Formation of Novel Photodimers from 4-Aryl-1,4-dihydropyridines

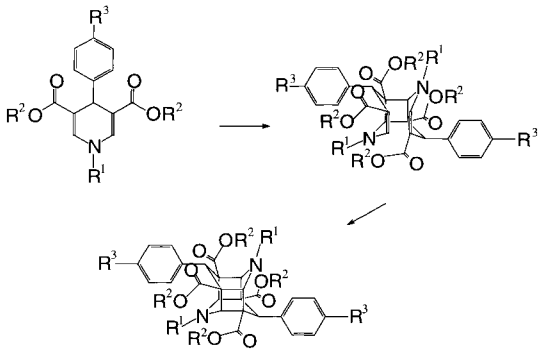
Andreas Hilgeroth*[a] and Ute Baumeister[b]

Abstract: *N*-substituted 3-alkoxycarbonyl-4-aryl-1,4-dihydropyridines have been photochemically investigated for the first time. In contrast to reports of analogous 3,5-dialkoxycarbonyl derivatives, they are unreactive in the solid state with shortest distances of potentially reacting double bonds of 6.883(3) Å for one derivative examined by x-ray crystal structure analysis. Solution irradiation with unfiltered light ($\lambda \geq 270$ nm) led to novel diazatetrakishomocubanes in 30–50% yields. Diazatetrakishomocubanes were also obtained by irradiation with filtered light ($\lambda > 313$ nm) besides head-to-tail connected *syn*-dimers. The irradiation of the *syn*-dimers with unfiltered light led to centrosymmetric cage dimers accompanied by some dimer fragmentation. Formation of the homocubanes via intermediate biradicals is supported by the available data.

Keywords: cubanes · dimerization · photochemistry · radicals · solid-state reactions

Introduction

The compounds 3,5-dialkoxycarbonyl-aryl-1,4-dihydropyridines have recently been reported to be highly photoreactive agents in the solid state.[1] They almost exclusively yielded head-to-tail cage dimers when irradiated at $\lambda \geq 270$ nm. The reaction proceeded via *syn*-dimeric intermediates as was demonstrated by solid-state ^{13}C NMR spectroscopy.[2] Thus the formation followed a double [2+2] cycloaddition reaction pathway (Scheme 1).



Scheme 1. Formation of head-to-tail cage dimers via *syn*-dimeric intermediates from 4-aryl-1,4-dihydropyridines ($R^1 = H$, $CH_2C_6H_5$, $R^2 = CH_3$, C_2H_5, and $R^3 = OCH_3$).

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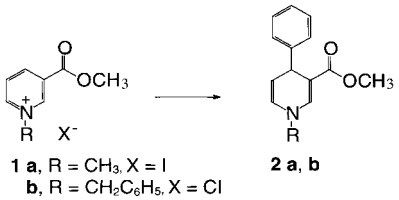
The *N*-substituted cage dimers possessing C_2 symmetry have been suggested to be novel inhibitors of HIV-1 protease (PR) on the basis of molecular modeling results.[3] For the first series of such derivatives, *N*-benzyl substituted compounds turned out to be the best PR inhibitors with inhibitory activities IC_{50} of about 20 μM.[4]

In order to vary the substitution patterns of the pharmacologically interesting cage compounds, 1,4-dihydropyridines with just one 3-alkoxycarbonyl substituent have been chosen as further synthetic starting compounds. There are only a few reports of the photooxidation of 4-substituted 1,4-dihydropyridines bearing one carbonyl substituent at the 3-position of the 1,4-dihydropyridine ring. The characteristic photooxidation products are pyridines.[5]

Here we report the photochemical properties of *N*-alkyl 4-aryl-1,4-dihydropyridines with one 3-methoxycarbonyl substituent and we focus on solid-state as well as solution reactivity. Irradiation at varying wavelengths has been carried out to get an insight into the reaction mechanism by which the observed different cage dimers are formed.

Results and Discussion

Synthesis of *N*-alkyl 3-methoxycarbonyl-4-phenyl-1,4-dihydropyridines: Starting 1,4-dihydropyridines **2a**, **2b** (Scheme 2) have been prepared from the corresponding pyridinium salts **a**,**b**[6] by treatment with equimolar amounts of phenylmagnesium chloride in anhydrous THF. Arylation occurred selectively at the 4-position of the pyridine ring by using catalytic copper(I) iodide with isolated yields of about 90%.



Scheme 2. Formation of **2a**,**b**. Reagents and conditions: PhMgCl, CuI (cat.).

Solid-state chemistry: For the investigation of the solid-state photoreactivity, crystalline 1,4-dihydropyridine materials grown from solutions in ethanol (**2a**) and methanol (**2b**) were used. Irradiation was carried out with Ultra Vitalux lamps exhibiting emission spectra at $\lambda \geq 270$ nm for several days under excitation of the dihydropyridine chromophore with $\lambda_{max} = 348$ nm (**2a**) and 346 nm (**2b**).

