Novel Solid-State Synthesis of Polyfunctionalized 3,9-Diazatetraasteranes

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Upon irradiation, crystalline 4-methoxyphenyl-1,4-dihydropyridines **1** undergo nearly quantitative [2+2]cycloaddition to form, via the ring-open intermediates **2**, the centrosymmetric, polyfunctionalized 3,9-diazatetraasteranes **3**. The centrosymmetric character of **3** was confirmed by ^{1}H NMR spectral data as well as by X-ray crystal structure analysis. The dimerization reactions prove to be topochemically controlled by the nearest distance between potentially reacting double bonds, as well as by the conformationally determined packing restraints. This latter factor is shown by the X-ray crystal structure analysis of one dimerizing and one photostable derivative of the monomers **1**.

The number of functionalized tetraasteranes reported is limited to a few examples which show an exclusively uniform substitution pattern and low yields (<10%)[1]. With their lipophilic character tetraasteranes show a close relationship to other carbocycles such as cubanes, homo- and bishomocubanes. Using new synthetic methods, such as photochemical carboxylation[2], these carbocycles can be functionalized in a controlled way to yield new derivatives with interesting pharmacological properties. Phenyl-substituted cubanes and bishomocubanes have been discovered as new anti-cancer agents, whilst carboxylated cubanes are reported to show anti-HIV activity[2a][3]. In order to investigate their pharmacological profile we are engaged in the preparation of polyfunctionalized tetraasteranes and aza-analogous compounds .

In the following we present a novel solid-state synthesis of the functionalized, aza-analogous tetraasteranes **3a**,**b**, **c**,**e**,**f**. In contrast to the formation of previously reported monofunctionalized tetraethyl-3,9-diazatetraasterane-1,5,7,11-tetracarboxylate[4] and the synthesis described for tetraasteranes gives our solid-state reaction the desired polyfunctionalized derivatives in nearly quantitative yields.

The starting compounds, i.e. the monomeric 1,4-dihydropyridines **1a**−**d**, were obtained by cyclocondensation from, respectively, 4-methoxybenzaldehyde, methyl or ethyl propiolate and ammonium acetate and benzylamine in acetic acid, following the method of Chennat and Eisner[5]. The corresponding *N*-methyl derivatives **1e** and **f** were produced by methylation of the 1,4-dihydropyridine anions in dimethylpropylenurea (DMPU).

On irradiation with an Ultra-Vitalux® lamp (300 W, $\lambda \geq$ 270 nm), the spectrum of which corresponds to sunlight, the crystalline 1,4-dihydropyridines **1a**−**f** absorb light between λ = 359 and 379 nm. The first reaction products are the head-to-tail *syn*-dimers **2a**,**b**,**c**,**e**,**f**, formed by a [2+2]cycloadditon reaction. Only **1d** is light-stable. Further irradiation of the isolated products **2a**,**b**,**c**,**e**,**f** leads to the cage dimers **3a**,**b**,**c**,**e**,**f** in quantitative yields by another [2+2]cycloaddition under excitation of the vinylogous carbamidester chromophore, which absorbs between 280 and 294 nm.

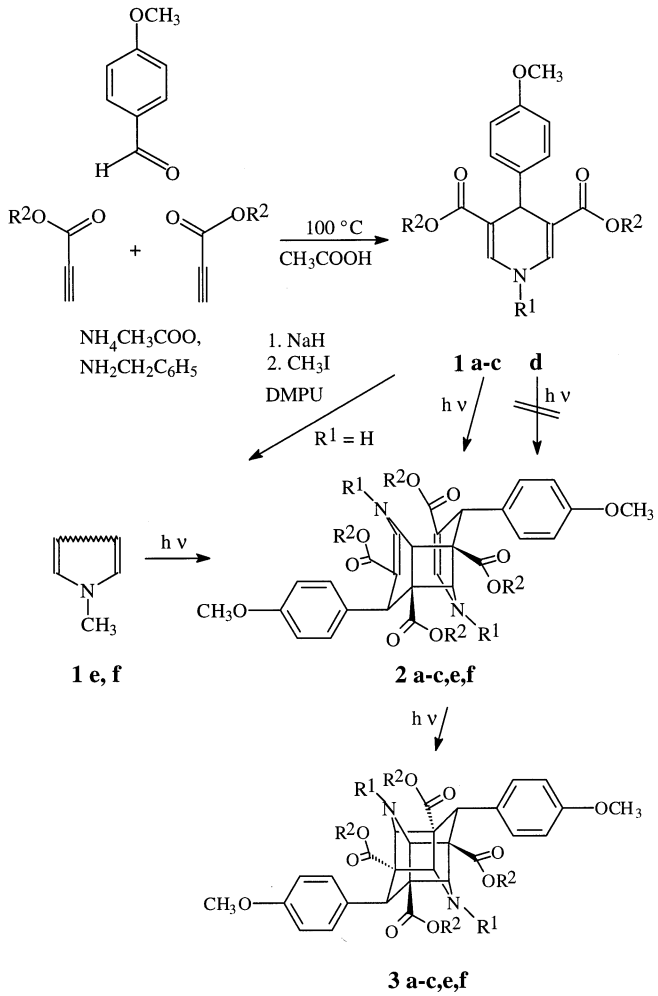
Both dimers **2** and **3** possess symmetric structures, as shown by their ^{1}H NMR spectra, consisting of only one set of signals for both 1,4-dihydropyridine subunits in the dimers (see Experimental Section). Furthermore, they are characterized, using IR spectroscopy, by two carbonyl bands for **2** and only one such band for **3**. Their molecular masses were determined by electrospray ionisation (ESI) as well as by field desorption (FD) mass spectrometry, while electron ionisation (EI-70 eV) leads to fragmentation of the dimers with resulting monomeric mole peaks. The centrosymmetry of the cage structure was also confirmed by an X-ray crystal structure determination of **3a**; this is discussed below.

