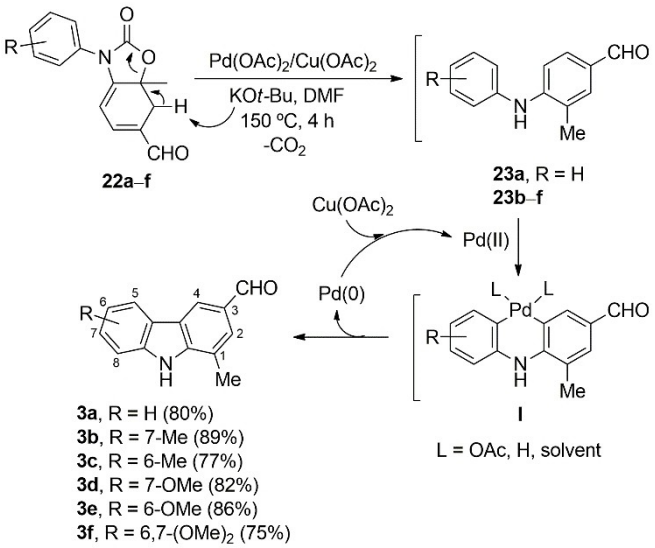
[a] DMF (1.2 mol equiv) and $POCl_3$ (1.3 mol equiv) in CH_2Cl_2, 20 °C, 24 h. [b] Isolated yields.

Table 5. Synthesis of **22a–g** starting from **18a–g** under Vilsmeier-Haack conditions.[a]



Entry	Substrate	R	Product	Yield [%][b]
1	**18a**	H	**22a**	80
2	**18b**	3-Me	**22b**	87
3	**18c**	4-Me	**22c**	80
4	**18d**	3-OMe	**22d**	92
5	**18e**	4-OMe	**22e**	85
6	**18f**	3,4-$(OMe)_2$	**22f**	83
7	**18g**	4-Cl	**22g**	85

[a] DMF (2.0 mol equiv) and $POCl_3$ (2.1 mol equiv) in CH_2Cl_2, 25 °C, 12–24 h. [b] Isolated yields.



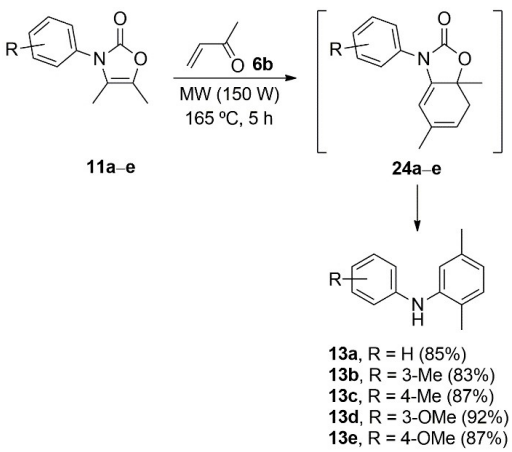
Scheme 4. A *t*-BuOK-promoted decarboxylation/aromatization cascade reaction and Pd(II)-catalyzed coupling synthesis of 3-formyl-1-methylcarbazoles **3a–f** starting from **22a–f**.

23a in low yield, with the recovery of most of the starting material. The formyl group was affected at higher temperatures, leading to an unsatisfactory conversion.