Since the crystalline 1,4-dihydropyridines remained unchanged, these materials are essentially photostable. X-ray crystal structure analysis of derivative **2a** (Figure 1) was carried out in order to characterize the topochemical properties responsible for this behavior.

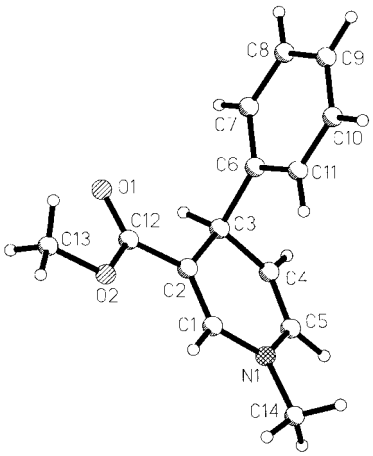


Figure 1. Molecular structure of **2a** in the crystal.

The 4-phenyl substituent in the molecular structure of **2a** (Figure 2) shows a pseudoaxial orientation as has been reported for the corresponding derivatives with carbonyl substituents in the 3- and 5-positions of the dihydropyridine ring.[1] This molecular conformation with pseudoaxial 4-phenyl positioning has also previously been favored by molecular modeling.[7]

Molecules form one-dimensional stacks generated by translation along [010] in the crystal lattice. Molecules of neighboring stacks show antiparallel orientation due to the centrosymmetrical arrangement. However, the shortest distance between potentially reacting double bonds of such a molecule pair is 6.883(3) Å between C1−C2a and C2−C1a, respectively. This distance substantially exceeds the previously postulated maximum distance of 4.2 Å for potentially reacting double bonds in the solid state.[8] Thus the photostability of the derivative results from unfavorable packing restraints.

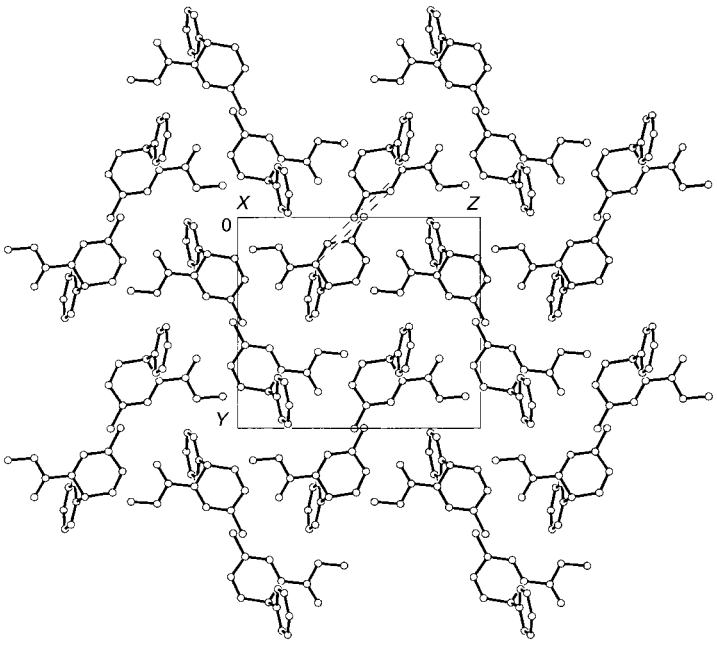
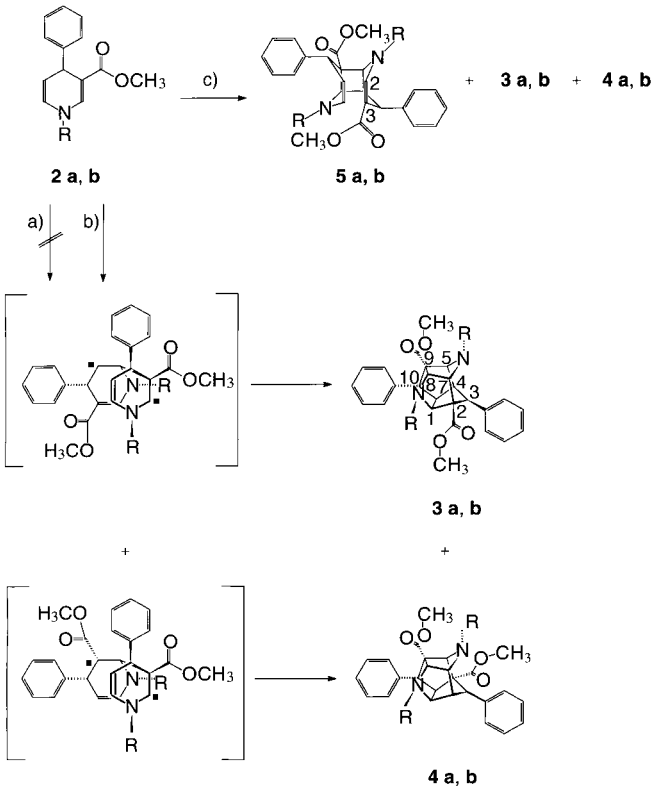


Figure 2. Crystal packing of **2a** (projection along [100]) and shortest distances between neighboring double bonds.