In order to gain insight into the topochemistry of the 4-methoxyphenyl-1,4-dihydropyridines **1** the dimerizing derivative **1c** and the photostable **1d** have been investigated by X-ray crystal structure analyses.

In their molecular structures, shown in Figure 1, the 4-methoxyphenyl substituents are pseudoaxially orientated,

  1434−193X/98/0606−1213 $ 17.50+.50/0

Scheme 1

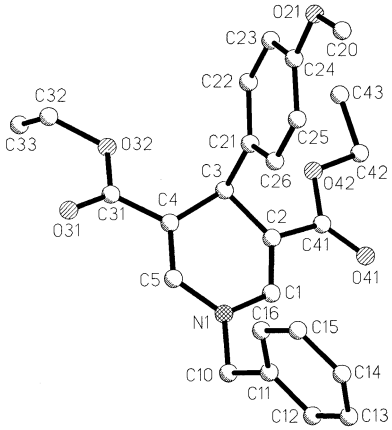


	R1	R2
a [14]	H	C_2H_5
b [5]	H	CH_3
c	Bzl	C_2H_5
d	Bzl	CH_3
e [14]	CH_3	C_2H_5
f	CH_3	CH_3

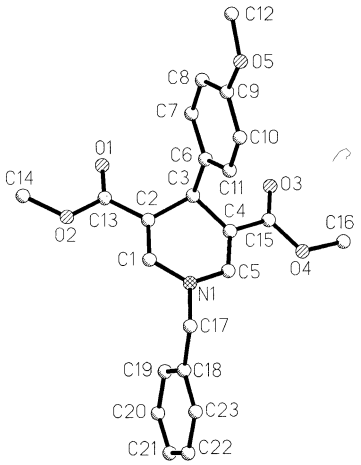
approximately bisecting the plane of the dihydropyridine ring.

Differences in the molecular structures of **1c** and **d** have been found in the orientation of their ester carbonyl groups in relation to the C2−C3 bond and the C4−C3 bond, with an antiperiplanar arrangement in **1c** {C3−C4−C31−O31 = −162.8(4)°, C3−C2−C41−O41 = 169.7(4)°} and a synperiplanar one in **1d** {C3−C4−C15−O3 = −7.61(3)°, C3−C2−C13−O1 = 11.33(3)°}. Furthermore, the 4-methoxyphenyl and the *N*-benzyl substituents of **1c** show *syn*-orientation with respect to the dihydropyridine plane with torsion angles C1−C2−C3−C21 and C2−C1−N1−C10 of 102.6(5)°and −176.0(4)°, respectively, while their arrangement in **1d** proves to be *anti* with −93.9(2)° for C1−C2−C3−C6 and 178.8(2)° for C2−C1−N1−C17.

Figure 1. Molecular structures of **1c** and **d**



1c



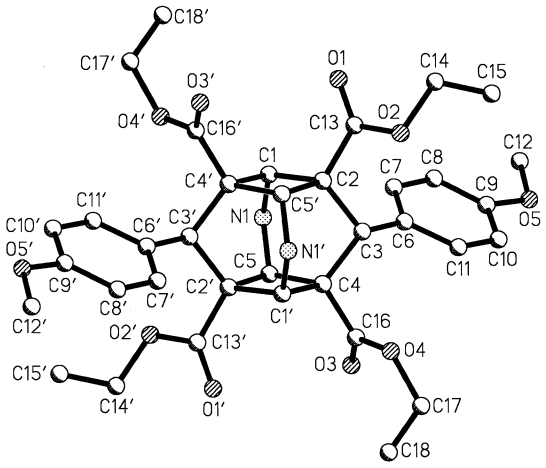
1d

Considering the formation of the cage dimer **3**, which is discussed below, it may be possible to identify the former 1,4-dihydropyridine rings in the analysed cage dimer of **3a** formed by the atoms C1, C2, C3, C4, C5, N1 and C1′, C2′, C3′, C4′, C5′, N1′. As in the monomeric 1,4-dihydropyridines they are characterized by their pseudoaxially orientated 4-methoxyphenyl substituents and, furthermore, the significantly shorter cyclobutane bond lengths, as shown in the following.

