JOC Article

Access to New 2-Oxofuro[2,3-*b*]pyrroles and 2-Methylenepyrroles through the Reaction of 1,2-Diaza-1,3-butadienes and γ-Ketoesters

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New and interesting 2-oxofuro[2,3-*b*]pyrroles and 19-methyl-15-oxa-20-azatricyclo[12.3.3.0^{1,14}]icos-18-en-18-carboxylates have been obtained in good yields by the one-pot reaction, in basic medium, of 1,2-diaza-1,3-butadienes with diethyl or dimethyl acetylsuccinate or methyl 2-(1,3-dioxo-2-cyclotetradecyl)acetate, respectively, under mild conditions. Treatment of the same starting materials with diethyl 2-acetylglutarate, in acidic medium, afforded unknown 2-methylenepyrrole derivatives in high yields. Novel 4-(3-oxopropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylates also have been achieved by reacting 1,2-diaza-1,3-butadienes with ethyl or methyl 4-acetyl-5-oxo-hexanoate.

Introduction

Lactones and lactams are important tools in organic chemistry and are valuable starting materials for the preparation of a large number of antibacterial agents. Thus, the synthesis and reactions of these compounds are of great interest both for organic and medicinal chemists and have been intensely studied for relatively simple derivatives.[1] Despite their potential importance, lactones fused with widely substituted heterocycle rings have been, in general, poorly presented in the literature. In particular, the synthesis and pharmacological activity of functionalized 2-oxofuro[2,3-*b*]indoles have been reported,[2,3] whereas, to the best of our knowledge, 2-oxofuro[2,3-*b*]pyrroles are unknown products.[4] Because 1,2-diaza-1,3-butadienes have been shown to be useful building blocks for the synthesis of five- and six-member heterocycles,[5] on the basis of our experience in this field,[6] we designed a strategy for the preparation of the aforementioned compounds through the reaction of these materials with appropriate γ-ketoesters. Our hypothesis has been successfully tested by reacting, under basic conditions, 1,2-diaza-1,3-butadienes with diethyl or dimethyl acetylsuccinate. In fact, this reaction furnished 6-amino-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a*H*-furo[2,3-*b*]pyrrole-3a,4-dicarboxylate derivatives as main products, with the concomitant formation of new and amply functionalized interesting 2-methylenepyrroles as minor products. By analogy, attractive 19-methyl-15-oxa-20-azatricyclo[12.3.3.0^{1,14}]icos-18-en-18-carboxylates have been achieved by treatment of the same starting materi-

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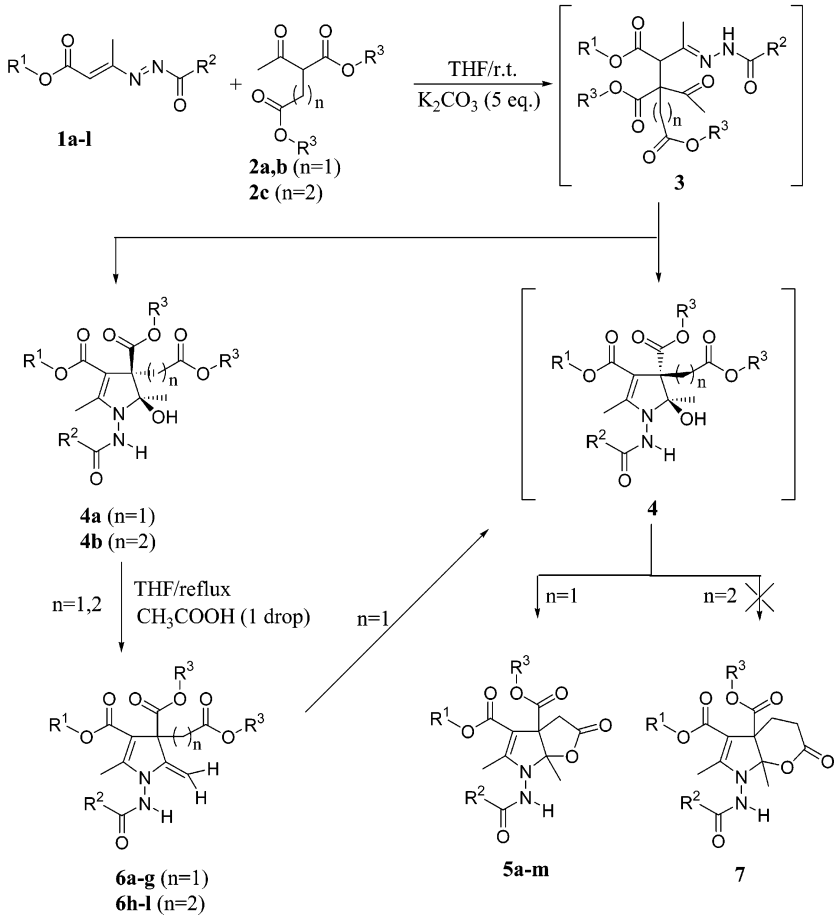
SCHEME 1



als with methyl 2-(1,3-dioxo-2-cyclotetradecyl)acetate. The similar reaction between 1,2-diaza-1,3-butadienes and diethyl 2-acetylglutarate gave new 2-methylenepyrrole derivatives as main products. It is noteworthy that both these two different reaction behaviors led to novel and useful derivatives in organic chemistry.

