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# Multicomponent Domino Reaction Promoted by $Mg(ClO_4)_2$: Highly Efficient Access to Functionalized 1,4-Dihydropyridines

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An efficient, one-pot multicomponent synthetic protocol toward substituted 1,4-dihydropyridines from aromatic amines, β-keto derivatives, and ethyl propiolate mediated by $Mg(ClO_4)_2$ is described. When *ortho*- or *meta*-substituted arylamines are used, two conformational isomers are generated. An NMR spectroscopic study of the energy barrier involved in the interconversion of the isomers is reported.

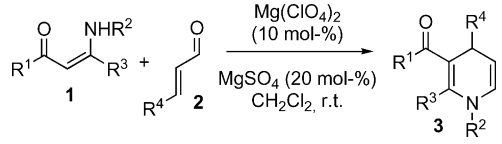


## Introduction

Multicomponent reactions[1] involving one-pot domino processes[2] are one of the most powerful tools to easily obtain complex molecular skeletons from simple substrates. Current literature continues to report new protocols for the preparation of 1,4-dihydropyridines (1,4-DHPs), which exhibit important pharmacological and biological activities.[3] In fact, 1,4-DHPs are among the most widely used drugs for the treatment of vascular disorders, and they find applications as calcium antagonists, vasodilators, bronchodilators, and anticancer agents. Moreover, they are NADH mimics[4] and can be involved in hydrogen-transfer reactions. The best known procedure for the synthesis of 1,4-DHP systems is the Hantzch condensation, which was set up more than one century ago.[5] However, due to their relevance, many efforts have been devoted to find new protocols for the synthesis of wide libraries of such important compounds.[6]

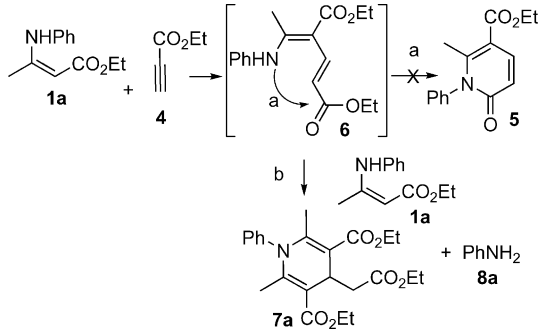
## Results and Discussion

During our studies on the application of perchlorate salts as powerful Lewis acids,[7] we recently reported a new method for the synthesis of asymmetric 1,4-DHPs by a $Mg(ClO_4)_2$ promoted addition–condensation reaction of β-enamino carbonylic derivatives and α,β-unsaturated aldehydes (Scheme 1).[8]




Scheme 1.

Studying the reaction with other α,β-unsaturated systems, we obtained a surprising result. In fact, the reaction of enamino ester **1a** with ethyl propiolate (**4**) did not give expected pyridone[9] **5** or Michael adduct **6**, but a considerable amount (20% yield after 70 h at r.t.) of dihydropyridine **7a** derived from a double conjugate addition of **1a** to **4** followed by an intramolecular condensation with elimination of aniline **8a** (Scheme 2). Given the importance of the 1,4-DHP system, a study to optimize this procedure by developing a useful synthesis of systems like **7a** would seem appropriate.




Scheme 2.

In the reaction depicted in Scheme 2, 1 equiv. of aniline **8a** was recovered, and as such, a one-pot procedure to ob-

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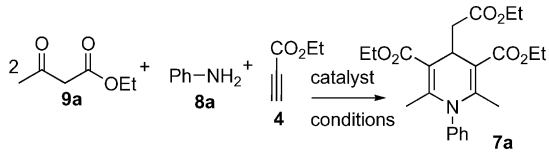
Table 1. Reaction of ethyl acetoacetate (**9a**; 2 equiv.) with aniline **8a** (1 equiv.) and ethyl propiolate (**4**; 1.2 equiv.) under various reaction conditions.




| Entry | Catalyst | Solvent | *T* [°C] | Time [h] | Conversion [%][a] |
|---|---|---|---|---|---|
| 1 | $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) | $CH_2Cl_2$ | r.t. | 90 | 3 |
| 2 | $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) | $CH_2Cl_2$ | 40 | 54 | 70 |
| 3 | $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) | THF | 50 | 54 | 71 |
| 4 | $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) | neat | 40 | 24 | 69 |
| 5 | $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) | neat | 50 | 24 | 95 |
| 6 | $Mg(ClO_4)_2$ (5 mol-%)/ $MgSO_4$ (20 mol-%) | neat | 50 | 24 | 85 |
| 7 | $Mg(ClO_4)_2$ (10 mol-%) | neat | 50 | 24 | 81 |

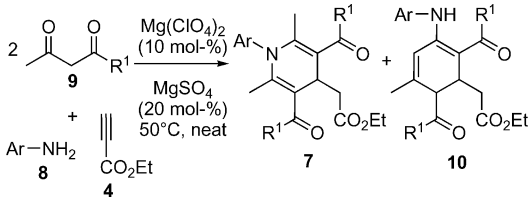
[a] Calculated by $^1$H NMR spectroscopy.

tain **7a** by starting from 2 equiv. of ethyl acetoacetate, 1 equiv. of amine, and a slight excess amount of ethyl propiolate (1.2 equiv.) seemed possible. In Table 1, preliminary results to optimize the procedure are reported. Best results were obtained when the reaction was carried out under solvent-free conditions at 50 °C. In fact, the addition of a solvent and/or a lower temperature decreased the reaction rate (Table 1, Entries 1–5). As in various other procedures we set up, the catalytic system $Mg(ClO_4)_2$ (10 mol-%)/$MgSO_4$ (20 mol-%) proved to be the best combination: a decrease in the amount of $Mg(ClO_4)_2$ or the absence of $MgSO_4$ led to worse results (Table 1, Entries 6 and 7).