A remarkable difference in cyclobutane bond lengths is observed in the molecular structure of **3a** shown in Figure 2, with the mean length of the two parallel orientated shorter bonds C1−C2, C4−C5 (and their centrosymmetric equivalents) of 1.558(6) Å[6] deviating from that of the longer ones C1−C4′, C2−C5′ (and their centrosymmetric equivalents) of 1.587(9) Å by 0.029 Å. Corresponding differences in the cyclobutane bond lengths are reported for the X-ray crystal structure of tetraethyl-3,9-diazatetraasterane-1,5,7,11-tetracarboxylate[7].

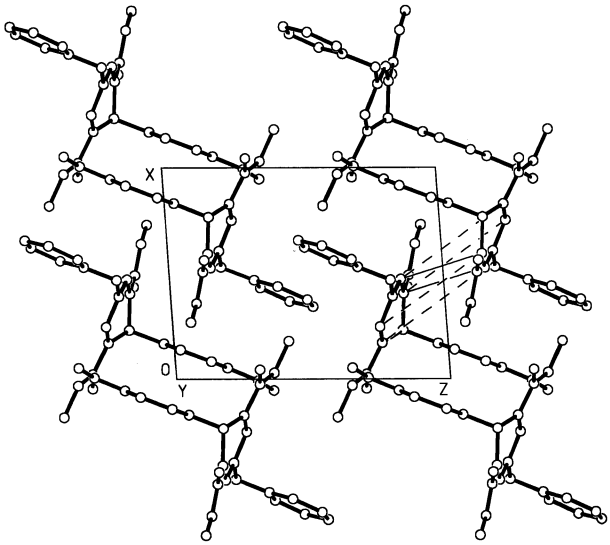
The molecules of **1c** are packed in an *anti*-parallel fashion in the crystal lattice as shown in Figure 3, forming one-dimensional stacks of translationally related molecules along [001].

Figure 2. Molecular structure of **3a**



According to the minimum translational movement criterion for solid-state reactions[8] the formation of the cage dimer **3c** takes place between centrosymmetrically related molecules of adjacant stacks via their neighbouring double bonds, with a favourable reaction distance **A**, **A′** of 3.490(6) Å and 3.492(6) Å, which lies considerably below the maximum distance criterion of 4.2 Å for dimerizing double bonds previously suggested by Schmidt et al.[8]. Considering the distances between potentially reacting double bonds of the *anti*-parallel packed derivative **1d** in Figure 4, an *anti*-dimer formation seems possible, with **B** being 3.997(3) Å, while **A** and **A′**, with values of 5.321(3) Å and 5.265(3) Å respectively, are too large for a dimerization reaction.

Figure 4. Crystal packing of **1d** (projection along [010]) with distances **A**, **A′** (C1···C4′, C2···C5′; dashed lines) and **B** (C1···C2′, C1′···C2; full lines) between potentially reacting double bonds of molecules of adjacant stacks



Nevertheless, monomeric **1d** proves to be photostable. In order to understand its non-reactivity the following geometrical calculations, taking into consideration a pair of molecules with distance **B,** have been performed (see Figure 5). For the formation of an *anti*-dimer displacements of the reacting double bonds along D_1 and D_2 must take place; these displacements are 1.927(4) Å and 1.353(4) Å, respectively.

Figure 3. Crystal packing of **1c** (projection along [001]) with distances **A**, **A′** (C1···C4′, C2···C5′; full lines) between reacting double bonds of molecules of adjacant stacks