Results and Discussion

1,2-Diaza-1,3-butadienes **1a**−***l*** easily reacted with diethyl or dimethyl acetylsuccinate **2a**,**b** in tetrahydrofuran at room temperature in the presence of 5 equiv of potassium carbonate. When the reagents disappeared, potassium carbonate was removed by filtration and, in the case of the reaction with **1a**−**d**,**h**,**i**, the crude product revealed, by TLC (thin-layer chromatography) checking, the presence of two spots as major components. The main products were isolated by crystallization from the appropriate solvents and were characterized by spectroscopic analyses as 6-amino-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a-*H*-furo[2,3-*b*]pyrrole-3a,4-dicarboxylate derivatives **5a**−**d**,**h**−**j** (yields, 66−82%) (Scheme 1, Table 1).

It was possible to isolate the second product by flash chromatography only in the case of the reaction between **1a** and **2a**, and this was identified to be 3-ethyl 4-methyl 1-[(anilinocarbonyl)amino]-3-(2-ethoxy-2-oxoethyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate **4a** by ^{1}H NMR spectroscopy.[7] In the other cases, during the chromatographic process, product **4** exhibited a conversion into the corresponding 2-methylenepyrroles **6a**−**g**. To optimize this process and to improve the yields for the formation of **6**, we decided to submit the intermediate **4a**, as well as the mixtures obtained after the filtration of compounds **5a**−**m**, to the treatment with a drop of acetic acid in THF under reflux. 2-Methylenepyrroles **6a**−**g** were formed in 2.0−12.0 h with yields of 15−26%, which referred to the starting 1,2-diaza-1,3-butadienes (Scheme 1, Table 1).

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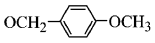
TABLE 1. Reaction Times and Yields of 6-Amino-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a-*H*-furo[2,3-*b*]pyrrole-3a-4-dicarboxylates 5a−m and 2-Methylenepyrroles 6a−g

1	R^1	R^2	2	R^3	4	5	yield[a] (%)	time (h)	6	yield[a] (%)	time[b] (h)
1a	CH_3	NHPh	**2a**	CH_2CH_3	**4a**	**5a**	74	0.5	**6a**	21	6.0
1b	$(CH_2)_2OCH_3$	NHPh	**2a**	CH_2CH_3		**5b**	68	1.0	**6b**	23	8.0
1c	CH_2CH_3		**2a**	CH_2CH_3		**5c**	66	1.0	**6c**	26	12.0
1d	CH_3	NH_2	**2a**	CH_2CH_3		**5d**	71	1.0	**6d**	23	2.0
1e	CH_2CH_3		**2a**	CH_2CH_3		**5e**	87	0.5			
1f	CH_3	OCH_2Ph	**2a**	CH_2CH_3		**5f**	78	0.5			
1g	CH_3	$OC(CH_3)_3$	**2a**	CH_2CH_3		**5g**	79	0.5			
1h	CH_2CH_3	NHPh	**2b**	CH_3		**5h**	74	0.5	**6e**	19	5.0
1d	CH_3	NH_2	**2b**	CH_3		**5i**	82	1.0	**6f**	15	3.0
1i	CH_2CH_3	NH_2	**2b**	CH_3		**5j**	77	2.0	**6g**	18	2.0
1j	CH_2CH_3	OCH_2Ph	**2b**	CH_3		**5k**	99	0.4			
1k	CH_2CH_3	$OC(CH_3)_3$	**2b**	CH_3		**5l**	97	0.1			
1l	CH_3	OCH_3	**2b**	CH_3		**5m**	91	0.7			

[a] Yield of pure isolated products, referring to the starting 1,2-diaza-1,3-butadienes. [b] Time of reflux.