Consequently, a completely different approach was investigated, taking into account that diarylamine **23a** has to be coupled under Pd(II) catalysis to afford 3-formylcarbazole **3a**.[24,26] To this end, diene **22a** was exposed to catalytic amounts (0.1–0.3 mol equiv) of $Pd(OAc)_2$ with an excess of $Cu(OAc)_2$ (2.0–5.0 mol equiv) in DMF, while tuning the reaction medium with distinct bases (NaOH, K_2CO_3, and *t*-BuOK) and acids ($AlCl_3$, AcOH, and pivalic acid), under thermal conditions (110–150 °C). The optimized conditions, consisting of $Pd(OAc)_2$ (0.3 mol equiv), $Cu(OAc)_2$ (2.0 mol equiv), and *t*-BuOK (2.0 mol equiv) in DMF at 150 °C for 4 h, not only provided **3a** from **22a**, but also 3-formyl-1-methylcarbazoles **3b–f** from the series of 6-formyl-7a-methyl-7,7a-dihydrobenzo[*d*]oxazol-2-(3*H*)-ones **22b–f** in high yields (Scheme 4). These transformations probably occurred by means of a decarboxylation/aromatization cascade process, evidenced by the presence of diarylamines **23a–f**, which were detected in the ^1H NMR spectra of the crude mixtures. The decarboxylation reaction was satisfactorily achieved by the *t*-BuOK-promoted elimination of one of the H-7 protons of the starting materials **22a–f**. A high temperature (150 °C) was required, as the reaction was largely incomplete with lower temperatures. In the presence of acids, low yields were obtained. Once the diarylamine **23** was formed, the Pd(II)-catalyzed C–H activation of both aryl rings took place by pursuing the coupling through palladacycle **I**,[31] which underwent reductive elimination to give carbazoles **3a–f** along with Pd(0). The latter was oxidized by $Cu(OAc)_2$ to regenerate the active Pd(II) catalyst species, thus restarting the catalytic cycle. Interestingly, carbazoles **3a** and **3e** can be considered as potential precursors of olivacine (**2a**) and 9-methoxyolivacine (**2b**),[21,32] respectively. Therefore, this approach represents a formal total synthesis of the two latter natural pyrido[4,3-*b*]carbazoles.

Regarding the synthesis of 1,4-dimethylcarbazoles **15**, the first approach in the search for an optimal strategy was to follow a route like the one developed for the 1-methylcarbazoles **14**. Due to the difficulty of directly obtaining the bicyclic dihydropyrans through the hetero-Diels-Alder reaction between 4-oxazolin-2-ones **11** and methyl vinyl ketone (**6b**),[27] the thermal reaction of these substrates was attempted. Accordingly, MW irradiation of 4-oxazolin-2-ones **11a–e** with **6b** resulted in diarylamines **13a–e** in high yields (Scheme 5). Remarkably, the latter were generated in a solvent-free single step without isolation of the diene precursors **24a–e**, which are normally isolated by heating at 160 °C for 24 h and found as a by-product along with the Michael conjugate addition product.[27] The unexpected outcome suggests that an MW effect[33] is involved.

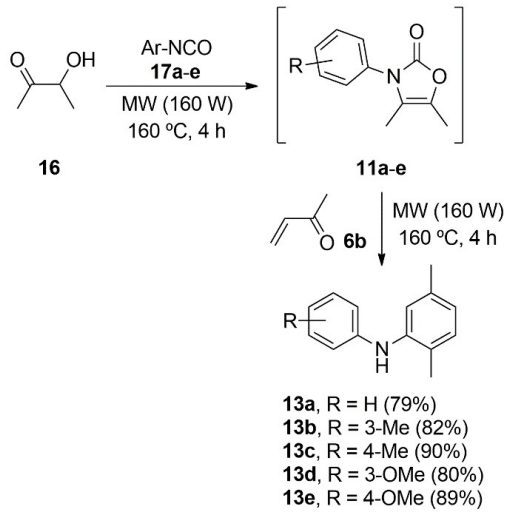
Yet another approach was explored, being a solvent-free one-pot three-step reaction involving the *in situ* formation not



Scheme 5. A cascade synthesis of diarylamines **13a–e** starting from **11a–e** and **6b**.

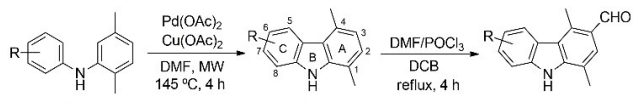
only of dienes **24**, but also of their precursors 4-oxazolin-2-ones **11**, the latter of which react with **6b** to deliver the corresponding diarylamines **13**. Thus, the reaction conditions shown in step (a) of Table 1 were applied, leading to the condensation of acetoin (**16**) with aryl isocyanates **17a–e** under MW irradiation to the *in situ* generation of **11a–e**. Subsequently, in a second step, the addition of **6b** gave rise to diarylamines **13a–e** in high overall yields (Scheme 6).

In contrast to the oxidative cyclization of monomethylated diarylamines **12a–f** to furnish carbazoles **14a–f** in good yields (Table 3), the Pd(II)-catalyzed coupling of the diarylamines **13a–e** was carried out under more severe conditions to provide 1,4-dimethylcarbazoles **15a–e** in lower yields (Table 6). This is probable because the steric hindrance of the methyl groups slows down the generation of the six-membered palladacycle between the two benzene rings, which is the key intermediate species prior to the formation of the diaryl C–C bond.[31] The latter process has been greatly improved by the use of pivalic acid,[34] allowing for the total synthesis of natural carbazole alkaloids,[35] including the efficient total synthesis of clausenal.[26b] However, the current application of the same process did not lead to any boost in yield.