Solution photoreactivity: Irradiation of solutions of 1,4-dihydropyridines **2a**,**b** in methanol/THF, carried out in a quartz flask, led to the exclusive formation of two different dimers: one with symmetric properties (**3**) (Scheme 3) as could be observed from just one set of proton signals for both



Scheme 3. Photoreactivity of 4-aryl-1,4-dihydropyridines **2**. Reagents and conditions: a) *hν*, solid state; b) *hν*, MeOH/THF, $\lambda \geq 270$ nm; c) *hν*, MeOH/THF, $\lambda > 313$ nm ($R = CH_3$, $CH_2C_6H_5$).

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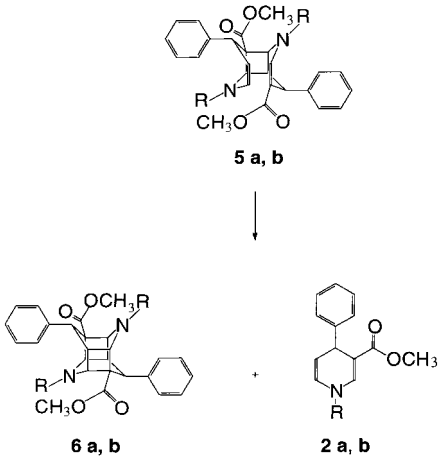
subunits and one IR carbonyl bond and the other one with asymmetric character (**4**) documented by a double set of proton signals as well as two IR carbonyl bonds.

X-ray crystal structure analyses of both dimers **3a** and **4a**[9] showed an unexpected arrangement of the dihydropyridine subunits in the dimers: instead of the known head-to-tail ring conjunction of all previous dihydropyridine dimerization products, the dihydropyridine ring planes in **3** and **4** make an angle of just 90°. Thus, the resulting dimers are novel tetrakishomocubanes instead of tetraasteranes. Mechanistic aspects of their formation will be discussed below. As a result of the pseudoaxial orientation of the phenyl substituents in the 1,4-dihydropyridines, all the phenyl rings in **3** and **4** show the same pseudoaxial arrangement to their dihydropyridine ring planes. Thus, the dimer formation may have resulted from the attack of one monomer at the back side of the other one, the side that faces away from the aryl moiety.

When irradiation was carried out with filtered (copper(II) sulfate solution) light at $\lambda > 313$ nm, the combined isolated yield of both dimers **3** and **4** decreased to about 60%. Another dimer was obtained that was characterized as the *syn*-dimer **5** by spectroscopic properties and, furthermore, by its cyclization to a cage compound as will be discussed later: the IR spectra showed two carbonyl bonds, one of the unconjugated ester carbonyl group at 1735 cm^{-1} (**5a**) and 1714 cm^{-1} (**5b**), and the other one of the conjugated carbonyl group at characteristic shorter wavelengths of 1659 cm^{-1} (**5a**) and 1680 cm^{-1} (**5b**). UV spectra show an absorption of the carbamide ester chromophore at 280 nm (**5a**) and 290 nm (**5b**).

Irradiation of the *syn*-dimers with unfiltered light led to centrosymmetrical cage dimers **6a** and **6b** (Scheme 4) under excitation of the remaining carbamide ester chromophore.



Scheme 4. Photolysis of *syn*-dimers **5**. Reagents and conditions: *hv*, MeOH/THF, $\lambda \geq 270$ nm (R = CH_3, $CH_2C_6H_5$).

The structure of the tetraasterane dimers **6** was confirmed by X-ray crystal structure analysis of compound **6a** (Figure 3) with a significant difference in cyclobutane bond lengths that has been reported for previous tetraasterane cage compounds derived from solid-state synthesis:[1] the mean bond lengths of the former dihydropyridine (C1a–C2a and C4a–C5a and its centrosymmetric equivalents with 1.561(2) and 1.548(2) Å) were significantly shorter than those that were obtained by the dimerization reaction (C1a–C4′ and C2a–C5′ and its centrosymmetric equivalents with 1.561(2) and 1.607(2) Å). The phenyl substituents in these dimers show pseudoaxial orientations towards the dihydropyridine planes as well.

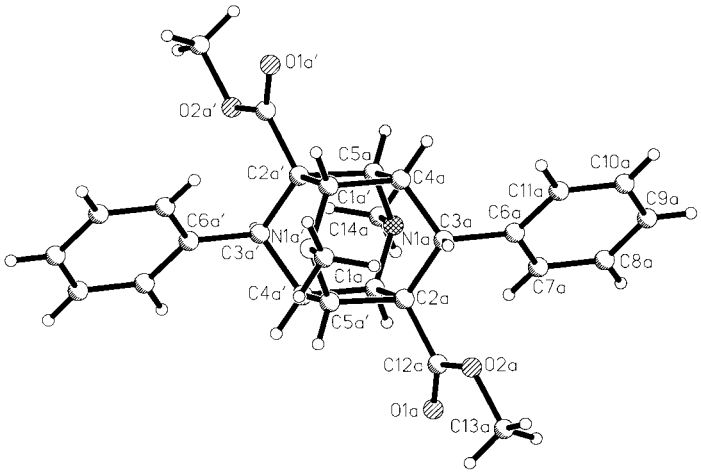


Figure 3. Molecular structure of **6a**.

