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The First Functionalized 6,12-Diazatetrakishomocubanes**

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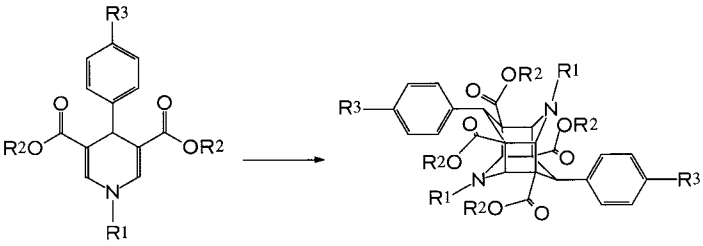
Despite all efforts, accessibility of cage compounds analogous to cubane is limited. These compounds have presented a constant synthetic challenge since the first cubane compound was obtained.[1, 2] The limited development of novel functionalization reactions such as photochemical carboxylation[2, 3] has led to the synthesis of compounds with interesting pharmacological effects: This includes the carcinogenic effect of phenyl-substituted cubanes and substituted bishomocubanes and the recently observed anti-HIV effect of carboxylated cubanes.[2, 4] Initial efforts in combinatorial chemistry of cubanes have made accelerated discovery of new substances possible.[5] Since this only involves derivatives and not new basic structures, the challenge of finding alternative possibilities for synthesizing new cage compounds remains.

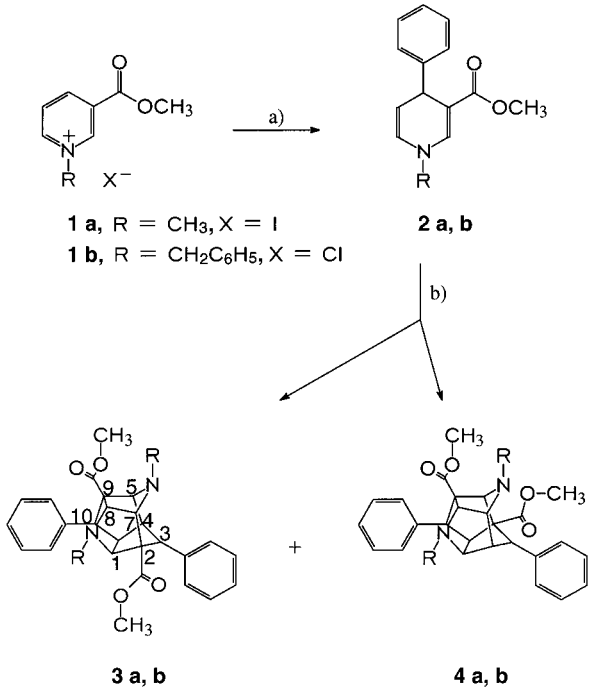
By the use of topochemically controlled photodimerization of symmetric 4-aryl-1,4-dihydropyridines to form centrosymmetric 3,9-diazatetraasteranes, we were recently able to develop a process for synthesizing tetraasteranes that are analogous to aza compounds in almost quantitative yield (Scheme 1).[6] These cubane analogons currently hold interest as novel HIV-1 protease inhibitors.[7]



Scheme 1. Formation of 3,9-diazatetraasteranes from 4-aryl-1,4-dihydropyridines.

Here, the first C_2-symmetric and asymmetric 6,12-diazatetrakishomocubanes are presented. They were obtained, totally unexpectedly, as the main products from the reaction of asymmetric 4-aryl-1,4-dihydropyridines, and enrich the pool of interesting cage compounds.

Starting from N-alkyl-substituted pyridinium compounds **1**,[8] the 4-aryl-1,4-dihydropyridines **2**[9] can be obtained in over 90% yield by regioselective reaction with equimolar amounts of phenylmagnesium chloride in the presence of catalytic amounts of copper(I) iodide[10] (Scheme 2).



Scheme 2. a) PhMgCl, CuI (cat.), THF, RT; b) *hν*, MeOH/THF.