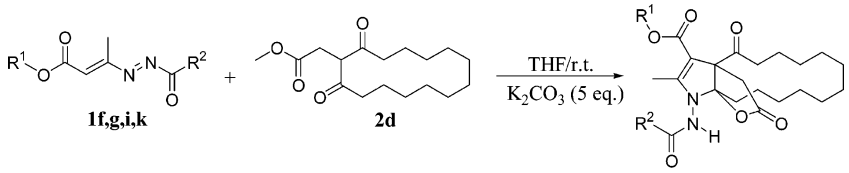
In the case of the reactions with **1e**−**g**,**j**−***l***, only 6-amino-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a-*H*-furo[2,3-*b*]pyrrole-3a,4-dicarboxylate derivatives **5e**−**g** and **5k**−**m** were formed in good to excellent yields (77−99%) (Scheme 1, Table 1). These results can be rationalized by postulating that the 1,4-conjugated addition (Michael type) of the nucleophile **2a** or **2b** to the terminal carbon atom of 1,2-diaza-1,3-butadiene **1** gave rise to the hydrazone intermediate **3**. The internal nucleophilic attack of the hydrazone nitrogen at the carbon of the keto function determined the ring closure to give 2-hydroxy-1-aminopyrroline intermediate **4** in both isomeric forms, *E* and *Z*. Probably in the basic medium (potassium carbonate) the conversion of the *Z* isomer into 2-oxo-furo[2,3-*b*]pyrroles **5** is the favorite process, and it occurs through the second annulation closure because of an internal nucleophilic attack of the hydroxy group at the ester function. This pathway is, instead, highly improbable for the *E* isomer of **4**, and in this case, the elimination of a molecule of water becomes predominant, leading to the formation of the exocyclic double bond and affording 2-methylenepyrrole **6**.

The addition of a drop of water to a solution of these latter compounds **6a**−**g** in tetrahydrofuran led to the formation of the corresponding 2-oxo-furo[2,3-*b*]pyrroles **5a**−**d**,**h**−**j** via 2-hydroxy-1-aminopyrrole in its *Z* isomeric form. On the basis of this evidence, it seems reasonable to conclude that the reaction takes place in accordance with the proposed mechanism.

To extensively investigate this reactivity, we examined the reaction between the 1,2-diaza-1,3-butadienes **1a**,**d**,**g**,**i**,**j** and diethyl 2-acetylglutarate **2c** in tetrahydrofuran at room temperature, in the presence of 5 equiv of potassium carbonate. When the reagents disappeared, potassium carbonate was removed by filtration, and the reaction mixture exhibited the presence of only one spot determined by TLC. It was possible to isolate this product by flash chromatography only in the case of the reaction between **1a** and **2c**, and this was identified as 3-ethyl 4-methyl 1-[(anilinocarbonyl)amino]-3-(3-ethoxy-3-oxopropyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate **4b** by ^{1}H NMR spectroscopy.[7] In the other cases, during the chromatographic process product **4** showed a tendency toward the easy loss of a water molecule, producing the relative 2-methylene-1-aminopyrrole derivatives **6h**−***l***. Thus, we decided to continue the reaction in tetrahydrofuran, under reflux, in the presence of a drop of acetic acid. In this way, 2-methylene-1-aminopyrroles **6h**−***l*** were obtained in good yields (73−83%) (Scheme 1, Table 2). Therefore, the base-promoted reaction of 1,2-diaza-1,3-butadienes **1a**,**d**,**g**,**i**,**j** with diethyl acetylglutarate **2c** does not proceed to the formation of 2-oxopyra[2,3-*b*]pyrroles **7**, probably on account of thermodynamic factors.

The reaction between 1,2-diaza-1,2-butadienes **1f**,**g**,**i**,**k** and methyl 2-(1,3-dioxo-2-cyclotetradecyl)acetate **2d** in tetrahydrofuran at room temperature, in the presence of 5 equiv of potassium carbonate, gave rise exclusively to the new and interesting 19-methyl-15-oxa-20-azatricyclo-[12.3.3.0^{1,14}]icos-18-en-18-carboxylates **8a**−**d** in good yields (56−95%) (Scheme 2, Table 3). This behavior proves that this easy procedure can be successfully used for further synthetic applications in the construction of attractive