Some fragmentation to monomeric 1,4-dihydropyridines **2a**,**b** could be observed by TLC during the irradiation of *syn*-dimers **5a** and **5b**. Irradiation of solutions of the cage dimers **6a** and **6b** themselves led to fragmentation back to the monomers. Thus, it becomes plausible that the above-mentioned formation of either *syn*-dimers **5a** and **5b** or their cyclization products **6a** and **6b** could not be observed after irradiation with unfiltered light.

Mechanistic aspects: In contrast to the 3,5-dialkoxycarbonyl-aryl-1,4-dihydropyridines, the 3-monosubstituted derivatives have two different double bonds, one conjugated and one nonconjugated. So there are several reaction possibilities for a primary excited molecule. Corresponding to recent studies on the photoreactivity of substituted ethylene derivatives with enhanced conjugation of the ethylene double bond,[10] a primary radical attack via C3 (conjugated double bond) of the excited dihydropyridine molecule may take place either at C2 (conjugated double bond) or C6 (nonconjugated double bond) of the other molecule; this is in accordance with the formation of all known 1,4-dihydropyridine dimers showing head-to-tail arrangements. The formation of *syn*-dimers **5** presumably follows a classical concerted [2+2] photocycloaddition reaction mechanism between the conjugated double bond of the excited molecule and the nonconjugated double bond of the other one in the ground state with both dihydropyridine planes making an angle of 180° as has been reported.[1, 11] A second intramolecular excitation of one carbamide ester chromophore is necessary to initiate a radical mechanism for the cyclization to cage dimers **6**.

It is likely that the formation of **3** and **4** involves primary biradicals, and thus it follows the initial reaction step of the reported [2+2] cycloaddition reactions of the primary attack via C3 of the excited molecule and either at C2 or C6 of the

other one with both dihydropyridine planes making an angle of 90°.[10, 11]

As has been demonstrated by the irradiation experiments with filtered light, the formation of **3** and **4** does not involve a second molecular excitation of the intermediate carbamide ester chromophore. The dimers are formed, even though the shorter wavelengths necessary to excite the carbamide ester chromophore are absent. Perhaps, consequent reactions of primary formed biradicals may lead to the cage closure.

In conclusion, the photoreactivity of 3-alkoxycarbonyl monosubstituted 4-aryl-1,4-dihydropyridines substantially differs from that of the corresponding 3,5-disubstituted derivatives. The monomers were found to be photostable in the solid state due to packing restraints. The previously unreported tetrakishomocubanes were formed in solution as well as *syn* and centrosymmetric cage compounds that were found to be unstable on further irradiation. The C_2 symmetry of the homocubanes qualifies them for binding to C_2-symmetric PR. Therefore they are of special interest as potential PR inhibitors. Moreover, recent studies suggested that such cage compounds were novel inhibitors of P-glycoprotein.[12] With respect to their biological activity, investigations on further structural variations of the homocubane skeleton are in progress.

Experimental Section

General: Commercial reagents were used as received, without additional purification. Melting points were determined with a Boetius apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 500 at 25 °C with TMS as the internal standard. IR spectra were measured as potassium bromide disks using a Bruker IFS-28. UV measurements were taken in chloroform with a diode-array spectrophotometer 8452A. Mass spectra were obtained with an AMD 402, and elemental analysis was carried out using a Leco CHNS-932 apparatus.

Procedure for the preparation of *N*-alkyl 4-phenyl-1,4-dihydropyridines (2)

Methyl 1,4-dihydro-1-methyl-4-phenylpyridine-3-carboxylate (***2a***): Pyridinium salt **1a** (1.5 g, 10 mmol) was suspended in anhydrous THF (100 mL). After addition of copper(I) iodide[9] (0.095 g, 0.5 mmol), a solution of phenylmagnesium chloride (1M) in THF (10 mL, 10 mmol) was added dropwise to the suspension. After 2 h, the solution was treated with an aqueous solution (60 mL) of ammonium chloride (60 mL, 113 mmol) and then extracted with diethyl ether (150 mL). For washing details of the ether phase, see ref. [9]. After final removal of the ether phase in vacuum, the oily residue was taken up in ethanol from which **2a** crystallized with a final yield of 91% (m.p. 115–120 °C; 2.086 g, 9.1 mmol).