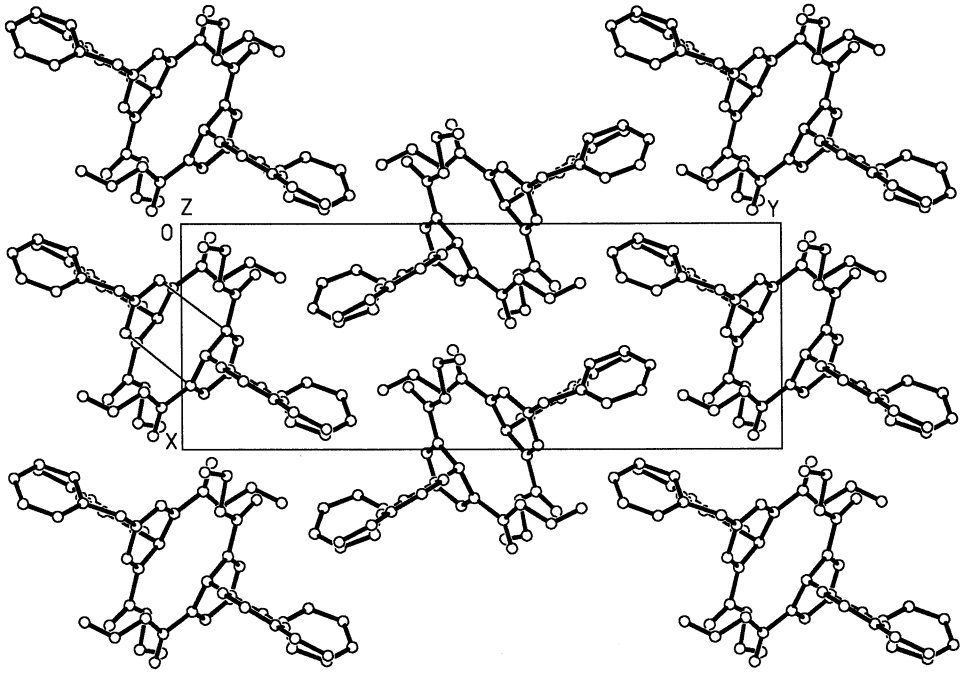
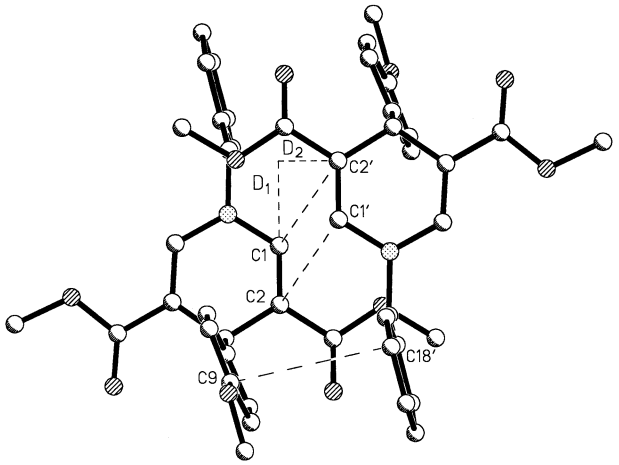


Figure 5. Pair of centrosymmetrically related molecules with distance **B** (dashed lines between C1···C2′ and C1′···C2) and geometrically calculated distances D_1 and D_2



However, assuming an approximately fixed conformation of the molecules (especially across the N1−C17 bond) the movement along D_2 would bring very close contact between the carbon atoms of the 4-methoxyphenyl substituent of one molecule and the carbon atoms of the *N*-benzyl substituent of the other molecule. This is indicated in Figure 5 by the distance C9··· C18′ {3.878(3) Å} within the crystal. The necessary movement would result in a distance of only 2.525 Å, much less than the sum of the corresponding van der Waals radii (3.4 Å)[9]. Hence, this movement is forbidden, and, consequently, dimerization does not take place.

In summary the novel solid-state synthesis presented leads to the formation, via their ring-open precursors **2,** of polyfunctionalized, aza-analogous tetraasteranes **3** in excellent yields, resulting from the favourable crystal packing of the monomeric substrates and their topochemically controlled reaction.

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Experimental Section

General: Commercial reagents were used as received without additional purification. − ^{1}H NMR: Bruker AC-200 F or Varian Gemini 200 (200 or 500 MHz; TMS as an internal standard). − M.p.′s: Linström apparatus (open capillaries, uncorrected values). − Analytical TLC: aluminium sheets coated with silica gel 60 F_{254} (Merck). − IR spectra: Perkin-Elmer 881 or Bruker IFS-28 (recorded in potassium bromide pellets). − UV: Diode Array spectrophotometer 8452A (chloroform). − MS: Varian Mat 311 A or AMD 402. − Elemental analysis: Leco CHNS-932.

Dialkyl 1-Benzyl-1,4-dihydro-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (**1c**, **d**): 1.96 g (20 mmol) of ethyl propiolate, 1.68 g (20 mmol) of methyl propiolate, 1.36 g (10 mmol) of 4-methoxybenzaldehyde and 1.07 g of (10 mmol) benzylamine were heated in 1 ml glacial acetic acid on a steam-bath for 15 min. While **1d** crystallized on cooling, the reaction mixture of **1c** was poured into 10 ml of ice-water and the precipitate filtered off . Both **1c** and **1d** were recrystallized from ethanol.

Diethyl 1-Benzyl-1,4-dihydro-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (**1c**): Yield: 2.95 g (70%), yellow crystals, m.p. 104−106°C. − IR: $\tilde{\nu}$ = 1705 cm^{-1}, 1664. − UV: λ_{max} (lg ε) = 254 nm (4.11), 292 sh, 368 (3.94). − ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, *J* = 7 Hz, 6 H, CH_2CH_3), 3.75 (s, 3 H, 4-H_3CO−Ph), 4.06 (q, *J* = 7 Hz, 4 H, CH_2CH_3), 4.57 (s, 2 H, NCH_2), 4.84 (s, 1 H, 4-H), 6.68−7.34 (m, 11 H, aromat. H, 2-, 6-H). − MS: *m/z* (%): 421 (1) [M$^+$], 392 (1) [M$^+$ − C_2H_5]. − $C_{25}H_{27}N_1O_5$ (421.5): calcd. C 71.24, H 6.46, N 3.32; found C 71.30, H 6.49, N 3.53.