Irradiation of solutions of 4-aryl-1,4-dihydropyridines **2** by Ultra-Vitalux lamps ($\lambda \geq 270$ nm), with excitation of the 1,4-dihydropyridine chromophores at $\lambda_{max} = 348$ nm (**2a**) or 346 nm (**2b**), resulted in the dimerization products **3** and **4** in overall yields of more than 80%. ^{1}H NMR spectroscopy showed that the C_2-symmetric compound **3** is characterized by a simple set of proton signals for the two 1,4-dihydropyridine

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units,[11] whereas the asymmetric product **4** reveals a corresponding double set for these two units.[12] The IR spectrum of **3** contains only one ester carbonyl band,[11] whereas that of **4** shows two bands.[12]

X-ray crystal structure analyses of both compounds (Figures 1a and 1b) were undertaken to clarify the configuration, and confirmed the existence of the totally unexpected structures.

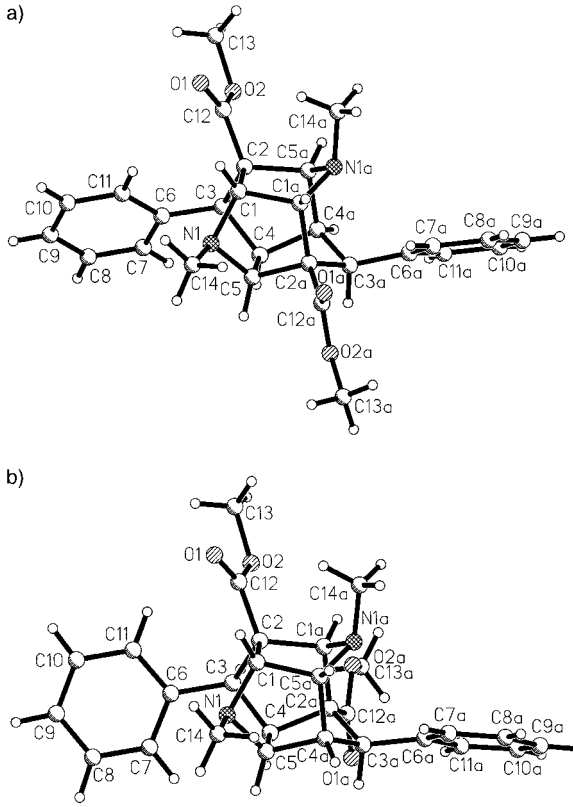
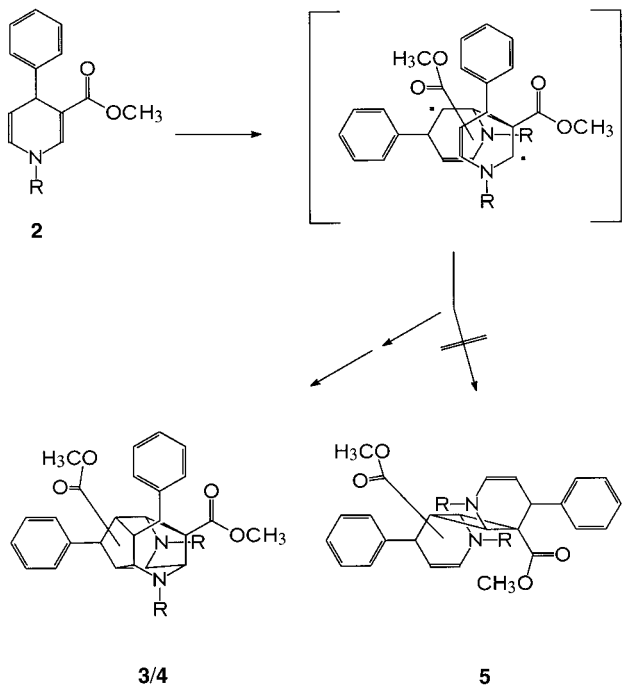


Figure 1. Molecular structures of **3a** (a) and **4a** (b) in the crystal.

In contrast to the previously observed head-to-tail 1,4-dihydropyridine dimers with centrosymmetric cage structures of 3,9-diazatetraasteranes or their C_2-symmetric, *syn*-dimeric intermediates,[6, 13] the linkage of the two 1,4-dihydropyridine rings in **3** and **4** are not in a head-to-tail arrangement of 180° to each other, but form an angle of only 90°. Stereochemically **3** is the product of common enantiometric forms, whereas **4** is made up of different enantiomers. Both compounds can formally be considered as resulting from the attack of one dihydropyridine molecule on the far side of the dihydropyridine ring of the second molecule (i.e., the side that does not face the aryl moiety). Steric reasons are responsible for the axial arrangement of the phenyl rings in this case.