^{1}H NMR (CD_3OD): $\delta = 7.87-7.09$ (m, 6H; aromatic H, 2-H), 5.94 (d, $^3J(H,H) = 7.8$ Hz, 1H; 6-H), 4.89 (dd, $^3J(H,H) = 7.8$, 4.7 Hz, 1H; 5-H), 4.41 (d, $^3J(H,H) = 4.7$ Hz, 1H; 4-H), 3.53 (s, 3H; $COOCH_3$), 3.10 (s, 3H; NCH_3); IR: $\tilde{\nu} = 1690\ cm^{-1}$; UV/Vis (methanol): λ_{max} (ε) = 232 (6166), 348 nm (4365 $mol^{-1}\,dm^3\,cm^{-1}$); MS (70 eV, EI): *m*/*z* (%): 229 (2) $[M]^+$, 169 (100) $[M-60]^+$; elemental analysis calcd (%) for $C_{14}H_{15}NO_2$ (229.3): C 73.34, H 6.59, N 6.11; found: C 73.10, H 6.53, N 5.92.

X-ray crystal structure analysis: A yellow crystal $C_{14}H_{15}NO_2$ (from ethanol), crystal size 0.80 × 0.48 × 0.27 mm, was measured at room temperature by using a Stoe-STADI4 Diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and a graphite monochromator. The number of reflections collected was 5984, and they were collected in the range $4.64° \le 2\Theta \le 55.94°$ in $2\theta/\omega$ scan mode; *h*,*k*,*l* range from −10, −15, −17 to 10, 15, 17. Crystal system: monoclinic, space group $P2_1/n$, $Z = 4$, $a = 8.0365(12)$ Å, $b = 11.721(2)$ Å, $c = 13.643(3)$ Å, $\beta = 104.85(2)°$; $V = 1242.2(3)$ Å^3; $\rho = 1.226\ g\,cm^{-3}$; $\mu = 0.082\ mm^{-1}$. No absorption correction was applied during data reduction. The structure was solved by direct methods (SHELXS-97). Structure refinement: full matrix least-squares methods on F^2 using SHELXL-97, all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference Fourier synthesis and isotropically refined. The refinement converged to a final $wR_2 = 0.1317$ for 2992 unique reflections and $R_1 = 0.0553$ for 1072 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 215 refined parameters.

Methyl 1-benzyl-1,4-dihydro-4-phenylpyridine-3-carboxylate (***2b***): Yield: 88% (2.69 g, 8.8 mmol); m.p. 80–82 °C.

^{1}H NMR ($CDCl_3$): $\delta = 7.38-7.23$ (m, 11H; aromatic H, 2-H), 5.89 (d, $^3J(H,H) = 7.8$ Hz, 1H; 6-H), 4.91 (dd, $^3J(H,H) = 7.8$, 4.7 Hz, 1H; 5-H), 4.52 (d, $^3J(H,H) = 4.7$ Hz, 1H; 4-H), 4.42 (s, 2H; NCH_2), 3.56 (s, 3H; $COOCH_3$); IR: $\tilde{\nu} = 1695\ cm^{-1}$; UV/Vis (methanol): λ_{max} (ε) = 218 (13183), 346 nm (4266 $mol^{-1}\,dm^3\,cm^{-1}$); MS (70 eV, EI): *m*/*z* (%): 305 (10) $[M]^+$, 290 (3) $[M-CH_3]^+$, 274 (4) $[M-OCH_3]^+$, 228 (100) $[M-Ph]^+$; elemental analysis calcd (%) for $C_{20}H_{19}NO_2$ (305.4): C 78.66, H 6.27, N 4.59; found: C 78.63, H 6.48, N 4.59.

Irradiation experiments

Method A, *solid-state irradiation at* $\lambda \ge 270$ *nm*: The compound 4-phenyl-1,4-dihydropyridine (**2a**) (1.0 g, 4.36 mmol) with a layer thickness of 1 mm was irradiated with an Ultra Vitalux lamp from a distance of 60 cm at a temperature of 25 °C. After several days, the 1,4-dihydropyridine was found to be unchanged as was proved by TLC.

Method B, *solution irradiation at* $\lambda \ge 270$ *nm*: The compound 4-phenyl-1,4-dihydropyridine (**2a**) (0.47 g, 2 mmol) was dissolved in THF (40 mL) under stirring. The solution was irradiated in a quartz flask with an Ultra Vitalux lamp from a distance of 60 cm at 25 °C. After eight weeks, the starting compound had almost vanished, and the formation of two products could be observed by TLC. The solvent was removed by evaporation. The adducts **3a** and **4a** were obtained by fractional crystallization.

Method C, *solution irradiation at* $\lambda > 313$ *nm*: The compound 4-phenyl-1,4-dihydropyridine (**2a**) was dissolved and irradiated as described above, except that irradiation was carried out in a bath of copper(II) sulfate (1.25M). After reduction of the solution volume, fractional crystallization led to isolation of compounds **5a**, **3a**, and **4a**.

The following yields of dimerization products are based on 0.47 g of **2** corresponding to 100%.