With optimal conditions in hands, the scope of the reaction was investigated. The reaction worked with differently substituted anilines. The presence of an electron-donating substituent on the aromatic ring did not influenced the reactivity (Table 2, Entries 1 and 2), whereas a weak deactivating group diminished the yields in the desired product (Table 2, Entries 4 and 5). In contrast, with hindered amines, such as 1-naphthylamine or 2-substituted aniline, a dramatic decrease in the yields of product **7** was observed and variable amounts of side product **10** were detected (Table 2, Entries 6–9). In particular, in the case of 2-*tert*-butylaniline, only **10i** was isolated and **7i** was not detected (Table 2, Entry 9).

The reaction can be performed with different keto esters, like *tert*-butyl acetoacetate, obtaining comparable yields of **7** (Table 2, Entries 10–12). Other 1,3-bidentate systems, like acetylacetone, worked well (Table 2, Entries 13 and 14), but some problems arose with the purification step. Although NMR spectroscopic analysis of the crude reaction mixture pointed out the almost exclusive presence of the desired product, after column chromatography, **7m**,**n** were isolated in moderate yields. Very likely, these derivatives are not very stable on silica gel and oxidation to the pyridine salt occurred, as in the case of 1,4-dihydropyridines such as **3**.[8] An analogous explanation can be given for the yield of compound **7l**. Unsatisfying results were obtained with aliphatic amines. The reaction of **9a** with benzylamine gave only 31% of the desired product, together with a complex mixture of unidentified byproducts.

Table 2. Reaction of keto derivatives **9** (2 equiv.) with amines **8** (1 equiv.) and ethyl propiolate (**4**; 1.2 equiv.).

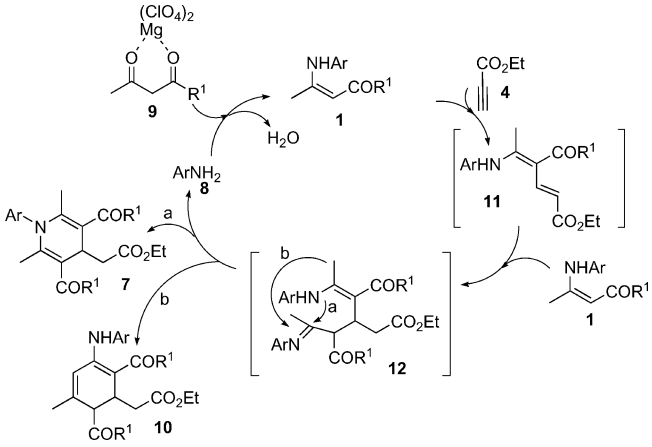



| Entry | $R^1$ | Ar | Time [h] | Product | Yields of **7** (**10**)[a] [%] |
|---|---|---|---|---|---|
| 1 | OEt | Ph | 24 | **7a** | 95 |
| 2 | OEt | (4-OMe)$C_6H_4$ | 24 | **7b** | 92 |
| 3 | OEt | (4-*i*Pr)$C_6H_4$ | 24 | **7c** | 76 |
| 4 | OEt | (3-Cl)$C_6H_4$ | 24 | **7d** | 73 (9) |
| 5 | OEt | (3-OH)$C_6H_4$ | 24 | **7e** | 60 (7) |
| 6 | OEt | (2-I)$C_6H_4$ | 48 | $\mathbf{7f_A}$+$\mathbf{7f_S}$ | 50 (17) |
| 7 | OEt | 1-naphthyl | 27 | $\mathbf{7g_A}$+$\mathbf{7g_S}$ | 55 (22) |
| 8 | OEt | (2-Ph)$C_6H_4$ | 48 | $\mathbf{7h_A}$+$\mathbf{7h_S}$ | 39 (25) |
| 9 | OEt | (2-*t*Bu)$C_6H_4$ | 48 | **7i** | 0 (27) |
| 10 | O*t*Bu | Ph | 32 | **7j** | 71 |
| 11 | O*t*Bu | (4-OMe)$C_6H_4$ | 52 | **7k** | 70 |
| 12 | O*t*Bu | (3-Cl)$C_6H_4$ | 50 | **7l** | 45[b] |
| 13 | Me | Ph | 78 | **7m** | 55[b] |
| 14 | Me | (4-OMe)$C_6H_4$ | 76 | **7n** | 57[b] |

[a] Isolated yields. [b] Conversion yields almost complete.

Concerning the reaction mechanism, a plausible explanation is depicted in Scheme 3. In the presence of magnesium perchlorate, which is known to be able to coordinate 1,3-bidentate compounds,[10] carbonyl derivative **9** rapidly condensed with the amine eliminating water and forming enamino derivative **1**. Compound **1** added to ethyl propiolate (**4**) to give Michael adduct **11**, as an intermediate, which underwent a second conjugate addition from **1** to give **12**. An intramolecular condensation (path a) gave desired 1,4-DHP **7** and 1 equiv. of amine **8**, which can restart the reaction cycle. However, when the *N*-substituent is too hindered, the N-atom resulted too crowded to perform intramolecular attack on intermediate **12**. Therefore, the condensation could occur through the addition of the methyl group (path b) giving rise to byproduct **10**.

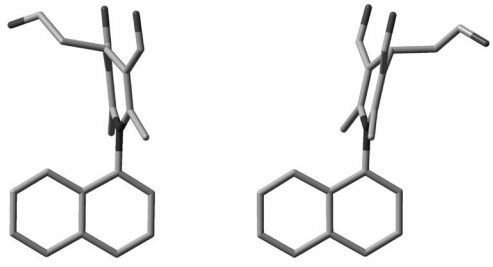
  



Scheme 3. A plausible mechanism proposed for the reaction.

The second Michael addition on **11** very likely occurs by **1** and not by **9**, as the first reaction, in which the formation of **7a** was observed, was performed by starting from β-enamino ester **1a** in an anhydrous medium; therefore, **1a** could not be hydrolyzed to **9a**.

It is interesting to observe that, due to the steric hindrance exerted by the two methyl groups, the plane of 1,4-DHP and the plane of the aromatic ring are forced to be orthogonal to each other. When *ortho*- or *meta*-substituted arylamines are employed in the reaction, two conformers, in which the substituent can be in a *syn* or *anti* relationship with respect to the $CH_2$ in the 4-position of the DHP ring (see Figure 1), can thus be generated. In the cases of *ortho*-substituted amines, the energy barrier involved in the interconversion of these two isomers is sufficiently high to allow the observation of separate NMR signals at ambient temperature.