The mechanism of the formation of the adducts **3** and **4** is of great interest. Starting from the formation of the primary diradical according to known photodimerization reactions, a nonconcerted [2+2]cycloaddition with bond rotation[14]—analogous to the mechanism of a classical [2+2]cycloaddition for the previously observed 1,4-dihydropyridine photodimerization[6, 13]—should lead to the formation of the *anti*-dimers **5** (Scheme 3). The formation of **3**/**4** via the hypothetical primary diradical adduct is currently under investigation.



Scheme 3. Formation of **3**/**4** via a primary diradical.

The synthesis presented here provides easy access to novel functionalized diaza cage compounds by means of an interesting mechanism of formation. Further work with structural variants as starting materials should increase the range of such functionalized cage compounds even further. The solid-state chemistry of asymmetric 4-aryl-1,4-dihydropyridines is also under investigation. The structural similarity of the C_2-symmetric tetrakishomocubanes **3** to the 3,9-diazatetraasteranes[15] gives rises to great interest in these compounds in particular as potential inhibitors of C_2-symmetric HIV-1 protease.

Experimental Section

The pyridinium salts **1a**, **b** (10 mmol) were suspended in anhydrous THF (100 mL). After addition of copper(I) iodide (0.5 mmol) a 1M solution of phenylmagnesium chloride (10 mL, 10 mmol) was added dropwise to the suspension. After stirring for 2 h, the solution was treated with an aqueous solution of ammonium chloride (60 mL) and then extracted with diethyl ether (150 mL). The ether phase was washed with 20% ammonia/ammonium chloride solution (1/1, 60 mL), water, 10% hydrochloric acid (2×), water, and sodium chloride solution, and then dried over sodium sulfate. After filtration, the ether was removed under vacuum and the oily residue was taken up in methanol. Upon cooling, **2a** or **2b** crystallized in 90% yield.

The 4-aryl-1,4-dihydropyridines **2a**, **b** (2 mmol) were dissolved in methanol/THF (40 mL) under stirring in a quartz glass flask. The solution was then irradiated with a Ultra-Vitalux lamp from a distance of 60 cm for four weeks. Quartz glass flasks were used to ensure that the short wavelengths of the light, which triggered the cyclization of the *syn*-dimers of symmetric 4-aryl-1,4-dihydropyridines to 3,9-diazatetraasteranes, were also able to penetrate.[6] As soon as no more starting materials could be detected by thin-layer chromatography and product formation without detectable intermediate product formation was shown to be complete, the solvent was removed by evaporation. The adducts **3a**, **b** and **4a**, **b** were obtained by fractional crystallization.

X-ray crystal structure analysis of **3a**: One white prism $0.72 \times 0.37 \times 0.19\ mm^3$ in size was measured at room temperature with a STADI4

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diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), and a graphite monochromator. A total of 14022 reflections were measured using a $\omega/2\Theta$ scan mode ($3.3^\circ \le 2\Theta \le 54.0^\circ$). Crystal system: tetragonal, space group $P4_2/n$, $Z = 8$, $a = 24.846(3)$, $b = 24.846(3)$, $c = 7.8219(13)$ Å; $V = 4828.6(12)$ Å^3; $\rho_{calcd} = 1.262\ g\,cm^{-3}$; $\mu = 0.084\ mm^{-1}$. The structure was solved directly with SHELXS97 with 7011 independent reflections, the structure was refined according to full-matrix least-squares procedures (SHELXL97); $wR^2 = 0.1919$ for 7011 reflections, $R^1 = 0.0986$ for 2706 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 311 refined parameters. The positions of the hydrogen atoms were calculated according to geometric considerations and refined isotropically.