Scheme 6. A one-pot cascade synthesis of diarylamines **13a–e** starting from **16** and isocyanates **17a–e**, followed by the addition of **6b**.

Table 6. Synthesis of 1,4-dimethylcarbazoles **15a–e**, and the conversion of **15a** and **15c** into 3-formyl-1,4-dimethylcarbazoles **4a–b**.[a]



Entry	13	R	Product	R	Yield [%][b]	Product	Yield [%][b]
1	**13a**	H	**15a**	H	68	**4a**	75
2	**13b**	3-Me	**15b**	7-Me	62	[c]	–
3	**13c**	4-Me	**15c**	6-Me	63	**4b**	76
4	**13d**	3-OMe	**15d**	7-OMe	59	[c]	–
5	**13e**	4-OMe	**15e**	6-OMe	56	**4c**	[d]

[a] Standard conditions: Step (a): $Pd(OAc)_2$ (0.3 mol equiv) and $Cu(OAc)_2$ (2.0–2.5 mol equiv), DMF, MW (130 W), 145 °C, 4 h. Step (b): $POCl_3$ (1.5 mol equiv) and DMF (1.0 mol equiv), DCB, reflux, 4 h. [b] Isolated yields. [c] A complex mixture of products. [d] See references[19f,20b,39].

Formylation of **15a–e** was not readily accomplished,[19d,20b,21b,36] because of the many activated positions on the carbazole structure that can react with the Vilsmeier-Haack formylation species.[37] Although the major products were the desired compounds **4a–b** with the formyl group at the C-3 position (Table 6), the *N*-formyl carbazole was also found as a minor by-product. With the use of *o*-dichlorobenzene (DCB) as the solvent, the yields increased.[36c,38] A more complex mixture of products was observed when **15b** and **15d** were formylated, owing itself to the activation of more sites at the C-ring by the electron-donating effect of the methyl and a methoxy group, respectively, at the C-7 carbon atom of the carbazole scaffold. For example, the formylation reaction of **15d** is known to afford a mixture of the 6- and 8-carbaldehyde derivatives.[20b,39]

This approach represents a new formal total synthesis of ellipticine (**1a**) through a short three-step process for the efficient preparation of its known precursor carbazole **4a**.[20] Seemingly, it also constitutes a formal total synthesis of natural 9-methoxyellipticine (**1b**), since carbazole **15e** has been previously employed as an efficient starting material during the last steps of the process, including **4c** as an intermediate.[19f,20b,39,40]

All the structures of intermediates and products of these synthetic pathways were characterized by ^1H and ^{13}C NMR spectroscopy, assisted by 2D (HSQC and HMBC) experiments, and high-resolution mass spectrometry (HRMS).

Conclusion

An efficient synthetic route to 1-methyl and 1,4-dimethyl-3-formylcarbazoles is herein described. It includes the preparation of the precursors of naturally occurring pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), olivacine (**2a**), and 9-methoxyolivacine (**2b**). The present strategy, consisting of novel, short, and simple synthetic routes, demonstrated a wide scope of application. That is, 4-oxazolin-2-ones **11** underwent a three-step conversion to both series of 1-methyl and 1,4-dimethyl-3-formylcarbazoles **3** and **4**. Many reactions were carried out under solvent-free conditions, and MW irradiation was involved in numerous processes, proving to be a very efficient energy source. Hence, this is a valuable alternative to the Cranwell-Saxton approach for the construction of the A-ring of methyl substituted carbazoles. Particularly noteworthy is the cascade transformation of dienes **22a–f** into 1-methyl-3-formylcarbazoles **3a–f**, as well as the one-step conversion of acetoin (**16**) and aryl isocyanates **17a–e** into the corresponding diarylamines **13a–e**. These findings confirm that diarylamines are efficient precursors for the synthesis of carbazoles and for the formal total synthesis of pyrido[4,3-*b*]carbazole alkaloids.