*syn* *anti*

Figure 1. DFT calculated *syn* and *anti* conformers of **7g**. Hydrogen atoms and OEt groups are omitted for clarity.

In the case of compound **7g**, the $^1H$ NMR spectrum indicates that the two atropisomers are present in a 66:34 proportion (see spectra in the Supporting Information). DFT calculations[11] predict that the DHP ring resembles a pseudoboat conformation, and that the *anti* isomer should be slightly more stable than the *syn* isomer. NOE spectra obtained on saturation of the $CH_2$ in the 4-position of the DHP ring (Supporting Information, Figure S1) confirm that the *anti* isomer, where the $CH_2$ is close to 2-H of the naphthalene ring, is the more stable atropisomer in solution (Figure 1). The lack of saturation transfer during the NOE experiments confirms that the energy barrier for the interconversion of the two atropisomers is larger than 20 kcal mol$^{-1}$ (DFT calculations indicate an Ar–N rotational barrier of about 27 kcal mol$^{-1}$). The two isomers could be separated by HPLC, and the energy barrier for the *anti–syn* conversion was derived by following the rising of the more stable isomer starting from the pure minor one. From the first-order kinetics equation for a process at the equilibrium, the appropriate rate constant was obtained (details are reported in Figure S2 in the Supporting Information) and the barrier for exchanging the more-stable (*anti*) into the less-stable (*syn*) isomer was derived ($\Delta G^{\neq}$ = 23.3 kcal mol$^{-1}$ at +23 °C).

The same approach was used in the case of iodo derivative **7f**, where, at a variance with **7g**, the *syn* isomer was determined by NOE spectra to be the more stable isomer (Supporting Information, Figure S3). The process leading to the interconversion of the isomers of **7f** was followed by monitoring the time dependence of the NMR signal of the $CH_2$ in the 4-position of the DHP ring of the pure *anti* isomer in $CD_3CN$ at +35 °C. The intensity of the $CH_2$ line of the *anti* isomer decreases, whereas that of the *syn* isomer begins to appear at lower field with an intensity that increases until an equilibrium, corresponding to a *syn*:*anti* ratio of 60:40 (in $CD_3CN$), is reached. In this case, the barrier is higher ($\Delta G^{\neq}$ = 24.2 kcal mol$^{-1}$ at +35 °C; see Figure S4 in the Supporting Information for details) than that of compound **7g**. Even if the two isomers are not completely stable at room temperature (lifetime ≈19 h at +25 °C), the present case represents one of the few examples of stable atropisomers not containing a biaryl moiety.[12]

When the *ortho* position is substituted by a phenyl group (compound **7h**), a 92:8 ratio of the two conformers is observed. Again, the *syn* isomer was found to be more stable by NOE experiments. DFT calculations also confirm the lower energy of the *syn* conformer, even if it would appear to be the more sterically hindered conformation. Unfortunately, this compound has a lower interconversion barrier (21.3 kcal mol$^{-1}$, obtained by 1D-EXSY at +40 °C; Supporting Information, Figure S5), and a physical separation of the two conformer is not feasible.

## Conclusions

We developed a new and simple multicomponent domino reaction for the synthesis of symmetric 1,4-dihydropyridines mediated by $Mg(ClO_4)_2$. The reported process is a one-pot procedure, it works under solvent free conditions, and high atom economy is observed; water is the only byproduct of the reaction. This methodology can be successfully applied to various β-keto derivatives and aromatic amines. When hindered amines are employed, two diastereomeric conformers are obtained, and they can be, in some cases, isolated. Efforts to explore the differences in the reactivities of diastereoisomeric 1,4-DHPs and to obtain conformationally stable atropisomers are in progress in our laboratory.

## Experimental Section

**General Remarks:** All reactions were carried out in an air atmosphere. Reagents were purchased from commercial sources and used as received.

**General Procedure for the Synthesis of 1,4-Dihydropyridines 7:** $Mg(ClO_4)_2$ (0.1 equiv., 0.075 mmol), $MgSO_4$ (0.2 equiv., 0.15 mmol), β-keto derivative **9** (2 equiv., 1.5 mmol), aromatic amine **8** (1 equiv., 0.75 mmol), and ethyl propiolate (**4**; 1.2 equiv., 0.9 mmol) were mixed together and heated at 50 °C. The mixture was left to stir until TLC and GC–MS analysis revealed the reaction was finished. After cooling, $CH_2Cl_2$ (10 mL) was added, and the catalyst was filtered off. The solvent was evaporated, and the crude mixture was purified by column chromatography on silica gel (petroleum ether/$Et_2O$).