X-ray Diffraction Analysis of **1c**[10]: A yellow rhombus shaped crystal $C_{25}H_{27}N_1O_5$ (from ethanol), crystal size 0.5 × 0.4 × 0.2 mm^3, was measured at room temp. by using a Nicolet R3m/V Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 5872 reflexions were collected in ω scanning mode in the range 3.6° ≤ 2Θ ≤ 54.0°; *h*,*k*,*l* range from −10,−1,−1 to 10,28,15. Crystal system: Monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 8.518(3) Å, *b* = 22.606(8) Å, *c* = 11.852(4) Å, β = 93.34(3)°; *V* = 2278(1) Å^3; D_x = 1.229 g cm^{-3}; μ = 0.085 mm^{-1}. The structure was solved by direct methods (SHELXTL 5.03[11]) using 4963 independent reflexions. Structure refinement: Full-matrix least-squares methods on F^2 using SHELXTL 5.03[11], all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms are in calculated positions. The refinement converged to a final wR^2 = 0.1349 for 4963 unique reflections and R^1 = 0.0537 for 959 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 284 refined parameters.

Dimethyl 1-Benzyl-1,4-dihydro-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (**1d**)**:** Yield: 2.55 g (65%), yellow crystals, m.p. 120−122°C. − IR: $\tilde{\nu}$ = 1703 cm^{-1}, 1604. − UV: λ_{max} (lg ε) = 254 nm (4.07), 292 sh, 368 (3.90). − ^{1}H NMR ($CDCl_3$): δ = 3.59 (s, 6 H, $COOCH_3$), 3.73 (s, 3 H, 4-H_3CO−Ph), 4.55 (s, 2 H, NCH_2), 4.83 (s, 1 H, 4-H), 6.71−7.43 (m, 11 H, aromat. H, 2-, 6-H). − MS: *m/z* (%): 393 (21) [M$^+$], 378 (5) [M$^+$ − CH_3]. − $C_{23}H_{23}N_1O_5$ (393,4): calcd. C 70.23, H 5.85, N 3.56; found C, 69.93; H, 5.88; N, 3.50.

X-ray Diffraction Analysis of **1d**[10]: A yellow rhombus shaped crystal $C_{23}H_{23}N_1O_5$ (from ethanol), crystal size 0.42 × 0.18 × 0.14 mm^3, was measured at room temp. by using a STADI4 Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 8784 reflexions were collected in ω/2Θ scanning mode in the range 1.81° ≤ 2Θ ≤ 53.96°; *h*,*k*,*l* range from −11,−13,−14 to 11,13,14. Crystal system: Triclinic, space group $P\bar{1}$, *Z* = 2, *a* = 9.0391(9) Å, *b* = 10.2296(9) Å, *c* = 11.2667(9) Å, α = 90.223(10)°, β = 93.637(7)°, γ = 103.846(8)°; *V* = 1009.3(2) Å^3; D_x = 1.295 g cm^{-3}; μ = 0.091 mm^{-1}. The structure was solved by direct methods (SHELXS-86[12]) using 4392 independent reflexions. Structure refinement: Full-matrix least-squares methods on F^2 using SHELXL-93[13], all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms are in calculated positions. The refinement converged to a final wR^2 = 0.1287 for 4392 unique reflections and R^1 = 0.0445 for 2392 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 263 refined parameters.

Dialkyl 1,4-Dihydro-4-(4-methoxyphenyl)-1-methylpyridine-3,5-dicarboxylate (**1e**, **f**): 1 g (3.02 mmol) of **1a**[14], or 1 g (3.3 mmol) of **1b**[5], respectively, dissolved in a minimum volume of dimethylpropylenurea (DMPU) were treated with the 7-fold excess of NaH suspension in oil (80%). After stirring for 1 h at 50°C a 3-fold excess of methyl iodide was added over a period of 30 min. After stirring for 1 h at room temp. the solution was hydrolysed with portions of water. After standing overnight, the separated, semi-solid product was filtered off and recrystallized from alcohol.

Diethyl 1,4-Dihydro-4-(4-methoxyphenyl)-1-methylpyridine-3,5-dicarboxylate (**1e**): Yield: 0.95 g (91%), yellow crystals, m.p. 90−91°C (ethanol, ref.[14] 94°C).

Dimethyl 1,4-Dihydro-4-(4-methoxyphenyl)-1-methylpyridine-3,5-dicarboxylate (**1f**): yield: 0.93 g (89%), yellow crystals, m.p. 200−202°C (methanol). − IR: $\tilde{\nu}$ = 1708 cm^{-1}, 1608. − UV: λ_{max} (lg ε) = 252 nm (3.82), 283 (3.19), 368 (3.68). − ^1H NMR ($CDCl_3$): δ = 3.23 (s, 3 H, NCH_3), 3.62 (s, 6 H, $COOCH_3$), 3.75 (s, 3 H, 4-H_3CO−Ph), 4.82 (s, 1 H, 4-H), 6.71− 7.26 (m, 6 H, aromat. H, 2-, 6-H). − MS: *m/z* (%): 317 (13) [M^+], 302 (7) [$M^+ - CH_3$]. − $C_{17}H_{19}NO_5$ (317.3): calcd. C 64.34, H 6.03, N 4.41; found C 64.34, H 6.01, N 4.45.