Experimental Section

Method A: In a threaded ACE glass pressure tube equipped with a magnetic stirring bar and sealed with a Teflon screw cap, a mixture of **16** (0.500 g, 5.68 mmol) and **17 a** (1.014 g, 8.52 mmol) was heated at 130 °C for 24 h under nitrogen atmosphere. Afterwards, CH_2Cl_2 (20 mL) was added, and the mixture was stirred at 20 °C for 30 min, before being filtered. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (hexane/EtOAc, 95 : 5) to give **11 a** (1.02 g, 95 %) as a white solid.

Method B: In a glass vial equipped with a magnetic stirring bar and sealed with a cap, a mixture of **16** (0.500 g, 5.68 mmol) and **17 a** (1.014 g, 8.52 mmol) was heated with MW irradiation (150 W) at 120 °C for 1.5 h under nitrogen atmosphere. Subsequently, CH_2Cl_2 (20 mL) was added, and the mixture was stirred at 20 °C for 30 min before being filtered. The solvent was removed under vacuum and the residue purified by column chromatography (silica gel, hexane/EtOAc, 98 : 2) to furnish **11 a** (1.04 g, 95 %) as a white solid.

More general experimental procedures for the synthesis of all compounds, characterization, and NMR spectra are described in the Supporting Information.

Acknowledgements

We thank Brenda Reyes and Ailyn N. García for their assistance in the experimental section, and Bruce A. Larsen for proofreading. J.T. and F.D. acknowledge the SIP/IPN (grants 20200227, 20210700, 20221003, and 20220900) and CONACYT (grants 282033, A1-S-17131 and 300520), and A.F.-B. and C.G.-R. are grateful to the Secretaría de Investigación y Estudios Avanzados/UAEMex (grant 4512/2018/CI) for financial support. E.B., R.I.H.-B., and C.A.G.-G. are beholden to the CONACYT for graduate scholarships awarded, and the SIP/IPN (BEIFI) for scholarship complements. C.H.E. gratefully acknowledges the CONACYT (grant A1-S-17131) and Ludwig K. Hellweg Foundation for postdoctoral fellowships. E.B.-M. thanks the NMR Laboratory of the CNMN-IPN for the availability of the spectrometers. F.D. and J.T. are fellows of the EDI-IPN and COFAA-IPN programs.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ellipticine · Methylcarbazoles · Microwave chemistry · 4-Oxazolin-2-ones · Palladium

[1] a) U. Pindur, *Chimia* **1990**, *44*, 406–412; b) H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427; c) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193–3328.

[2] H.-J. Knölker, K. R. Reddy, *Chemistry and Biology of Carbazole Alkaloids, in The Alkaloids Chemistry and Biology* (Ed: G. A. Cordell), Academic Press, Amsterdam, **2008**, Vol. 65.

[3] a) D. P. Chakraborty, *Planta Med.* **1980**, *39*, 97–111; b) P. Bhattacharyya, A. Chakraborty, *Phytochemistry* **1984**, *23*, 471–472; c) N. Ruangrungsi, J. Ariyaprayoon, G. L. Lange, M. G. Organ, *J. Nat. Prod.* **1990**, *53*, 946–952; d) P. Bhattacharyya, A. K. Maiti, K. Basu, B. K. Chowdhury, *Phytochemistry* **1994**, *35*, 1085–1086.

[4] C. Ito, S. Katsuno, M. Itoigawa, N. Ruangrungsi, T. Mukainaka, M. Okuda, Y. Kitagawa, H. Tokuda, H. Nishino, H. Furukawa, *J. Nat. Prod.* **2000**, *63*, 125–128.

[5] P. K. Teja, P. Patel, D. Bhavsar, C. Bindusri, K. Jadhav, S. K. Chauthe, *Phytochemistry* **2021**, *190*, 112865.

[6] S. Goodwin, A. F. Smith, E. C. Horning, *J. Am. Chem. Soc.* **1959**, *81*, 1903–1908.

[7] K. N. Kilminster, M. Sainsbury, B. Webb, *Phytochemistry* **1972**, *11*, 389–392.

[8] a) R. B. Woodward, G. A. Iacobucci, F. A. Hochstein, *J. Am. Chem. Soc.* **1959**, *81*, 4434–4435; b) G. H. Svoboda, G. A. Poore, M. L. Montfort, *J. Pharm. Sci.* **1968**, *57*, 1720–1725; c) A. Ahond, H. Fernandez, M. Julia-Moore, C. Poupat, V. Sánchez, P. Portier, S. K. Kan, T. Sévenet, *J. Nat. Prod.* **1981**, *44*, 193–199; d) Y.-M. Lin, M. Juichi, R, -Y. Wu, K.-H. Lee, *Planta Med.* **1985**, 545–546.