**NMR Spectroscopy:** If not specified, NMR spectra were recorded at 400 MHz for $^1H$ and 100.6 MHz for $^{13}C$ in $CDCl_3$. Assignments of the $^1H$ and $^{13}C$ signals of **7f–h** were obtained by bidimensional experiments (g-COSY, gs-HSQC, and gs-HMBC sequences). The NOE experiments were obtained at 600 MHz by means of the DPFGSE-NOE[13] sequence. To selectively irradiate the desired signal, a 50-Hz wide shaped pulse was calculated with a refocusing-SNOB shape and a pulse width of 37 ms. Mixing time was set to 1.5 to 2.0 s. 1D-EXSY spectra of **7h** were obtained by using the same DPFGSE pulse sequence, and rising the mixing time from 0.025 to 1.2 s.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7a):** Yield: 296 mg, 95%. $^1H$ NMR: $\delta$ = 1.23 (t, $J$ = 7.2 Hz, 3 H), 1.32 (t, $J$ = 7.3 Hz, 6 H), 2.02 (s, 6 H), 2.44 (d, $J$ = 6.5 Hz, 2 H), 4.08 (q, $J$ = 7.2 Hz, 2 H), 4.21 (q, $J$ = 7.3 Hz, 4 H), 4.38 (t, $J$ = 6.5 Hz, 1 H), 7.05–7.10 (m, 2 H), 7.20–7.30 (m, 3 H) ppm. $^{13}C$ NMR: $\delta$ = 14.1 ($CH_3$), 14.2 ($CH_3$), 18.3 ($CH_3$), 31.2 (CH), 41.6 ($CH_2$), 59.87 ($CH_2$), 59.91 ($CH_2$), 103.8 (C), 128.5 (CH), 129.2 (CH), 130.1 (CH), 140.1 (C), 148.3 (C), 167.7 (C), 171.7 (C) ppm. HRMS: calcd. for $C_{23}H_{29}NO_6$ 415.1994;, found 415.1992.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7b):** Yield: 307 mg, 92%. $^1H$ NMR: $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H), 1.32 (t, $J$ = 7.1 Hz, 6 H), 2.04 (s, 6 H), 2.43 (d, $J$ = 6.7 Hz, 2 H), 3.85 (s, 3 H), 4.08 (q, $J$ = 7.1 Hz, 2 H), 4.23 (q, $J$ = 7.1 Hz, 4 H), 4.38 (t, $J$ = 6.7 Hz, 1 H), 6.90–7.00 (m, 2 H), 7.10–7.15 (m, 2 H) ppm. $^{13}C$ NMR: $\delta$ = 14.0 ($CH_3$), 14.1 ($CH_3$), 18.1 ($CH_3$), 31.1 (CH), 41.4 ($CH_2$), 55.2 ($CH_3$), 59.7 ($CH_2$), 59.8 ($CH_2$), 103.6 (C), 114.2 (CH), 130.9 (CH), 130.6 (C), 148.7 (C), 159.1 (C), 167.6 (C), 171.9 (C) ppm. HRMS (EI): calcd. for $C_{24}H_{31}NO_7$ 445.2100; found 445.2100.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-1-(4-isopropylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7c):** Yield: 260 mg, 76%. $^1H$ NMR: $\delta$ = 1.23 (t, $J$ = 7.2 Hz, 3 H), 1.28 (d, $J$ = 6.8 Hz, 6 H), 1.31 (t, $J$ = 7.1 Hz, 6 H), 2.02 (s, 6 H), 2.41 (d, $J$ = 6.4 Hz, 2 H), 2.96 (h, $J$ = 6.8 Hz, 1 H), 4.07 (q, $J$ = 7.2 Hz, 2 H), 4.15–4.25 (m, 4 H), 4.37 (t, $J$ = 6.4 Hz, 1 H), 7.05–7.10 (m, 2 H), 7.25–7.30 (m, 2 H) ppm. $^{13}C$ NMR: $\delta$ = 14.2 ($CH_3$), 14.3 ($CH_3$), 18.4 ($CH_3$), 23.9 ($CH_3$), 31.2 (CH), 33.7(CH), 59.9 ($CH_2$), 60.0 ($CH_2$), 103.8 (C), 127.2 (CH), 139.9 (CH), 137.7 (C), 148.7 (C), 149.4 (C), 167.8 (C), 172.0 (C) ppm. HRMS (EI): calcd. for $C_{26}H_{35}NO_6$ 457.2464; found 457.2465.

**Diethyl 1-(3-Chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7d):** Yield: 250 mg, 73%. $^1H$ NMR: $\delta$ = 1.23 (t, $J$ = 7.2 Hz, 3 H), 1.31 (t, $J$ = 7.1 Hz, 6 H), 2.03 (s, 6 H), 2.44 (d, $J$ = 6.0 Hz, 2 H), 4.08 (q, $J$ = 7.2 Hz, 2 H), 4.21 (q, $J$ = 7.1 Hz, 4 H), 4.36 (t, $J$ = 6.0 Hz, 1 H), 7.10–7.15 (m, 1 H), 7.25–7.28 (m, 1 H), 7.40–7.45 (m, 2 H) ppm. $^{13}C$ NMR: $\delta$ = 14.0 ($CH_3$), 14.1 ($CH_3$), 18.3 ($CH_3$), 31.1 (CH), 41.5 ($CH_2$), 59.88 ($CH_2$), 59.91 ($CH_2$), 104.5 (C), 128.6 (CH), 128.9 (CH), 130.1 (CH), 130.4 (CH), 134.8 (C), 141.3 (C), 147.6 (C), 167.5 (C), 171.8 (C) ppm. HRMS (EI): calcd. for $C_{23}H_{28}ClNO_6$ 449.1605; found 449.1602.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-1-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7e):** Yield: 194 mg, 60%. $^1H$ NMR: $\delta$ = 1.27 (t, $J$ = 7.2 Hz, 3 H), 1.31 (t, $J$ = 7.2 Hz, 6 H), 1.99 (s, 6 H), 2.42 (d, $J$ = 6.5 Hz, 2 H), 4.12 (q, $J$ = 7.2 Hz, 2 H), 4.16–4.28 (m, 4 H), 4.38 (t, $J$ = 6.5 Hz, 1 H), 6.60–6.65 (m, 1 H), 6.73–6.77 (m, 1 H), 6.90–6.95 (m, 1 H), 7.20–7.25 (m, 1 H), 8.18 (br. s, 1 H) ppm. $^{13}C$ NMR: $\delta$ = 14.0 ($CH_3$), 14.2 ($CH_3$), 18.3 ($CH_3$), 31.4 (CH), 41.5 ($CH_2$), 60.1 ($CH_2$), 60.6 ($CH_2$), 103.2 (C), 115.8 (CH), 117.2 (CH), 121.5 (CH), 129.7 (CH), 140.8 (C), 149.0 (C), 157.8 (C), 168.0 (C), 173.2 (C) ppm. HRMS (EI): calcd. for $C_{23}H_{29}NO_7$ 431.1944; found 431.1946.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-1-(2-iodophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7f):** Yield: 203 mg, 50%. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 1.22 ($t_A$, $J$ = 7.1 Hz, 1.33 H), 1.25 ($t_S$, $J$ = 7.1 Hz, 1.67 H), 1.32 ($t_S$ + $t_A$, $J$ = 7.1 Hz, 6 H), 1.92 ($s_S$, 3.35 H), 2.04 ($s_A$, 2.65 H), 2.47 ($d_A$, $J$ = 5.4 Hz, 0.9 H), 2.64 ($d_S$, $J$ = 6.6 Hz, 1.1 H), 4.07 ($m_{S+A}$, 2 H), 4.15–4.25 ($m_{S+A}$, 4 H), 4.37 ($t_A$, $J$ = 5.4 Hz, 0.45 H), 4.42 ($t_S$, $J$ = 6.8 Hz, 0.55 H), 7.10–7.15 ($m_{S+A}$, 1 H), 7.10–7.15 ($m_{S+A}$, 1 H), 7.21 ($dd_S$, $J$ = 7.8, 1.5 Hz, 0.55 H), 7.39 ($dd_A$, $J$ = 7.7, 1.5 Hz, 0.45 H), 7.42–7.45 ($m_{S+A}$, 1 H), 7.93 ($dd_A$, $J$ = 8.0, 1.3 Hz, 0.45 H), 7.96 ($dd_S$, $J$ = 7.8 Hz, 1.5 0.55 H) ppm. $^{13}C$ NMR (150.8 MHz, $CDCl_3$): $\delta$ = 14.21 ($CH_{3,S}$), 14.24 ($CH_{3,A}$), 14.28 (2 $CH_{3,S}$), 14.33 (2 $CH_{3,A}$), 18.0 (2 $CH_{3,A}$), 18.7 (2 $CH_{3,S}$), 31.3 ($CH_S$), 31.5 ($CH_A$), 42.2 ($CH_{2,A}$), 44.0 ($CH_{2,S}$), 59.91 ($CH_{2,A}$), 59.97 ($CH_{2,A}$), 59.98 ($CH_{2,S}$), 60.1 (2 $CH_{2,S}$), 102.2 ($C_A$), 103.5 ($C_S$), 104.0 ($C_A$), 104.5 ($C_S$), 128.9 ($CH_S$), 130.0 ($CH_A$), 130.1 ($CH_A$), 130.2 ($CH_S$), 130.7 ($CH_A$), 132.0 ($CH_S$), 139.97 ($CH_S$), 139.99 ($CH_A$), 142.6 ($C_S$), 143.7 ($C_A$), 146.5 (2 $C_S$), 147.9 (2 $C_A$), 167.8 (2 $CO_A$), 167.9 (2 $CO_S$), 171.7 ($CO_S$), 172.3 ($CO_A$) ppm. HRMS (EI): calcd. for $C_{23}H_{28}INO_6$ 541.0961; found 541.0962.