Dimerization Reactions: 1 g of crystalline 1,4-dihydropyridine **1** with a layer thickness of 1 mm was irradiated with an Ultra-Vitalux® lamp from a distance of 60 cm at a measured temperature of 25°C. After 3−4 d of irradiation (product formation monitored by TLC) the products **2** and **3**, were dissolved in boiling toluene and ethanol, respectively, from which they crystallized. The following yields are based on 1g of **1**, corresponding to a 100% yield of **3** obtained by the direct irradiation of **1**.

Tetraethyl 1,5,8,8bβ-Tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-b:3,4-b']dipyridine-3,4aβ,7,8aβ(4H,4bβH)tetracarboxylate (**2a**): Yield: 0.4g (40%), white needles, m.p. 273−276°C (ethanol). − IR: $\tilde{\nu}$ = 3289 cm^{-1}, 1731, 1660, 1620. − UV: λ_{max} (lg ε) = 240 nm (3.75), 283 (4.02). − ^1H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7 Hz, 6 H, 4a,8a-$COOCH_2CH_3$), 1.10 (t, *J* = 7 Hz, 6 H, 3,7-$COOCH_2CH_3$), 3.55 (A*M*X_3, *J* = 11 Hz, 7 Hz, 2 H, 4a,8a-$COOCH_MCH_3$), 3.65 (s, 6 H, 4-H_3CO−Ph), 3.67 (*A*MX_3, *J* = 11 Hz, 7 Hz, 2 H, 4a,8a-$COOCH_ACH_3$), 3.82 (A*M*X_3, *J* = 11 Hz, 7 Hz, 2 H, 3,7-$COOCH_MCH_3$), 3.86 (s, 2 H, 4-, 8-H), 3.99 (*A*MX_3, *J* = 11 Hz, 7 Hz, 2 H, 3,7-$COOCH_ACH_3$), 4.45 (s, 2 H, 4b-, 8b-H), 6.66−6.88 (m, 8 H, aromat. H), 7.23 (d, after D_2O addition: s, *J* = 6 Hz, 2 H, 2-, 6-H), 7.63 (d, *J* = 6 Hz, 2 H, exchangable, *N*H). − FD-MS: *m/z* (%): 662 (100) [M^+]. − $C_{36}H_{42}N_2O_{10}$ (542.6): calcd. C 65.26, H 6.34, N 4.23; found C 65.24, H 6.29, N 4.04.

Tetramethyl 1,5,8,8bβ-Tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-b:3,4-b']dipyridine-3,4aβ,7,8aβ(4H,4bβH)tetracarboxylate (**2b**): Yield: 0.65 g (65%), white scales, m.p. 273−275°C (toluene). − IR: $\tilde{\nu}$ = 3330 cm^{-1}, 1731, 1662, 1631. − UV: λ_{max} (lg ε) = 242 nm (3.91), 280 (4.16). − ^1H NMR ([D_6]DMSO): δ = 3.21 (s, 6 H, 4a,8a-$COOCH_3$), 3.44 (s, 6 H, 3,7-$COOCH_3$), 3.65 (s, 6 H, 4-H_3CO−Ph), 3.86 (s, 2 H, 4-, 8-H), 4.43 (s, 2 H, 4b-, 8b-H), 6.66−6.86 (m, 8 H, aromat. H), 7.27 (d, after D_2O addition: s, *J* = 6 Hz, 2 H, 2-, 6-H), 7.67 (d, *J* = 6 Hz, 2 H, exchangable, *N*H). − FD-MS: *m/z* (%): 606 (100) [M^+]. − $C_{32}H_{34}N_2O_{10}$ (606.6): calcd. C 63.37, H 5.61, N 4.62; found C 63.21, H 5.65, N 4.54.