Dimethyl 6,12-dimethyl-3,10-diphenyl-6,12-diazapentacyclo[6.3.1.0^{2,7}.0^{4,11}.0^{5,9}]-dodecane-2,9-dicarboxylate (3a): Method B: 39% yield (0.183 g, 0.39 mmol); Method C: 26% yield (0.122 g, 0.27 mmol); m.p. 212–218 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.18-7.05$ (m, 10H; aromatic H), 4.59 (t, $^4J(H,H) = 1.9$ Hz, 2H; 7-, 8-H), 3.84 (dt, $^3J(H,H) = 9.4$, 2 × $^4J(H,H) = 1.9$ Hz, 2H; 1-, 5-H), 3.69 (s, 6H; $COOCH_3$), 3.37 (d, $^3J(H,H) = 1.9$ Hz, 2H; 3-, 10-H), 3.18 (AA′HH′RR′XX′, $^3J(H,H) = 9.4$, 1.9, 2 × $^4J(H,H) = 1.9$ Hz, 2H; 4-, 11-H), 2.04 (s, 6H; NCH_3); IR: $\tilde{\nu} = 1723\ cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 458 (3) $[M]^+$, 427 (2) $[M-OCH_3]^+$, 229 (34) $[M/2]^+$, 152 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{28}H_{30}N_2O_4$ (458.6): C 73.34, H 6.59, N 6.11; found: C 73.26, H 6.51, N 6.17.

Dimethyl 6,12-dibenzyl-3,10-diphenyl-6,12-diazapentacyclo[6.3.1.0^{2,7}.0^{4,11}.0^{5,9}]-dodecane-2,9-dicarboxylate (3b): Method B: 48% yield (0.226 g, 0.37 mmol); Method C: 28% yield (0.132 g, 0.22 mmol); m.p. 213–226 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.26-6.31$ (m, 20H; aromatic H), 4.87 (t, $^4J(H,H) = 1.8$ Hz, 2H; 7-, 8-H), 3.70 (s, 6H; $COOCH_3$), 3.68 (dt, $^3J(H,H) = 8.2$ Hz, 2 × $^4J(H,H) = 1.8$ Hz, 2H; 1-, 5-H), 3.57 (d, $^2J(H,H) = 13.2$ Hz, 2H; NCH_A), 3.36 (d, $^3J(H,H) = 1.8$ Hz, 2H; 3-, 10-H), 3.36 (d, $^2J(H,H) = 13.2$ Hz, 2H; NCH_B), 3.18 (AA′HH′RR′XX′, $^3J(H,H) = 8.2$, 1.8 Hz, 2 × $^4J(H,H) = 1.8$ Hz, 2H; 4-, 11-H); IR: $\tilde{\nu} = 1715\ cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 610 (2) $[M]^+$, 579 (1) $[M-OCH_3]^+$, 305 (47) $[M/2]^+$, 228 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{40}H_{38}N_2O_4$ (610.8): C 78.66, H 6.27, N 4.59; found: C 78.76, H 6.28, N 4.49.

Dimethyl 6,12-dimethyl-3,10-diphenyl-6,12-diazapentacyclo[6.3.1.0^{2,7}.0^{4,11}.0^{5,9}]-dodecane-2,11-dicarboxylate (4a): Method B: 42% yield (0.197 g, 0.43 mmol); Method C: 35% yield (0.164 g, 0.36 mmol); m.p. 188–191 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.19-7.03$ (m, 10H; aromatic H), 4.58 (d, $^4J(H,H) = 2.9$ Hz, 1H; 1-H), 4.43 (dd, $^3J(H,H) = 4.5$, $^4J(H,H) = 2.7$ Hz, 1H; 7-H), 3.76 (ddd, $^3J(H,H) = 8.9$, 4.9, $^4J(H,H) = 2.7$ Hz, 1H; 5-H), 3.75, 3.73 (2 × s, 6H; $COOCH_3$), 3.51 (ddd, $^3J(H,H) = 8.9$, 4.5, $^4J(H,H) = 2.9$ Hz, 1H; 8-H), 3.38 (d, $^3J(H,H) = 3.3$ Hz, 1H; 10-H), 3.36 (d, $^3J(H,H) = 3.1$ Hz, 1H; 3-H), 3.29 (ddd, $^3J(H,H) = 8.9$, 4.9, 3.3 Hz, 1H; 9-H), 3.25 (dd, $^3J(H,H) = 8.9$, 3.1 Hz, 1H; 4-H), 2.04, 2.00 (2 × s, 6H; NCH_3); IR: $\tilde{\nu} = 1713$, $1725\ cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 458 (15) $[M]^+$, 427 (4) $[M-$

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$OCH_3]^+$, 228 (35) $[M/2-1]^+$, 152 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{28}H_{30}N_2O_4$ (458.6): C 73.34, H 6.59, N 6.11; found: C 73.02, H 6.40, N 5.97.