**Diethyl 4-(2-Ethoxy-2-oxoethyl)-2,6-dimethyl-1-(naphthalen-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (7g):** Yield: 192 mg, 55%. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 1.25 ($t_A$, $J$ = 7.2 Hz, 2 H), 1.24 ($t_S$, $J$ = 7.2 Hz, 1 H), 1.32 ($t_S$ + $t_A$, $J$ = 7.1 Hz, 6 H), 1.921 and 1.923 ($s_A$ + $s_S$, 6 H), 2.52 ($d_A$, $J$ = 6.0 Hz, 1.3 H), 2.65 ($d_S$, $J$ = 6.4 Hz, 0.7 H), 4.11 ($q_A$, $J$ = 7.2 Hz, 1.3 H), 4.13 ($q_S$, $J$ = 7.1 Hz, 0.7 H), 4.17–4.26 ($m_A$ + $m_S$, 4 H), 4.46 ($t_A$, $J$ = 6.0 Hz, 0.65 H), 4.53 ($t_S$, $J$ = 6.4 Hz, 0.35 H), 7.29 ($dd_S$, $J$ = 7.1, 1.0 Hz, 0.35 H), 7.43 ($dd_A$, $J$ = 7.1, 1.2 Hz, 0.65 H), 7.51–7.62 ($m_A$ + $m_S$, 3 H), 7.68 ($m_A$, 0.65 H), 7.90–7.96 ($m_A$ + $m_S$, 2.35 H) ppm. $^{13}C$ NMR (150.8 MHz, $CDCl_3$): $\delta$ = 14.23 ($CH_{3,A}$), 14.31 ($CH_{3,S}$), 14.34 ($CH_{3,A+S}$), 17.4 ($CH_{3,A}$), 18.7 ($CH_{3,S}$), 31.4 ($CH_A$), 31.8 ($CH_S$), 42.0 ($CH_{2,A}$), 43.3 ($CH_{2,S}$), 59.98 (2 $OCH_{2,A}$), 60.01 (2 $OCH_{2,S}$) 60.06 ($OCH_{2,A}$), 60.11 ($OCH_{2,S}$), 103.5 ($C_A$), 104.1 ($C_S$), 122.3 ($CH_S$), 123.2 ($CH_A$), 124.9 ($CH_S$), 125.7 ($CH_A$), 126.7 ($CH_A$), 126.9 ($CH_S$), 127.5 ($CH_A$), 127.7 ($CH_A$), 127.8 ($CH_S$), 128.5 ($CH_S$), 128.6 ($CH_A$), 128.8 ($CH_S$), 129.2 ($CH_S$), 129.4 ($CH_A$), 132.0 ($C_S$), 132.6 ($C_A$), 134.1 ($C_A$), 134.3 ($C_S$), 136.4 ($C_S$), 137.5 ($C_A$), 148.2 (2 $C_S$), 149.1 (2 $C_A$), 167.9 (2 $CO_A$), 168.0 (2 $CO_S$), 171.8 ($CO_S$), 172.2 ($CO_A$) ppm. HRMS (EI): calcd. for $C_{27}H_{31}NO_6$ 465.2151; found 465.2154.