SCHEME 2



SCHEME 3

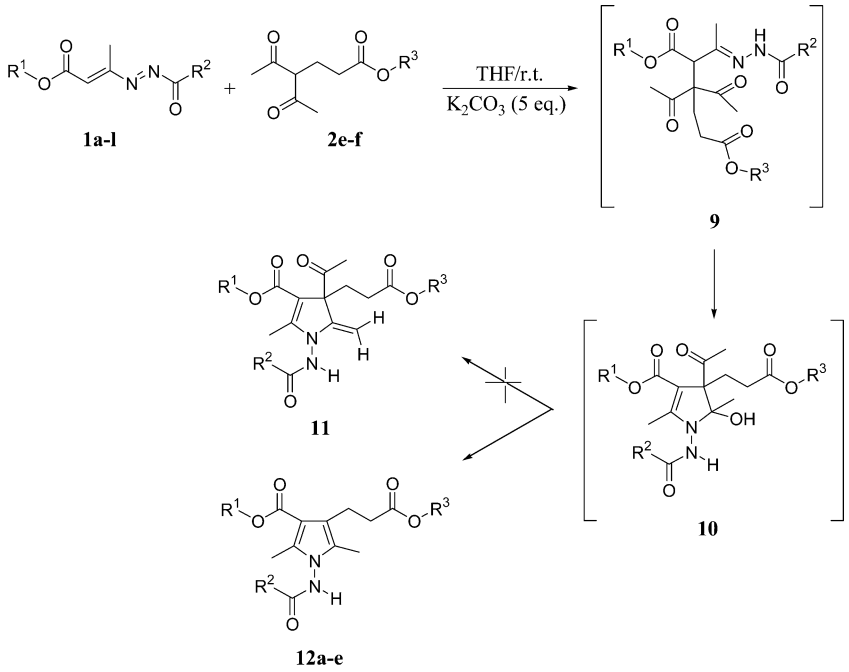


TABLE 2. Reaction Times and Yields of 2-Hydroxy-2,3-dihydro-1*H*-1-aminopyrrole 4a and 2-Methylenepyrroles 6h−*l*

1	R^1	R^2	2	R^3	4	6	yield[a] (%)	time[b] (h)
1a	CH_3	NHPh	**2c**	CH_2CH_3	**4b**	**6h**	76	12.0
1d	CH_3	NH_2	**2c**	CH_2CH_3		**6i**	80	4.0
1g	CH_3	$OC(CH_3)_3$	**2c**	CH_2CH_3		**6j**	73	8.0
1i	CH_2CH_3	NH_2	**2c**	CH_2CH_3		**6k**	81	9.0
1j	CH_2CH_3	OCH_2Ph	**2c**	CH_2CH_3		**6*l***	83	5.0

[a] Yield of pure isolated products. [b] Time of reflux; the disappearance of the starting reagents occurs in 0.5 h.

TABLE 3. Reaction Times and Yields of 19-Methyl-15-oxa-20-azatricyclo[12.3.3.0^{1,14}]icos-18-en-18-carboxylates 8a−d

1	R^1	R^2	8	yield[a] (%)	time (h)
1g	CH_3	$OC(CH_3)_3$	**8a**	95	1.5
1i	CH_2CH_3	NH_2	**8b**	56	3.0
1j	CH_2CH_3	OCH_2Ph	**8c**	78	2.0
1k	CH_2CH_3	$OC(CH_3)_3$	**8d**	85	2.0

[a] Yield of pure isolated products.

tricyclic fused heterorings, which are not easily obtained by other methods.

To tentatively widen the scope of this synthetic methodology, we performed the reaction of 1,2-diaza-1,3-butadienes **1g**,**i**,**k** with ethyl or methyl 4-acetyl-5-oxohexanoates **2e**,**f** in tetrahydrofuran, at room temperature,

TABLE 4. Reaction Times and Yields of 4-(3-Oxopropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylates 12a−e

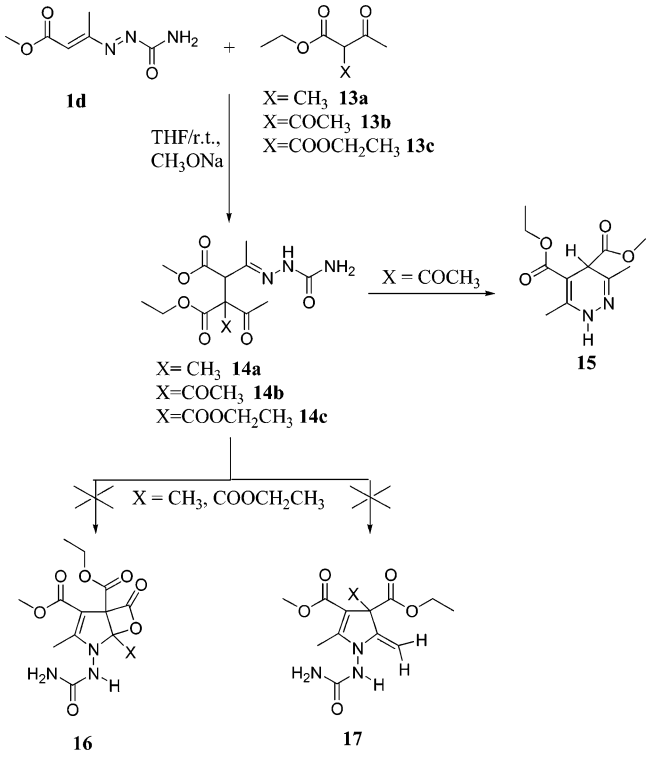
1	R^1	R^2	2	R^3	12	yield[a] (%)	time (h)
1g	CH_3	$OC(CH_3)_3$	**2e**	CH_2CH_3	**12a**	83	3.5
1i	CH_2CH_3	NH_2	**2e**	CH_2CH_3	**12b**	87	4.5
1g	CH_3	$OC(CH_3)_3$	**2f**	CH_3	**12c**	78	3.0
1i	CH_2CH_3	NH_2	**2f**	CH_3	**12d**	86	4.0
1k	CH_2CH_3	$OC(CH_3)_3$	**2f**	CH_3	**12e**	86	4.0

[a] Yield of pure isolated products.

in the presence of 5 equiv of potassium carbonate. After the formation of the hydroxypyrroline intermediate **10**, two different pathways were possible: the first proceeded with the elimination of a water molecule to give 2-methylenepyrrole **11**, whereas the second one occurred with a loss of an acetic acid moiety to obtain 4-(3-oxopropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylates **12**. In accordance with the results of our previous studies,[8] only the presence of these latter products **12a**−**d** was observed, and they were isolated by flash chromatography in good yields (78−87%) (Scheme 3, Table 4).