[9] S. Michel, F. Tillequin, M. Koch, *J. Nat. Prod.* **1980**, *43*, 294–295.

[10] S. Michel, F. Tillequin, M. Koch, *J. Nat. Prod.* **1982**, *45*, 489–494.

[11] J. Schmutz, F. Hunziker, *Pharm. Acta Helv.* **1958**, *33*, 341–347.

[12] G. B. Marini-Bettolo, P. Carvalho-Ferreira, *Ann. Chim.* **1959**, *49*, 869–876.

[13] R. H. Burnell, D. D. Casa, *Can. J. Chem.* **1967**, *45*, 89–92.

[14] a) M. A. Ondetti, V. Deulofeu, *Tetrahedron Lett.* **1959**, 1–4; b) M. Gorman, N. Neuss, N. J. Cone, J. A. Deyrup, *J. Am. Chem. Soc.* **1960**, *82*, 1142–1145; c) M. A. Ondetti, V. Deulofeu, *Tetrahedron* **1961**, *15*,160–166.

[15] a) M. Stiborová, C. A. Bieler, M. Wiessler, E. Frei, *Biochem. Pharmacol.* **2001**, *62*, 1675–1684; b) M. Stiborová, J. Sejbal, L. Bořek-Dohalská, D. Aimová, J. Poljaková, K. Forsterová, M. Rupertová, J. Wiesner, J. Hudeček, M. Wiessler, E. Frei, *Cancer Res.* **2004**, *64*, 8374–8380; c) M. G. Ferlin, C. Marzano, V. Gandin, S. Dall'Acqua, L. D. Via, *ChemMedChem* **2009**, *4*, 363–377; d) E. C. O'Sullivan, C. M. Miller, F. M. Deane, F. O. McCarthy, *Emerging Targets in the Bioactivity of Ellipticines and Derivatives, in: Studies in Natural Products Chemistry* (Ed: Atta-ur-Rahman), Elsevier, Oxford, **2013**, Vol. 39, Ch. 6, pp. 189–232.

[16] a) C. Auclair, A. Pierre, E. Voisin, O. Pepin, S. Cros, C. Colas, J.-M. Saucier, B. Verschuere, P. Gros, C. Paoletti, *Cancer Res.* **1987**, *47*, 6254–6261; b) V. Pierson, A. Pierre, Y. Pommier, P. Gros, *Cancer Res.* **1988**, *48*, 1404–1409; c) G. W. Gribble, *Synthesis and Antitumor Activity of Ellipticine Alkaloids and Related Compounds, in The Alkaloids* (Ed: A. Brossi), Academic Press, New York, **1990**, Vol. 39, Ch 7, pp. 239–352; d) T. Alqahtani, A. Alswied, D. Sun, *Cancers* **2021**, *13*, 3288; e) N. Nader, E. Sotelo, *Chem. Pharm. Bull.* **2002**, *50*, 1479–1483.

[17] a) A. Clarysse, A. Brugarolas, P. Siegenthaler, R. Abele, F. Cavalli, R. de Jager, G. Renard, M. Rozencweig, H. H. Hansen, *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 243–247; b) M. Suffness, G. A. Cordell, *Antitumor Alkaloids, in The Alkaloids: Chemistry and Pharmacology* (Ed: A. Brossi), Academic Press, New York, **1985**, Vol. 25; c) T. K. Chaitanya, R. Nagarajan, *Org. Biomol. Chem.* **2011**, *9*, 4662–4670; d) T. Itoh, N. Hatae, T. Nishiyama, T. Choshi, S. Hibino, T. Yoshimura, M. Ishikura, *Med. Chem. Res.* **2018**, *27*, 412–419.

[18] a) C. Guillonneau, A. Nault, E. Raimbaud, S. Leonce, L. K. Berther, S. Goldstein, *Bioorg. Med. Chem.* **2005**, *13*, 175–184; b) B. Tylińska, B. Wiatrak, *Biology* **2021**, *10*, 564.