Tetraethyl 1,5-Dibenzyl-1,5,8,8bβ-tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-b:3,4-b']dipyridine-3,4aβ,7,8aβ(4H,4bβH)tetracarboxylate (**2c**): Yield: 0.6 g (60%), white prisms, m.p. 195−197°C (ethanol). − IR: $\tilde{\nu}$ = 1739 cm^{-1}, 1672, 1626. − UV: λ_{max} (lg ε) = 240 nm (4.13), 293 (4.39). − ^1H NMR ($CDCl_3$): δ = 0.92 (t, *J* = 7 Hz, 6 H, 4a,8a-$COOCH_2CH_3$), 1.17 (t, *J* = 7 Hz, 6 H, 3,7-$COOCH_2CH_3$), 3.57 (A*M*X_3, *J* = 11 Hz, 7 Hz, 2 H, 4a,8a-$COOCH_MCH_3$), 3.68 (s, 6 H, 4-H_3CO-Ph), 3.69 (*A*MX_3, *J* = 11 Hz, 7 Hz, 2 H, 4a,8a-$COOCH_ACH_3$), 3.99 (A*M*X_3, *J* = 11 Hz, 7 Hz, 2 H, 3,7-$COOCH_MCH_3$), 4.02 (s, 2 H, 4-, 8-H), 4.08 (*A*MX_3, *J* = 11 Hz, 7 Hz, 2 H, 3,7-$COOCH_ACH_3$), 4.45 (s, 2 H, 4b, 8b-H), 4.59, 4.67 (AB, *J* = 15 Hz, 4 H, NCH_2), 6.50−7.41 (m, 18 H, aromat. H), 7.57 (s, 2 H, 2-, 6-H). − ESI-MS: *m/z* (%): 881 (100) [M + K^+], 865 (17) [M + Na^+]. − $C_{50}H_{54}N_2O_{10}$ (842.9): calcd. C 71.26, H 6.41, N 3.33; found C 71.11, H 6.57, N 3.14.

Tetraethyl 1,5,8,8bβ-Tetrahydro-4,8-bis(4-methoxyphenyl)-1,5-dimethylcyclobuta[1,2-b:3,4-b']dipyridine-3,4aβ,7,8aβ(4H,4bβH)tetracarboxylate (**2e**): Yield: 0.52 g (52%), white powder, m.p. 197−199°C (ethanol). − IR: $\tilde{\nu}$ = 1728 cm^{-1}, 1684, 1611. − UV: λ_{max} (lg ε) = 241 nm (3.99), 291 (4.29). − ^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7 Hz, 6 H, 4a,8a-$COOCH_2CH_3$), 1.17 (t, *J* = 7 Hz, 6 H, 3,7-$COOCH_2CH_3$), 3.70 (s, 12 H, NCH_3, 4-H_3CO−Ph), 3.99 (q, *J* = 7 Hz, 4 H, 4a,8a-$COOCH_2CH_3$), 4.09 (q, *J* = 7 Hz, 4 H, 3,7-$COOCH_2CH_3$), 4.90, 4.85 (2 s, 2 H, 4-, 8-H), 5.85, 5.81 (2 s, 2 H, 4b-, 8b-H), 6.68−6.83 (m, 8 H, aromat. H), 8.30 (s, 2 H, 2-, 6-H). − ESI-MS: *m/z* (%): 729 (100) [M + K^+], 713 (50) [M + Na^+], 691 (36) [M + H^+]. − $C_{38}H_{46}N_2O_{10}$ (690.1): calcd. C 66.09, H 6.67, N 4.06; found C 65.86, H 6.65, N 3.96.

Tetramethyl 1,5,8,8bβ-Tetrahydro-4,8-bis(4-methoxyphenyl)-1,5-dimethylcyclobuta[1,2-b:3,4-b']pyridine-3,4aβ,7,8aβ(4H,4bβH)-tetracarboxylate (**2f**): Yield: 0.6 g (60%), white powder, m.p. 247−249°C (toluene). − IR: $\tilde{\nu}$ = 1732 cm^{-1}, 1689, 1635. − UV: λ_{max} (lg ε) = 242 nm (4.01), 294 (4.31). − ^1H NMR ([D_6]DMSO): δ = 3.20 (s, 6 H, 4a,8a-$COOCH_3$), 3.26 (s, 6 H, 3,7-$COOCH_3$), 3.44 (s, 6 H, NCH_3), 3.67 (s, 6 H, 4-H_3CO−Ph), 3.78 (s, 2 H, 4-, 8-H), 4.23 (s, 2 H, 4b-, 8b-H), 6.68−6.87 (m, 8 H, aromat. H), 7.44 (s, 2 H, 2-, 6-H). − FD-MS: *m/z* (%): 634 (100) [M^+]. − $C_{34}H_{38}N_2O_{10}$ (634.7): calcd. C 64.35, H 5.99, N 4.42; found C 64.63, H 6.10, N 4.25.

Tetraethyl 6,12-Bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (**3a**): Yield: 0.92 g (92%), white scales, m.p. 241−243°C (toluene). − IR: $\tilde{\nu}$ = 3227 cm^{-1}, 1724. − ^1H NMR ($CDCl_3$): δ = 1.0 (t, *J* = 7 Hz, 12 H, $COOCH_2CH_3$), 3.70 (s, 6 H, 4-H_3CO−Ph), 3.80 (s, 2 H, 6-, 12-H), 3.91 (q, *J* = 7 Hz, 8 H, $COOCH_2CH_3$), 4.24 (s, 4 H, 2-, 4-, 8-, 10-H), 4.70 (s, br, 2 H, exchangable, *N*H), 6.66−7.43 (m, 8 H, aromat. H). − ESI-MS: *m/z* (%): 701 (100) [M+K^+], 685 (41) [M + Na^+], 663 (63) [M + H^+]. − $C_{36}H_{42}N_2O_{10}$ (662.7): calcd. C 65.26, H 6.34, N 4.23; found C 65.07, H 6.32, N, 4.12.