Finally, we also investigated the reaction of ethyl 2-methylacetoacetate **13a** with 1,2-diaza-1,3-butadiene **1d**. The nucleophilic conjugate 1,4-addition did not take place in the presence of potassium carbonate; it required sodium methoxide and gave 1-ethyl 4-methyl 2-acetyl-3-{1-[2-(aminocarbonyl)hydrazono]ethyl}-2-methylsuccinate **14a**. All attempts to convert it into **16** or **17** under several reaction conditions failed (Scheme 4). It has also

SCHEME 4



been described that when 1,2-diaza-1,3-butadienes were treated with ethyl 2-acetylacetoacetate **13b** or with diethyl acetylmalonate **13c** in basic medium, no formation of lactones was detected. These results are in agreement with an earlier reported observation that 1-unsubstituted 1,4-dihydropyridazines **15** were the reaction products.[9]

Conclusion

The present investigation demonstrates that the reaction between 1,2-diaza-1,3-butadienes and diethyl or dimethyl acetylsuccinate provides straightforward access to new 2-oxo-furo[2,3-*b*]pyrrole derivatives that increase the classes of nonpeptide bicyclic heterocycles, which have become a recent focus of β-turn mimetic design. This one-pot synthesis method proceeds under very mild reaction conditions and requires easily available starting materials. These furo[2,3-*b*]pyrrole derivatives, which are prepared in one step, present a large multifunctionality that is difficult to obtain by successive reactions of an afunctionalized starting skeleton. Even these molecules could be a very interesting approach to new types of scaffolds for the construction of apeptidic drugs. By analogy, applying the same synthetic methodology to 2-(1,3-dioxo-2-cyclotetradecyl)acetate, we obtained interesting and attractive 19-methyl-15-oxa-20-azatricyclo-[12.3.3.0^{1,14}]icos-18-en-18-carboxylates, in which three heterorings were fused. Furthermore, a similar synthetic approach that used 2-acetylglutarate surprisingly did not furnish the expected 2-oxo-pyran[2,3-*b*]pyrrole but offered a convenient route to 2-methylenepyrrole derivatives. In conclusion, we described the synthesis of two new classes of heterocyclic systems that should be of interest as products and intermediates in organic, biological, pharmaceutical, and agricultural chemistry.

Experimental Section

General Methods. Reagent and solvent purification, work-up procedures, and analyses were performed in general as described in the Supporting Information and elsewhere.[6m]

General Procedure for the Synthesis of 3-Ethyl 4-Methyl 1-[(Anilinocarbonyl)amino]-3-(2-ethoxy-2-oxoethyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate 4a and 6-Amino-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a-*H*-furo[2,3-*b*]pyrrole-3a,4-dicarboxylates 5a−m. To a magnetically stirred solution of 1,2-diaza-1,3-butadienes **1a**−***l*** (1.0 mmol), prepared as a mixture of *E*/Z isomers, as reported elsewhere,[10,11] and diethyl or dimethyl acetylsuccinate **2a,b** (1.0 mmol) in THF (25 mL) was added potassium carbonate (5.0 equiv). The mixture was allowed to stand at room temperature until the disappearance of the reagents (0.5−2.0 h) and the formation of two spots as major components (**4** and **5**) was detected by TLC. Potassium carbonate was removed by filtration, and the reaction solvent was evaporated under reduced pressure. Products **5a**−**m** were crystallized by adding to the crude the appropriate solvents: for **5a**,**c**,**e**,**f**,**h**−**j** ethyl acetate−light petroleum ether (at 40−60 °C) and for **5b**,**d**,**g**,**k**−**m** ethyl acetate−cyclohexane were added. In the case of the reaction between **1a** and **2a**, along with **5a**, product **4a** was isolated as a colorless oil by flash chromatography on silica gel and was immediately subjected to ^{1}H NMR analysis because of its poor stability.

3-Ethyl 4-methyl 1-[(anilinocarbonyl)amino]-3-(2-ethoxy-2-oxoethyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate (4a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13−1.25 (m, 6 H), 1.60 and 1.74 (2 s, 3 H), 2.13 and 2.19 (2 s, 3 H), 3.17 and 3.31 (AB-system, 2 H, J = 15.6 Hz), 3.62 and 3.65 (2 s, 3 H), 3.97 and 4.25 (m, 4 H), 5.42 and 5.78 (2 br s, 1 H), 7.20 and 7.70 (m, 6 H), 8.06 and 8.13 (2 br s, 1 H).