**Diethyl 1-(Biphenyl-2-yl)-4-(2-ethoxy-2-oxoethyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7h):** Yield: 144 mg, 39%. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 1.21 ($t_A$, $J$ = 7.1 Hz, 0.24 H), 1.23 ($t_S$, $J$ = 7.1 Hz, 2.76 H), 1.27 ($t_S$, $J$ = 7.1 Hz, 5.5 H), 1.28 ($t_A$, $J$ = 7.1 Hz, 0.5 H), 1.50 ($d_S$, $J$ = 7.2 Hz, 1.84 H), 1.92 ($s_A$, 0.24 H), 2.07 ($s_S$, 2.76 H), 2.45 ($d_A$, $J$ = 5.2 Hz, 0.16 H), 3.99 ($q_S$, $J$ = 7.1 Hz,

2.76 H), 4.06 ($q_S$, $J$ = 7.1 Hz, 0.24 H), 4.08–4.19 ($m_{S+A}$, 4 H), 4.21 ($t_S$, $J$ = 7.2 Hz, 0.92 H), 4.34 ($t_A$, $J$ = 5.2 Hz, 0.08 H), 7.17 (m, 2.7 H), 7.29–7.51 (m, Ar, 6.2 H), 7.57 ($dd_A$, $J$ = 7.8, 1.6 Hz, 0.1 H) ppm. $^{13}$C NMR (150.8 MHz, $CDCl_3$; only the signals of the major conformer are reported): $\delta$ = 14.2 ($CH_3$), 14.25 (2 $CH_3$), 19.0 (2 $CH_3$), 30.6 (CH), 41.3 ($CH_2$), 43.9 ($CH_2$), 59.7 ($CH_2$), 59.9 ($CH_2$), 103.6 (C), 127.8 (CH), 128.1 (CH), 128.4 (2 CH), 128.7 (2CH), 129.0 (CH), 131.4 (CH), 131.8 (CH), 137.8 (C), 138.4 (C), 142.2 (C), 147.8 (2 C), 167.9 (2CO), 171.6 (CO) ppm. HRMS (EI): calcd. for $C_{29}H_{33}NO_6$ 491.2308; found 491.2306.

**Di-*tert*-butyl 4-(2-Ethoxy-2-oxoethyl)-2,6-dimethyl-1-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylate (7j):** Yield: 251 mg, 71%. $^1$H NMR: $\delta$ = 1.23 (t, $J$ = 7.0 Hz, 3 H), 1.52 (s, 18 H), 1.99 (s, 6 H), 2.41 (d, $J$ = 6.2 Hz, 2 H), 4.09 (q, $J$ = 7.0 Hz, 2 H), 4.32 (t, $J$ = 6.2 Hz, 1 H), 7.15–7.20 (m, 2 H), 7.35–7.45 (m, 3 H) ppm. $^{13}$C NMR: $\delta$ = 14.4 ($CH_3$), 18.6 ($CH_3$), 28.5 ($CH_3$), 32.2 (CH), 41.9 ($CH_2$), 60.1 ($CH_2$), 79.9 (C), 105.5 (C), 128.7 (CH), 129.5 (CH), 130.6 (C), 140.7 (C), 147.5 (C), 167.4 (C), 172.3 (C) ppm. HRMS (EI): calcd. for $C_{27}H_{37}NO_6$ 471.2621; found 471.2621.

**Di-*tert*-butyl 4-(2-Ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7k):** Yield: 263 mg, 70%. $^1$H NMR: $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H), 1.51 (s, 18 H), 1.99 (s, 6 H), 2.39 (d, $J$ = 6.2 Hz, 2 H), 3.85 (s, 3 H), 4.08 (q, $J$ = 7.1 Hz, 2 H), 4.30 (t, $J$ = 6.2 Hz, 1 H), 6.90–6.95 (m, 2 H), 7.05–7.10 (m, 2 H) ppm. $^{13}$C NMR: $\delta$ = 14.1 ($CH_3$), 18.2 ($CH_3$), 28.2 ($CH_3$), 31.9 (CH), 41.6 ($CH_2$), 55.4 ($CH_3$), 59.8 ($CH_2$), 79.6 (C), 105.1 (C), 114.2 (CH), 131.1 (CH), 133.0 (C), 147.8 (C), 159.2 (C), 167.1 (C), 172.1 (C) ppm. HRMS (EI): calcd. for $C_{28}H_{39}NO_7$ 501.2726; found 501.2728.

**Di-*tert*-butyl 1-(3-Chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7l):** Yield: 170 mg, 45%. $^1$H NMR: $\delta$ = 1.22 (t, $J$ = 7.3 Hz, 3 H), 1.49 (s, 18 H), 1.98 (s, 6 H), 2.40 (d, $J$ = 6.0 Hz, 2 H), 4.07 (q, $J$ = 7.3 Hz, 2 H), 4.27 (t, $J$ = 6.0 Hz, 1 H), 7.08–7.13 (m, 1 H), 7.35–7.40 (m, 2 H) ppm. $^{13}$C NMR: $\delta$ = 14.2 ($CH_3$), 18.3 ($CH_3$), 28.2 ($CH_3$), 32.0 (CH), 41.7 ($CH_2$), 60.0 ($CH_2$), 79.9 (C), 105.9 (C), 128.9 (2 CH), 130.1 (CH), 130.7 (CH), 134.9 (C), 141.8 (C), 146.7 (C), 167.0 (C), 172.1 (C) ppm. HRMS: calcd. for $C_{27}H_{36}ClNO_6$ 505.2231; found 505.2233.

**Ethyl 2-(3,5-Diacetyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridin-4-yl)acetate (7m):** Yield: 146 mg, 55%. $^1$H NMR: $\delta$ = 1.24 (t, $J$ = 7.3 Hz, 3 H), 1.98 (s, 6 H), 2.35 (d, $J$ = 7.1 Hz, 2 H), 2.41 (s, 6 H), 4.09 (q, $J$ = 7.1 Hz, 2 H), 4.32 (t, $J$ = 7.1 Hz, 1 H), 7.15–7.20 (m, 2 H), 7.40–7.50 (m, 3 H) ppm. $^{13}$C NMR: $\delta$ = 14.1 ($CH_3$), 18.7 ($CH_3$), 29.9 ($CH_3$), 31.7 (CH), 41.3 ($CH_2$), 60.6 ($CH_2$), 114.0 (C), 128.9 (CH), 129.5 (CH), 130.1 (CH), 139.8 (C), 146.2 (C), 171.6 (C), 198.8 (C) ppm. HRMS (EI): calcd. for $C_{21}H_{25}NO_4$ 355.1783; found 355.1781.