X-ray Diffraction Analysis of **3a**[10]: A colourless prism shaped crystal $C_{36}H_{42}N_2O_{10}$ (from toluene), crystal size 0.8 × 0.51 × 0.21 mm^3, was measured at room temp. by using a STADI4 Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 9642 reflexions were collected in ω/2Θ scanning mode in the range 3.6° ≤ 2Θ ≤ 60.0°; *h,k,l* range from −8,0,0 to 8,25,20 and from −8,−25,−20 to 8,0,0. Crystal system: Monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 6.2178(5) Å, *b* = 18.290(2) Å, *c* = 1414.768(1) Å, β = 99.223(7)°; *V* = 1657.7(2) $Å^3$; D_x = 1.328 g · cm^{-3}; μ = 0.097 mm^{-1}. The structure was solved by direct methods (SHELXL-86[12]) using 4821 independent reflexions. Structure refinement: Full-matrix least-squares methods on F^2 using SHELXL-93[13], all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms are in calculated positions. The refinement converged to a final wR^2 = 0.1934 for 4821 unique reflections and R^1 = 0.0616 for 2623 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 225 refined parameters.

Tetramethyl 6,12-Bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (**3b**): Yield: 0.91 g (91%), white powder, m.p. 272−275°C (toluene). − IR: $\tilde{\nu}$ = 3330 cm^{-1}, 1731 . − ^1H NMR ([D_6]DMSO): δ = 3.41 (s, 12 H, $COOCH_3$), 3.69 (s, 6 H, 4-H_3CO−Ph), 3.79 (s, 2 H, 6-, 12-H), 4.01 (d, after D_2O addition: s, *J* = 3 Hz, 4 H, 2-, 4-, 8-, 10-H), 4.57 (t, *J* = 3 Hz, 2 H, exchangable, *N*H), 6.72−7.34 (m, 8 H, aromat. H). − ESI-MS: *m/z* (%): 645 (100) [M + K^+], 629 (67) [M + Na^+], 607 (13) [M + H^+]. − $C_{32}H_{34}N_2O_{10}$ (606.6): calcd. C 63.37, H 5.61, N 4.62; found C 63.30, H 5.61, N 4.54.

Tetraethyl 3,9-Dibenzyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (**3c**): Yield: 0.96 g (96%), white powder, m.p. 170−173°C (ethanol). − IR: $\tilde{\nu}$ = 1725 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 7 Hz, 12 H, $COOCH_2CH_3$), 3.75 (s, 6 H, 4-H_3CO−Ph), 3.99 (q, *J* = 7 Hz, 8 H, $COOCH_2CH_3$), 4.24 (s, 2 H, 6-, 12-H), 4.26 (s, 4 H, 2-, 4-, 8-, 10-H), 4.48 (s, 4 H, NCH_2), 6.59−7.34 (m, 18 H, aromat. H). − FD-MS: *m/z* (%): 842 (100) [M$^+$]. − $C_{50}H_{54}N_2O_{10}$ (842.9): calcd. C 71.26, H 6.41, N 3.33; found C 71.05, H 6.29, N 3.20.

Tetraethyl 6,12-Bis(4-methoxyphenyl)-3,9-dimethyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (**3e**): Yield: 0.90 g (90%), white powder, m.p. 210−213°C (ethanol). − IR: $\tilde{\nu}$ = 1723 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, *J* = 7 Hz, 12 H, $COOCH_2CH_3$), 3,10 (s, 6 H, NCH_3), 3.71 (s, 6 H, 4-H_3CO−Ph), 3.98 (q, *J* = 7 Hz, 8 H, $COOCH_2CH_3$), 4.06 (s, 4 H, 2-, 4-, 8-, 10-H), 4.11 (s, 2 H, 6-, 12-H), 6.64−7.21 (m, 8 H, aromat. H). − ESI-MS: *m/z* (%): 729 (100) [M + K$^+$], 713 (8) [M + Na$^+$]. − $C_{38}H_{46}N_2O_{10}$ (690.8): calcd. C 66.09, H 0.67, N 4.00; found C 66.05, H 6.72, N 3.99.

Tetramethyl 6,12-Bis(4-methoxyphenyl)-3,9-dimethyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (**3f**): Yield: 0.96 g (96%), white scales, m.p. 252−254°C (toluene). − IR: $\tilde{\nu}$ = 1721 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.00 (s, 6 H, NCH_3), 3.50 (s, 12 H, $COOCH_3$), 3.69 (s, 6 H, 4-H_3CO−Ph), 3.95 (s, 4 H, 2-, 4-, 8-, 10-H), 4.05 (s, 2 H, 6-, 12-H), 6.71−7.08 (m, 8 H, aromat. H). − FD-MS: *m/z* (%): 634 (100) [M$^+$]. − $C_{34}H_{38}N_2O_{10}$ (634.7): calcd. C 64.35, H 5.99, N 4.42; found C 64.56, H 6.0, N 4.24.

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