Diethyl 6-({[(4-methoxybenzyl)oxy]carbonyl}amino)-5,6a-dimethyl-2-oxo-2,3,6,6a-tetrahydro-3a-*H*-furo[2,3-*b*]-pyrrole-3a,4-dicarboxylate (5e): mp 121−123 °C; IR (Nujol) ν_{max} 3258, 1770, 1753, 1670, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03−1.26 (m, 6 H), 1.38 and 1.50 (2 s, 3 H), 2.14 and 2.18 (2 s, 3 H), 2.98 and 3.69 (AB-system, 2 H, J = 18.4 Hz), 3.77 (s, 3 H), 3.96−4.27 (m, 4 H), 5.09 (s, 2 H), 6.85 (d, 2 H, J = 8.4 Hz), 7.01 and 7.17−7.31 (s and m, 3 H); ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 11.6 (q), 13.9 (q), 14.2 (q), 18.4 (q), 37.9 (s), 55.1 (q), 59.7 (t), 62.1 (t), 62.2 (t), 67.6 (t), 67.7 (t), 101.0 (s), 101.3 (s), 103.4 (s), 103.5 (s), 113.8 (d), 127.3 (s), 130.0 (d), 130.2 (s), 155.8 (s), 159.6 (s), 160.3 (s), 164.0 (s), 168.9 (s), 173.2 (s); EIMS *m*/*z* 476 (7) [M$^+$], 432 (66), 311 (90), 223 (100). Anal. Calcd for $C_{23}H_{28}N_2O_9$: C, 57.98; H, 5.92; N, 5.88. Found: C, 57.69; H, 5.78; N, 5.73.

General Procedure for the Synthesis of 3-(2-Ethoxy-2-oxoethyl)-5-methyl-2-methylene-2,3-dihydro-1-aminopyrroles 6a−g. The crude product, which was obtained after the filtration of compounds **5a**−**d**,**h**−**j** and the evaporation of the crystallization solvents, as well as pure **4a** were refluxed in THF after the addition of a drop of acetic acid. The conversion into pertinent 2-methylenepyrroles **6a**−**g** occurred in 2−12 h (as tested by TLC). Products **6a**−**g** were purified by flash chromatography on a silica gel column and crystallized from diethyl ether−light petroleum ether (at 40−60 °C).

Diethyl 1-{[(3-fluoro)anilinocarbonyl]amino}-3-(2-ethoxy-2-oxoethyl)-5-methyl-2-methylene-2,3-dihydropyrrole-3,4-dicarboxylate (6c): mp 159−161 °C; IR (Nujol) ν_{max} 3319, 3205, 1753, 1718, 1695, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13−1.29 (m, 9 H), 2.38 (s, 3 H), 3.13 and 3.54 (AB-

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system, 2 H, J = 17.2 Hz), 4.10−4.20 (m, 6 H), 4.36 and 4.48 (AB-system, 2 H, J = 2.8 Hz), 6.63 (s, 1 H), 6.70−6.85 (m, 1 H), 7.13−7.26 (m, 2 H), 7.40−7.49 (m, 2 H), 8.73 (s, 1 H); ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 11.7 (q), 14.2 (q), 14.3 (q), 14.6 (q), 41.7 (t), 54.6 (s), 59.9 (t), 61.4 (t), 62.2 (t), 83.4 (t), 102.7 (s), 107.2 (d, $^2J_{CF}$ = 26.6 Hz), 110.3 (d, $^2J_{CF}$ = 20.4 Hz), 115.1 (d), 130.0 (d, $^3J_{CF}$ = 9.8 Hz), 140.3 (s, $^3J_{CF}$ = 10.6 Hz), 150.9 (s), 155.0 (s), 158.2 (s), 163.1 (s, $^1J_{CF}$ = 228.0 Hz), 164.4 (s), 170.6 (s), 172.3 (s). EIMS m/z 478 (6) [M^+ + 1], 477 (29) [M^+], 432 (12), 405 (27), 404 (100). Anal. Calcd for $C_{23}H_{28}N_3O_7F$: C, 57.85; H, 5.91; N, 8.80. Found: C, 57.72; H, 5.98; N, 8.73.