**Ethyl 2-[3,5-Diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl]acetate (7n):** Yield: 164 mg, 57%. $^1$H NMR: $\delta$ = 1.25 (t, $J$ = 7.0 Hz, 3 H), 1.99 (s, 6 H), 2.34 (d, $J$ = 7.1 Hz, 2 H), 2.41 (s, 6 H), 3.86 (s, 3 H), 4.10 (q, $J$ = 7.2 Hz, 2 H), 4.31 (t, $J$ = 7.0 Hz, 1 H), 6.95–7.00 (m, 2 H), 7.05–7.10 (m, 2 H) ppm. $^{13}$C NMR: $\delta$ = 14.4 ($CH_3$), 18.9 ($CH_3$), 30.1 ($CH_3$), 31.9 (CH), 41.5 ($CH_2$), 55.8 ($CH_3$), 60.8 ($CH_2$), 114.2 (C), 114.8 (CH), 131.1 (CH), 132.5 (C), 146.9 (C), 159.8 (C), 171.8 (C), 199.0 (C) ppm. HRMS (EI): calcd. for $C_{22}H_{27}NO_5$ 385.1889; found 385.1887.

**Diethyl 4-(3-Chlorophenylamino)-2-(2-ethoxy-2-oxoethyl)-6-methylcyclohexa-3,5-diene-1,3-dicarboxylate (10d):** Yield: 30 mg, 9%. $^1$H NMR: $\delta$ = 1.20–1.35 (m, 9 H), 2.00 (d, $J$ = 1.5 Hz, 3 H), 2.28 (dd, $J$ = 14.5, 10.5 Hz, 1 H), 2.42 (dd, $J$ = 14.5, 4.5 Hz, 1 H), 3.15 (d, $J$ = 1.5 Hz, 1 H), 3.86 (ddd, $J$ = 4.5, 10.5, 1.5 Hz, 1 H), 4.10–4.25 (m, 6 H), 6.06 (br. q, $J$ = 1.5 Hz, 1 H), 6.85–6.90 (m, 1 H), 6.95–7.05 (m, 1 H), 7.05–7.10 (m, 1 H), 7.22 (t, $J$ = 8.0 Hz, 1 H),10.35 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.1 ($CH_3$), 14.2 ($CH_3$), 14.4 ($CH_3$), 24.3 ($CH_3$), 32.7 (CH), 36.9 ($CH_2$), 48.2 (CH), 59.6 ($CH_2$), 60.4 ($CH_2$), 61.1 ($CH_2$), 94.1 (C), 118.5 (CH), 121.1 (CH), 122.8 (CH), 123.7 (CH), 129.9 (CH), 134.5 (C), 141.0 (C), 142.1 (C), 149.8 (C), 169.3 (C), 171.3 (C), 172.2 (C) ppm. HRMS (EI): calcd. for $C_{23}H_{28}ClNO_6$ 449.1605; found 449.1603.

**Diethyl 2-(2-Ethoxy-2-oxoethyl)-4-(3-hydroxyphenylamino)-6-methylcyclohexa-3,5-diene-1,3-dicarboxylate (10e):** Yield: 23 mg, 7%. $^1$H NMR: $\delta$ = 1.25–1.35 (m, 9 H), 1.97 (d, $J$ = 1.5 Hz, 3 H), 2.29 (dd, $J$ = 14.5, 10.5 Hz, 1 H), 2.42 (dd, $J$ = 14.5, 4.6 Hz, 1 H), 3.14 (d, $J$ = 1.4 Hz, 1 H), 3.87 (ddd, $J$ = 4.5, 10.5, 1.5 Hz, 1 H), 4.10–4.25 (m, 6 H), 6.14 (br. q, $J$ = 1.5 Hz, 1 H), 6.50–6.60 (m, 3 H), 7.13 (t, $J$ = 8.0 Hz, 1 H), 10.30 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.1 ($CH_3$), 14.2 ($CH_3$), 14.5 ($CH_3$), 24.3 ($CH_3$), 32.8 (CH), 37.1 ($CH_2$), 48.2 (CH), 59.5 ($CH_2$), 60.4 ($CH_2$), 61.2 ($CH_2$), 92.6 (C), 110.3 (CH), 111.2 (CH), 115.3 (CH), 119.2 (CH), 129.9 (CH), 140.6 (C), 141.5 (C), 150.7 (C), 156.7 (C), 169.4 (C), 172.0 (C), 172.4 (C) ppm. HRMS (EI): calcd. for $C_{23}H_{29}NO_7$ 431.1944; found 4311.1942.

**Diethyl 2-(2-Ethoxy-2-oxoethyl)-4-(2-iodophenylamino)-6-methylcyclohexa-3,5-diene-1,3-dicarboxylate (10f):** Yield: 69 mg, 17%. $^1$H NMR: $\delta$ = 1.20–1.35 (m, 9 H), 1.96 (d, $J$ = 1.5 Hz, 3 H), 2.31 (dd, $J$ = 14.5, 10.9 Hz, 1 H), 2.45 (dd, $J$ = 14.5, 4.3 Hz, 1 H), 3.15 (d, $J$ = 1.5 Hz, 1 H), 3.88 (ddd, $J$ = 4.3, 10.9, 1.5 Hz, 1 H), 4.10–4.30 (m, 6 H), 5.78 (dq, $J$ = 1.5 Hz, 1 H), 6.75–6.80 (m, 1 H), 7.10–7.05 (m, 1 H), 7.25–7.30 (m, 1 H), 7.80–7.85 (m, 1 H), 10.24 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.4 ($CH_3$), 14.5 ($CH_3$), 14.8 ($CH_3$), 24.5 ($CH_3$), 33.1 (CH), 37.1 ($CH_2$), 48.4 (CH), 59.9 ($CH_2$), 60.6 ($CH_2$), 61.2 ($CH_2$), 94.0 (C), 95.0 (C), 119.3 (CH), 124.2 (CH), 125.5 (CH), 128.9 (CH), 139.6 (CH), 141.6 (C), 141.7 (C), 149.6 (C), 169.3 (C), 171.6 (C), 172.5 (C) ppm. HRMS (EI): calcd. for $C_{23}H_{28}NO_6I$ 541.0961; found 541.0961.