[19] a) R. B. Miller, J. G. Stowell, *J. Org. Chem.* **1983**, *48*, 886–888; b) V. K. Kansal, P. Potier, *Tetrahedron* **1986**, *42*, 2389–2408; c) S. Hibino, E. Sugino, *J. Heterocycl. Chem.* **1990**, *27*, 1751–1755; d) R. J. Hall, J. Marchant, A. M. F. Oliveira-Campos, M.-J. R. P. Queiroz, P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3439–3450; e) C. M. Miller, F. O. McCarthy, *RSC Adv.* **2012**, *2*, 8883–8918; f) M. Ibrahim-Ouali, F. Dumur, *Arkivoc* **2018**, *2018*, 216–243; g) U. Schmidt, G. Theumer, A. Jäger, O. Kataeva, B. Wan, S. G. Franzblau, H.-J. Knölker, *Molecules* **2018**, *23*, 1402; h) Ö. Dilek, S. Patir, T. Tilki, E. Ertürk, *J. Org. Chem.* **2019**, *84*, 7901–7916.

[20] a) P. A. Cranwell, J. E. Saxton, *J. Am. Chem. Soc.* **1962**, *84*, 3482–3487; b) A. H. Jackson, P. R. Jenkins, P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1698–1704; c) Y. Murakami, Y. Yokoyama, N. Okuyama, *Tetrahedron Lett.* **1983**, *24*, 2189–2192; d) A. G. Mustafin, I. N. Khalilov, R. R. Ismagilov, Z. M. Baimetov, L. V. Spirikhin, I. B. Abdrakhmanov, G. A. Tolstikov, *Russ. Chem. Bull.* **1999**, *48*, 2121–2126; e) M. Dračínský, J. Sejbal, B. Rygerová, M. Stiborová, *Tetrahedron Lett.* **2007**, *48*, 6893–6895;

f) H.-Y. Lee, G. S. Chen, C.-S. Chen, J.-W. Chern, *J. Heterocycl. Chem.* **2010**, *47*, 454–458; g) T. Konakahara, Y. B. Kiran, Y. Okuno, R. Ikeda, N. Sakai, *Tetrahedron Lett.* **2010**, *51*, 2335–2338.

[21] a) N. S. Narsimhan, S. M. Gokhale, *J. Chem. Soc. Chem. Commun.* **1985**, 86–87; b) Y. Yokoyama, N. Okuyama, S. Iwadate, T. Momoi, Y. Murakami, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1319–1329; c) I. Hogan, P. D. Jenkins, M. Sainsbury, *Tetrahedron* **1990**, *46*, 2943–2964.

[22] a) H.-J. Knölker, *Top. Curr. Chem.* **2005**, *244*, 115–148; b) H.-J. Knölker, *Chem. Lett.* **2009**, *38*, 8–13; c) K. A. Kumar, P. Kannaboina, D. K. Dhaked, R. A. Vishwakarma, P. V. Bharatam, P. Das, *Org. Biomol. Chem.* **2015**, *13*, 1481–1491; d) L. Wen, L. Tang, Y. Yang, Z. Zha, Z. Wang, *Org. Lett.* **2016**, *18*, 1278–1281.

[23] a) A. B. Mandal, A. Gómez, G. Trujillo, F. Méndez, H. A. Jiménez, M. J. Rosales, R. Martínez, F. Delgado, J. Tamariz, *J. Org. Chem.* **1997**, *62*, 4105–4115; b) A. B. Mandal, F. Delgado, J. Tamariz, *Synlett* **1998**, 87–89.

[24] a) R. Bautista, P. Bernal, L. E. Montiel, F. Delgado, J. Tamariz, *Synthesis* **2011**, 929–933; b) R. Bautista, A. Benavides, H. A. Jiménez-Vázquez, J. Tamariz, *Nat. Prod. Res.* **2013**, *27*, 1749–1757, and references cited therein; c) J. L. Avila-Melo, A. Benavides, A. Fuentes-Gutiérrez, J. Tamariz, H. A. Jiménez-Vázquez, *Synthesis* **2021**, *53*, 2201–2211.

[25] R. Bautista, A. V. Jerezano, J. Tamariz, *Synthesis* **2012**, *44*, 3327–3336.

[26] a) R. Bautista, P. A. Montoya, A. Rebollar, E. Burgueño, J. Tamariz, *Molecules* **2013**, *18*, 10334–10351; b) R. I. Hernández-Benitez, D. Zárate-Zárate, F. Delgado, J. Tamariz, *Synthesis* **2017**, *49*, 4357–4371.