General Procedure for the Synthesis of 3-Ethyl 4-Methyl 1-[(Anilinocarbonyl)amino]-3-(3-ethoxy-3-oxopropyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate (4b) and 2-Methylenepyrroles 6h−*l*. To a magnetically stirred solution of 1,2-diaza-1,3-butadienes **1a**,**d**,**g**,**i**,**j** (1.0 mmol), prepared as a mixture of *E*/Z isomers as reported elsewhere,[10,11] and 2-acetylglutarate **2c** (1.0 mmol) in THF (25 mL) was added potassium carbonate (5.0 equiv). The mixture was allowed to stand at room temperature until the disappearance of the reagents (0.5 h, monitored by TLC). Then, potassium carbonate was removed by filtration. In the case of the reaction between **1a** and **2c**, product **4b** was purified by flash chromatography on a silica gel column and immediately subjected to ^{1}H NMR analysis because of its poor stability. In all the other cases, the isolation of pure **4** was not possible and the crude product, which was obtained after the filtration of potassium carbonate, as well as pure **4b** were refluxed in THF after the addition of a drop of acetic acid. The conversion into pertinent 2-methylenepyrroles **6h**−***l*** occurred in 4−12 h (as tested by TLC). Products **6h**−***l*** were purified by flash chromatography on silica gel and then crystallized from diethyl ether−light petroleum ether (at 40−60 °C).

3-Ethyl 4-methyl 1-[(anilinocarbonyl)amino]-3-(2-ethoxy-3-oxopropyl)-5-methyl-2-hydroxy-2,3-dihydropyrrole-3,4-dicarboxylate (4b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07−1.21 (m, 6 H), 1.40 (2 s, 3 H), 1.42−1.68 and 2.05−2.97 (2 m, 4 H), 2.01 and 2.04 (2 s, 3 H), 3.50 and 3.54 (2 s, 3 H), 3.94−4.14 (m, 4 H), 6.14 and 6.39 (2 br s, 1 H), 8.23, 8.58, 8.66, and 9.02 (4 br s, 2 H).

Diethyl 1-[(aminocarbonyl)amino]-3-(3-ethoxy-3-oxopropyl)-5-methyl-2-methylene-2,3-dihydropyrrole-3,4-dicarboxylate (6k): mp 100−102 °C; IR (Nujol) ν_{max} 3461, 3260, 1745, 1671, 1660, 1617 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.18 (m, 9 H), 1.84−3.96 (m, 4 H), 2.18 and 2.22 (2 s, 3 H), 3.91−4.45 (m, 8 H), 5.83 (br s, 2 H), 7.50 and 8.10 (2 br s, 1 H); ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 11.0 (q), 11.1 (q), 13.6 (q), 13.7 (q), 13.8 (q), 13.9 (q), 14.0 (q), 29.4 (t), 29.6 (t), 30.3 (t), 30.9 (t), 56.6 (s), 56.9 (s), 59.1 (t), 59.3 (t), 60.4 (t), 60.8 (t), 61.1 (t), 61.5 (t), 83.8 (t), 102.1 (s), 149.8 (s), 150.4 (s), 159.0 (s), 159.1 (s), 163.8 (s), 171.4 (s), 171.6 (s), 173.1 (s), 173.4 (s), 174.5 (s); EIMS m/z 398 (2) [M^+ + 1], 397 (12) [M^+], 352 (4), 324 (86), 296 (8), 279 (17), 278 (100). Anal. Calcd for $C_{18}H_{27}N_3O_7$: C, 54.40; H, 6.85; N, 10.57. Found: C, 54.31; H, 6.98; N, 10.72.

General Procedure for the Synthesis of 19-Methyl-15-oxa-20-azatriciclo[12.3.3.0^{1,14}]icos-18-en-18-carboxylates 8a−d. To a magnetically stirred solution of 1,2-diaza-1,3-butadienes **1g**,**i**,**j**,**k** (1.0 mmol), prepared as a mixture of *E*/Z isomers, as reported elsewhere,[10,11] and methyl 2-(1,3-dioxo-2-cyclotetradecyl)acetate **2d** (1.0 mmol) in THF (25 mL) was added potassium carbonate (5.0 equiv). The mixture was allowed to stand at room temperature until the disappearance of the reagents (1.5−3.0 h, as monitored by TLC), and then potassium carbonate was removed by filtration. The reaction solvent was evaporated under reduced pressure; products **8a**−**d** were purified by flash chromatography on a silica gel column and crystallized from diethyl ether−light petroleum ether (at 40−60 °C).

Methyl 20-[(*tert*-butoxycarbonyl)amino]-19-methyl-15-oxa-20-azatriciclo[12.3.3.0^{1,14}]icos-18-en-18-carboxylate (8a): mp 97−99 °C; IR (Nujol) ν_{max} 3320, 3212, 1760, 1698, 1672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.39 (m, 20 H), 1.48 (s, 9 H), 1.71−1.84 (m, 2 H), 2.28 (s, 3 H), 2.89 and 3.73 (AB-system, 2 H, J = 18.4 Hz), 3.66 (s, 3 H), 6.76 and 6.98 (2 s, 1 H); ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 12.2 (q), 19.1 (t), 21.6 (t), 23.8 (t), 25.0 (t), 25.4 (t), 25.7 (t), 26.6 (t), 27.1 (t), 28.3 (q), 30.5 (t), 32.5 (t), 36.1 (t), 38.1 (t), 51.5 (q), 65.4 (s), 82.4 (s), 102.3 (s), 105.4 (s), 154.9 (s), 162.5 (s), 164.8 (s), 174.0 (s), 204.6 (s); EIMS m/z 493 (6) [M^+ + 1], 492 (19) [M^+], 436 (34), 420 (5), 392 (100). Anal. Calcd for $C_{26}H_{40}N_2O_7$: C, 63.39; H, 8.18; N, 5.69. Found: C, 63.49; H, 8.25; N, 5.73.