**Diethyl 2-(2-Ethoxy-2-oxoethyl)-6-methyl-4-(naphthalen-1-ylamino)-cyclohexa-3,5-diene-1,3-dicarboxylate (10g):** Yield: 22 mg, 77%. $^1$H NMR: $\delta$ = 1.20–1.40 (m, 9 H), 1.92 (d, $J$ = 1 Hz 5, 3 H), 2.35 (dd, $J$ = 14.6, 10.4 Hz, 1 H), 2.51 (dd, $J$ = 14.4, 4.2 Hz, 1 H), 3.17 (d, $J$ = 1.7 Hz, 1 H), 3.949 (ddd, $J$ = 4.2, 10.4, 1.6 Hz, 1 H), 4.10–4.30 (m, 6 H), 5.78 (br. q, $J$ = 1.5 Hz, 1 H), 7.10–7.15 (m, 1 H), 7.40–7.55 (m, 2 H), 7.60–7.75 (m, 2 H), 7.80–7.85- (m, 1 H), 8.05–8.10 (m, 1 H), 10.79 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.2 ($CH_3$), 14.3 ($CH_3$), 14.6 ($CH_3$), 24.3 ($CH_3$), 32.9 (CH), 37.3 ($CH_2$), 48.3 (CH), 59.4 ($CH_2$), 60.3 ($CH_2$), 61.0 ($CH_2$), 92.5 (C), 119.1 (CH), 121.4 (CH), 122.6 (CH), 125.0 (CH), 125.4 (CH), 126.30 (CH), 126.33 (CH), 128.1 (CH), 134.3 (C), 135.4 (C), 139.4 (C), 141.7 (C), 151.7 (C), 169.7 (C), 171.5 (C), 172.3 (C) ppm. HRMS (EI): calcd. for $C_{27}H_{31}NO_6$ 465.2151; found 465.2153.

**Diethyl 4-(Biphenyl-2-ylamino)-2-(2-ethoxy-2-oxoethyl)-6-methylcyclohexa-3,5-diene-1,3-dicarboxylate (10h):** Yield: 92 mg, 25%. $^1$H NMR: $\delta$ = 1.15–1.30 (m, 9 H), 1.95 (d, $J$ = 1.3 Hz, 3 H), 2.20 (dd, $J$ = 14.4, 10.5 Hz, 1 H), 2.37 (dd, $J$ = 14.4, 4.1 Hz, 1 H), 3.10 (br. s, 1 H), 3.89 (br. dd, $J$ = 4.1, 10.5 Hz, 1 H), 4.05–4.25 (m, 6 H), 5.78 (m, 1 H), 7.05–7.10 (m, 1 H), 7.15–7.25 (m, 1 H), 7.25–7.45 (m, 7 H), 10.01 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.1 ($CH_3$), 14.2 ($CH_3$), 14.4 ($CH_3$), 24.3 ($CH_3$), 32.8 (CH), 37.2 ($CH_2$), 48.2 (CH), 59.2 ($CH_2$), 60.2 ($CH_2$), 60.9 ($CH_2$), 93.0 (C), 119.1 (CH), 124.6 (CH), 125.4 (CH), 127.2 (CH), 127.8 (CH), 128.4 (CH), 129.2 (CH), 130.7 (CH), 136.2 (C), 136.9 (C), 138.9 (C), 141.4 (C), 150.3 (C), 168.9 (C), 171.4 (C), 172.3 (C) ppm. HRMS (EI): calcd. for $C_{29}H_{33}NO_6$ 491.2308; found 491.2310.

**Diethyl 4-(2-*tert*-Butylphenylamino)-2-(2-ethoxy-2-oxoethyl)-6-methylcyclohexa-3,5-diene-1,3-dicarboxylate (10i):** Yield: 95 mg,

27%. $^1$H NMR: $\delta$ = 1.20–1.35 (m, 9 H), 1.40 (s, 9 H), 1.89 (d, $J$ = 1.3 Hz, 3 H), 2.31 (dd, $J$ = 14.4, 10.5 Hz, 1 H), 2.49 (dd, $J$ = 14.4, 4.6 Hz, 1 H), 3.11 (d, $J$ = 1.3 Hz, 1 H), 3.89 (ddd, $J$ = 4.6, 10.5, 1.3 Hz, 1 H), 4.10–4.25 (m, 6 H), 5.78 (d, $J$ = 1.3 Hz, 1 H), 6.85–6.95 (m, 1 H), 7.10–7.20 (m, 2 H), 7.35–7.45 (m, 1 H), 10.34 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 14.4 ($CH_3$), 14.5 ($CH_3$), 14.8 ($CH_3$), 24.5 ($CH_3$), 30.7 ($CH_3$), 33.2 (CH), 35.2 (C), 37.9 ($CH_2$), 48.7 (CH), 59.4 ($CH_2$), 60.5 ($CH_2$), 61.1 ($CH_2$), 91.2 (C), 119.1 (CH), 126.0 (CH), 126.6 (CH), 126.9 (CH), 129.7 (CH), 138.1 (C), 142.1 (C), 145.4 (C), 151.9 (C), 169.9 (C), 171.7 (C), 172.6 (C) ppm. HRMS (EI): calcd. for $C_{27}H_{37}NO_6$ 471.2621; found 471.2623.

**Calculations:** Computations were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs:[11] the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies.

**Supporting Information** (see footnote on the first page of this article): NOE spectra and kinetic data of compounds **7f**–**h**; $^1$H and $^{13}$C NMR spectra of **7a**–**n**; computational data of **7f**–**h**.

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