Dimethyl 6,12-dibenzyl-3,10-diphenyl-6,12-diazapentacyclo[6.3.1.0^{2,7}.0^{4,11}.0^{5,9}]-dodecane-2,11-dicarboxylate (4b): Method B: 32% yield (0.151 g, 0.25 mmol); Method C: 31% yield (0.146 g, 0.24 mmol); m.p. > 360 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.35-7.19$ (m, 20H; aromatic H), 4.83 (d, $^2J(H,H) = 10.5$ Hz, 1H; NCH_A), 4.82 (d, $^2J(H,H) = 10.5$ Hz, 1H; NCH_B), 4.67 (d, $^4J(H,H) = 1.8$ Hz, 1H; 1-H), 4.33 (dd, $^3J(H,H) = 4.3$, $^4J(H,H) = 2.1$ Hz, 1H; 7-H), 4.29 (d, $^2J(H,H) = 13.3$ Hz, 1H; NCH_A), 4.27 (d, $^2J(H,H) = 13.3$ Hz, 1H; NCH_B), 4.03 (ddd, $^3J(H,H) = 10.5$, 5.1, $^4J(H,H) = 2.1$ Hz, 1H; 5-H), 3.73 (ddd, $^3J(H,H) = 10.5$, 4.3, $^4J(H,H) = 1.8$ Hz, 1H; 8-H), 3.65, 3.63 (2 × s, 6H; $COOCH_3$), 3.52 (d, $^3J(H,H) = 2.9$ Hz, 1H; 10-H), 3.48 (d, $^3J(H,H) = 2.8$ Hz, 1H; 3-H), 3.45 (dd, $^3J(H,H) = 10.5$, 2.8 Hz, 1H; 4-H), 3.36 (ddd, $^3J(H,H) = 10.5$, 5.1, 2.9 Hz, 1H; 9-H); IR: $\tilde{\nu} = 1731$, 1733 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 610 (1) $[M]^+$, 579 (1) $[M-OCH_3]^+$, 305 (36) $[M/2]^+$, 228 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{40}H_{38}N_2O_4$ (610.8): C 78.66, H 6.27, N 4.59; found: C 78.36, H 6.58, N 4.58.

Dimethyl 1,5,8,8bβ-tetrahydro-1,5-dimethyl-4,8-diphenyl-cyclobuta[1,2-b:3,4-b′]dipyridine-3,7(4H,4aβH,4bβH)dicarboxylate (5a): Method C: 33% yield (0.155 g, 0.34 mmol); m.p. 100–105 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.78$ (br s, 1H; 2-H), 7.29–7.15 (m, 10H; aromatic H), 5.11 (d, $^3J(H,H) = 7.0$ Hz, 1H; 6-H), 4.83 (dd, $^3J(H,H) = 7.0$, 4.0 Hz, 1H; 7-H), 4.45 (d, $^3J(H,H) = 7.0$ Hz, 1H; 4b-H), 3.80 (d, $^3J(H,H) = 9.5$ Hz, 1H; 8b-H), 3.68 (d, $^3J(H,H) = 2.5$ Hz, 1H; 4-H), 3.63 (s, 3H; C3–$COOCH_3$), 3.51 (d, $^3J(H,H) = 4.0$ Hz, 1H; 8-H), 3.47 (s, 3H; C8a–$COOCH_3$), 3.46 (ddd, $^3J(H,H) = 9.5$, 7.0, 2.5 Hz, 1H; 4a-H), 2.76 (s, 3H; C1–NCH_3), 2.64 (s, 3H; C5–NCH_3); IR: $\tilde{\nu} = 1659$, 1735 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 242 (14125), 280 nm (5888 mol^{-1} dm^3 cm^{-1}); MS (ESI): *m*/*z* (%): 459 (100) $[M+H^+]$; elemental analysis calcd (%) for $C_{28}H_{30}N_2O_4$ (458.6): C 73.34, H 6.59, N 6.11; found: C 73.04, H 6.59, N 6.07.

Dimethyl 1,5-dibenzyl-1,5,8,8bβ-tetrahydro-4,8-diphenyl-cyclobuta[1,2-b:3,4-b′]dipyridine-3,7(4H,4aβH,4bβH)dicarboxylate (5b): Method C: 38% yield (0.179 g, 0.29 mmol); m.p. 180–185 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.72$ (s, 1H; 2-H), 7.32–6.91 (m, 20H; aromatic H), 4.97 (d, $^3J(H,H) = 6.0$ Hz, 1H; 6-H), 4.83 (dd, $^3J(H,H) = 7.0$, 4.0 Hz, 1H; 7-H), 4.66 (d, $^2J(H,H) = 15.3$ Hz, 1H; C1–NCH_A), 4.61 (d, $^2J(H,H) = 15.3$ Hz, 1H; C1–NCH_B), 4.32 (d, $^3J(H,H) = 7.8$ Hz, 1H; 4b-H), 4.31 ("d", $^3J(H,H) = 6.0$ Hz, 1H; 7-H), 4.15 (d, $^2J(H,H) = 13.8$ Hz, 1H; C5–NCH_A), 4.02 (d, $^2J(H,H) = 13.8$ Hz, 1H; C5–NCH_B), 4.00 (d, $^3J(H,H) = 9.6$ Hz, 1H; 8b-H), 3.99 (d, $^3J(H,H) = 2.6$ Hz, 1H; 4-H), 3.56 ("s", 4H; C3–$COOCH_3$, 8-H), 3.51 (s, 3H; C8a–$COOCH_3$), 3.38 (ddd, $^3J(H,H) = 9.6$, 7.8, 2.6 Hz, 1H; 4a-H); IR: $\tilde{\nu} = 1680$, 1714 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 218 (15849), 346 nm (6760 mol^{-1} dm^3 cm^{-1}); MS (ESI): *m*/*z* (%): 610 (1) $[M]^+$, 579 (1) $[M-OCH_3]^+$, 305 (40) $[M/2]^+$, 228 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{40}H_{38}N_2O_4$ (610.8): C 78.66, H 6.27, N 4.59; found: C 78.38, H 6.38, N 4.58.