General Procedure for the Synthesis of 4-(3-Oxopropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylates 12a−e. To a magnetically stirred solution of 1,2-diaza-1,3-butadienes **1g**,**i**,**k** (1.0 mmol), prepared as a mixture of *E*/Z isomers, as reported elsewhere,[10,11] and ethyl or methyl 4-acetyl-5-oxo-hexanoate **2e**,**f** (1.0 mmol) in THF (25 mL) was added potassium carbonate (5.0 equiv). The mixture was allowed to stand at room temperature until the disappearance of the reagents (3.0−4.5 h, as monitored by TLC) and then refluxed in THF. The formation of 4-(3-oxopropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylates **12a**−**e** occurred in 4−12 h (as tested by TLC). Potassium carbonate was removed by filtration, and products **12a**−**e** were purified by flash chromatography on silica gel and crystallized from ethyl acetate−light petroleum ether (at 40−60 °C).

Ethyl 4-(3-methoxy-3-oxopropyl)-1-[(aminocarbonyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (12d): mp 157−159 °C; IR (Nujol) ν_{max} 3450, 3270, 3212, 1740, 1685, 1672, 1623 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3 H, J = 6.8 Hz), 1.94 (s, 3 H), 2.25 (s, 3 H), 2.21−2.42 (m, 2 H), 2.73−2.85 (m, 2 H), 3.54 (s, 3 H), 4.13 (q, 2 H, J = 7.2 Hz), 6.15 (br s, 2 H), 9.04 (s, 1 H); ^{13}C NMR (100.65 MHz, DMSO-d_6) δ 8.3 (q), 10.7 (q), 14.2 (q), 20.9 (t), 35.0 (t), 51.0 (q), 58.6 (t), 106.9 (s), 115.4 (s), 126.2 (s), 135.9 (s), 157.2 (s), 164.7 (s), 173.0 (s); EIMS m/z 312 (1) [M^+ + 1], 311 (100) [M^+]. Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 54.15; H, 6.75; N, 13.31.

General Procedure for the Synthesis of 1-Ethyl 4-Methyl 2-Acetyl-3-{1-[2-(aminocarbonyl)hydrazono]ethyl}-2-methylsuccinate (14a). To a magnetically stirred solution of 1,2-diaza-1,3-butadiene **1d** (1.0 mmol), prepared as a mixture of *E*/Z isomers, as reported elsewhere,[10,11] and ethyl 2-methylacetoacetate **13a** (1.0 mmol) in THF (25 mL) was added sodium methoxide (0.1 equiv). The mixture was allowed to stand at room temperature until the disappearance of the reagents (1.5 h, as monitored by TLC). The reaction solvent was evaporated under reduced pressure, and product **14a** was purified by chromatography on a silica gel column and then crystallized from ethyl acetate−light petroleum ether (at 40−60 °C).

1-Ethyl 4-methyl 2-acetyl-3-{1-[2-(aminocarbonyl)hydrazono]ethyl}-2-methylsuccinate (14a): mp 100−102 °C; IR (Nujol) ν_{max} 3471, 1775, 1723, 1690, 1683 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08−1.28 (m, 6 H), 1.82 and 1.85 (2 s, 3 H), 2.07 and 2.21 (2 s, 3 H), 3.53 and 3.58 (2 s, 3 H), 3.98−4.17 (m, 2 H), 4.25 (s, 1 H), 6.02 (br s, 2 H), 9.30 (s, 1 H); ^{13}C NMR (100.65 MHz, DMSO-d_6) δ 12.7 (q), 14.2 (q), 14.6 (q), 18.0 (q), 19.2 (q), 26.4 (q), 50.8 (d), 52.7 (q), 57.1 (s), 58.1 (s), 61.6 (t), 62.0 (t), 142.7 (s), 157.9 (s), 166.1 (s), 171.1 (s), 172.3 (s), 205.0 (s); EIMS m/z 315 (6) [M^+], 297 (11), 272 (19), 254 (9), 224 (100). Anal. Calcd for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.41; H, 6.78; N, 13.46.

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Supporting Information Available: General procedures for the preparation of compounds **5a**−**m**, **6a**−**g**, **6h**−***l***, **8a**−**d**, **12a**−**c,** and **14a**; product characterization data and ^{1}H and ^{13}C NMR peak listing for **5a**−**m**, **6a**−**g**, **6h**−***l***, **8a**−**d**, **12a**−**c,** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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