[27] B. M. Santoyo, C. González-Romero, O. Merino, R. Martínez-Palou, A. Fuentes-Benites, H. A. Jiménez-Vázquez, F. Delgado, J. Tamariz, *Eur. J. Org. Chem.* **2009**, 2505–2518.

[28] B. M. Santoyo, C. González-Romero, D. Zárate-Zárate, R. I. Hernández-Benitez, V. Pelayo, E. Barrera, C. H. Escalante, A. Fuentes-Benites, G. Martínez-Morales, J. López, M. A. Vázquez, F. Delgado, H. A. Jiménez-Vázquez, J. Tamariz, *Chirality* **2019**, *31*, 719–749.

[29] R. Martínez, H. A. Jiménez-Vázquez, J. Tamariz, *Tetrahedron* **2000**, *56*, 3857–3866.

[30] C. González-Romero, R. Martínez-Palou, H. A. Jiménez-Vázquez, A. Fuentes, F. Jiménez, J. Tamariz, *Heterocycles* **2007**, *71*, 305–322.

[31] a) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer, H.-J. Knölker, *Chem. Eur. J.* **2012**, *18*, 770–776; b) T. Gensch, N. Richter, G. Theumer, O. Kataeva, H.-J. Knölker, *Chem. Eur. J.* **2016**, *22*, 11186–11190.

[32] J. Gilbert, D. Rousselle, C. Gansser, C. Viel, *J. Heterocycl. Chem.* **1979**, *16*, 7–11.

[33] a) L. Perreux, A. Loupy, *Nonthermal Effects of Microwaves in Organic Synthesis, in Microwaves in Organic Synthesis* (Ed: A. Loupy), Wiley-VCH, Weinheim, **2002**, Ch 3, pp. 61–114; b) R. Martínez-Palou, *J. Mex. Chem. Soc.* **2007**, *51*, 252–264; c) C. O. Kappe, *Chem. Soc. Rev.* **2008**, *37*, 1127–1139; d) A. M. Rodríguez, P. Prieto, A. de la Hoz, A, Díaz-Ortiz, D. R. Martín, J. I. García, *ChemistryOpen* **2015**, *4*, 308–317; e) S. Horikoshi, T. Watanabe, A. Narita, Y. Suzuki, N. Serpone, *Sci. Rep.* **2018**, *8*, 5151–5161.

[34] B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022–5028.

[35] a) C. Börger, H.-J. Knölker, *Tetrahedron* **2012**, *68*, 6727–6736; b) V. P. Kumar, K. K. Gruner, O. Kataeva, H.-J. Knölker, *Angew. Chem. Int. Ed.* **2013**, *52*, 11073–11078; *Angew. Chem.* **2013**, *125*, 11279–11283; c) R. Hesse, A. Jäger, A. W. Schmidt, H.-J. Knölker, *Org. Biomol. Chem.* **2014**, *12*, 3866–3876; d) K. A. Kumar, P. Kannaboina, C. K. Jaladanki, P. V. Bharatam, P. Das, *ChemistrySelect* **2016**, *3*, 601–607.

[36] a) I. Hogan, P. Jenkins, M. Sainsbury, *Tetrahedron Lett.* **1988**, *29*, 6505–6508; b) P. M. Dharmasena, P. V. R. Shannon, *Tetrahedron Lett.* **1994**, *35*, 7119–7122; c) F. M. Deane, C. M. Miller, A. R. Maguire, F. O. McCarthy, *J. Heterocycl. Chem.* **2011**, *48*, 814–823.

[37] O. Meth-Cohn, *The Vilsmeier-Haack Reaction, in Compr. Org. Synth.* (Eds: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 2, pp. 777–794.

[38] A. A. Mousawi, A. Arar, M. Ibrahim-Ouali, S. Duval, F. Dumur, P. Garra, J. Toufaily, T. Hamieh, B. Graff, D. Gigmes, J.-P. Fouassier, J. Lalevée, *Photochem. Photobiol. Sci.* **2018**, *17*, 578–585.

[39] L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, T. Teitei, *Aust. J. Chem.* **1967**, *20*, 2715–2727.

[40] R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, R. W. Kierstead, E. Grunberg, *J. Med. Chem.* **1975**, *18*, 755–760.

Manuscript received: March 29, 2022
Revised manuscript received: May 24, 2022
Accepted manuscript online: May 25, 2022