Dimethyl 3,9-dimethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]-dodecane-1,11-dicarboxylate (6a): The preparation followed Method B using *syn*-dimer **5a** (0.1 g, 0.22 mmol). After four weeks of irradiation, the *syn*-dimer vanished as could be observed from TLC. Besides the detection of cage compound **6a** that crystallized on solution evaporation, the decomposition to starting compound 1,4-dihydropyridine was observed. Yield: 25% (0.025 g, 0.05 mmol); m.p. 225–230 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.23-7.09$ (m, 10H; aromatic H), 4.14 (dt, $^3J(H,H) = 8.2$, $^4J(H,H) = 1.6$ Hz, 2H; 2-, 10-H), 3.88 (d, $^3J(H,H) = 2.7$ Hz, 2H; 6-, 12-H), 3.57 (s, 6H; $COOCH_3$), 3.41 (dt, $^3J(H,H) = 9.4$, $^4J(H,H) = 1.6$ Hz, 2H; 4-, 8-H), 3.34 (ddd, $^3J(H,H) = 9.4$, 8.2, 2.7 Hz, 2H; 5-, 7-H), 2.79 (s, 6H; NCH_3); IR: $\tilde{\nu} = 1723$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 458 (1) $[M]^+$, 229 (27) $[M/2]^+$, 152 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{28}H_{30}N_2O_4$ (458.6): C 73.34, H 6.59, N 6.11; found: C 73.47, H 6.55, N 6.25.

X-ray crystal structure analysis: A yellow crystal $C_{28}H_{30}N_2O_4$ (from THF), crystal size 0.57 × 0.36 × 0.21 mm, was measured at room temperature by using a Stoe-STADI4 Diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and a graphite monochromator. The number of reflections collected was 13670 and these were collected in the range $3.38° \le 2\Theta \le 60.0°$ in $2\theta/\omega$ scan mode; *h*,*k*,*l* range from −11, −16, −18 to 11, 16, 18. Crystal system: triclinic, space group $P\bar{1}$, $Z = 2$, $a = 8.2399(5)$ Å, $b = 11.7575(9)$ Å, $c = 13.3497(6)$ Å, $\alpha = 112.962(5)°$, $\beta = 98.604(5)°$, $\gamma = 92.728(5)°$; $V = 1169.44(13)$ Å^3; $\rho = 1.302$ g cm^{-3}; $\mu = 0.087$ mm^{-1}. No absorption correction was applied during data reduction. The structure was solved by direct methods (SHELXS-97). Structure refinement: full matrix least-squares methods on F^2 using SHELXL-97, all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference Fourier synthesis and isotropically refined. The refinement converged to a final $wR_2 = 0.1580$ for 6835 unique reflections and $R_1 = 0.0577$ for 4594 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 427 refined parameters.

Dimethyl 3,9-dibenzyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]-dodecane-1,11-dicarboxylate (6b): The preparation followed that reported for **6a** using *syn*-dimer **5b** (0.1 g, 0.16 mmol). Yield: 30% (0.03 g, 0.05 mmol); m.p. 172–177 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.23-6.91$ (m, 20H; aromatic H), 4.32 (dt, $^3J(H,H) = 7.8$, $^4J(H,H) = 1.6$ Hz, 2H; 2-, 10-H), 4.15 (d, $^2J(H,H) = 13.5$ Hz, 2H; NCH_A), 4.02 (d, $^2J(H,H) = 13.5$ Hz, 2H; NCH_B), 4.00 (d, $^3J(H,H) = 2.6$ Hz, 2H; 6-, 12-H), 3.56 (s, 6H; $COOCH_3$), 3.39 (ddd, $^3J(H,H) = 9.6$, 7.8, 2.6 Hz, 2H; 5-, 7-H), 3.36 (dt, $^3J(H,H) = 9.6$, $^4J(H,H) = 1.6$ Hz, 2H; 4-, 8-H); IR: $\tilde{\nu} = 1725$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 610 (2) $[M]^+$, 579 (2) $[M-OCH_3]^+$, 304 (71) $[M/2-1]^+$, 228 (100) $[M/2-Ph]^+$; elemental analysis calcd (%) for $C_{40}H_{38}N_2O_4$ (610.8): C 78.66, H 6.27, N 4.59; found: C 78.80, H 6.28, N 4.49.

Crystallographic data (excluding structure factors) for the structures **2a**, **6a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157612. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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