X-ray crystal structure analysis of **4a**: A yellow crystal $0.57 \times 0.48 \times 0.34\ mm^3$ in size was measured at room temperature with a STADI4 diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), and a graphite monochromator. A total of 13516 reflections were measured using a $\omega/2\Theta$ scan mode ($3.3^\circ \le 2\Theta \le 54.9^\circ$). Crystal system: triclinic, space group $P\bar{1}$, $Z = 2$, $a = 9.6489(3)$, $b = 9.8280(5)$, $c = 13.2209(6)$ Å, $\alpha = 82.092(5)$, $\beta = 69.261(5)$, $\gamma = 84.237(4)^\circ$; $V = 1159.53(10)$ Å^3; $\rho_{calcd} = 1.313\ g\,cm^{-3}$; $\mu = 0.088\ mm^{-1}$. The structure was solved directly with SHELXS97 using 6758 independent reflections, the structure was refined according to full-matrix least-squares procedures (SHELXL97); $wR^2 = 0.1340$ for 6758 reflections, $R^1 = 0.0477$ for 5035 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 405 refined parameters. The positions of the hydrogen atoms were calculated geometrically and refined isotropically.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133187. 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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[9] All new compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and mass spectrometry, solubility permitting, and by elemental analysis. Selected physical data for **2a**: yellow crystals, m.p. 115–120 °C; IR (KBr): $\tilde{\nu} = 1682\ cm^{-1}$ (C=O); ^{1}H NMR (500 MHz, CD_3OD, 25 °C, TMS): $\delta = 3.10$ (s, 3H; NCH_3), 3.53 (s, 3H; $COOCH_3$), 4.41 (d, $^3J(H,H) = 4.7$ Hz, 1H; 4-H), 4.89 (dd, $^3J(H,H) = 7.8$, 4.7 Hz, 1H; 5-H), 5.94 (d, $^3J(H,H) = 7.8$ Hz, 1H; 6-H), 7.09–7.87 (m, 6H; aromat. H, 2-H); UV/Vis (methanol): $\lambda_{max}(\varepsilon) = 348$ (4324), 232 (6229); MS (70 eV): *m*/*z* (%): 229 (2) [M^+], 212 (9) [M^+], 169 (100) [$M^+ - 60$].

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[11] Selected physical data for **3a**: white needles, yield: 39%, m.p. 212–218 °C, IR (KBr): $\tilde{\nu} = 1723\ cm^{-1}$ (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.04$ (s, 6H; NCH_3), 3.18 (AA′HH′RR′XX′, $^3J(H,H) = 9.4$, 1.9 Hz, $2 \times {}^4J(H,H) = 1.9$ Hz, 2H; 4-, 11-H), 3.37 (d, $^3J(H,H) = 1.9$ Hz, 2H; 3-, 10-H), 3.69 (s, 6H; $COOCH_3$), 3.84 (dt, $^3J(H,H) = 9.4$ Hz, $2 \times {}^4J(H,H) = 1.9$ Hz, 2H; 1-, 5-H), 4.59 (t, $^4J(H,H) = 1.9$ Hz, 2H; 7-, 8-H), 7.05–7.18 (m, 10H; aromat. H); UV/Vis (chloroform): $\lambda_{max}(\varepsilon) = 250$ (973); MS (70 eV): *m*/*z* (%): 458 (3) [M^+], 229 (34) [$M^+/2$], 214 (6) [$M^+/2 - CH_3$], 152 (100) [$M^+/2 - Ph$].

[12] Selected physical data for **4a**: small yellow spheres, yield: 42%, m.p. 188–191 °C, IR (KBr): $\tilde{\nu} = 1725$, $1713\ cm^{-1}$ (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.00$, 2.04 ($2 \times$ s, 6H; NCH_3), 3.73, 3.75 ($2 \times$ s, 6H; $COOCH_3$), 3.25 (dd, $^3J(H,H) = 8.9$, 3.1 Hz, 1H, 4-H), 3.29 (ddd, $^3J(H,H) = 8.9$, 4.9, 3.3 Hz, 1H; 9-H), 3.36 (d, $^3J(H,H) = 3.1$ Hz, 1H; 3-H), 3.38 (d, $^3J(H,H) = 3.3$ Hz, 1H; 10-H), 3.51 (ddd, $^3J(H,H) = 8.9$, 4.5 Hz, $^4J(H,H) = 2.9$ Hz, 1H; 8-H), 3.76 (ddd, $^3J(H,H) = 8.9$, 4.9 Hz, $^4J(H,H) = 2.7$ Hz, 1H; 5-H), 4.43 (dd, $^3J(H,H) = 4.5$ Hz, $^4J(H,H) = 2.7$ Hz, 1H, 7-H), 4.58 (d, $^4J(H,H) = 2.9$ Hz, 1H; 1-H), 7.03–7.19 (m, 10H; aromat. H); UV/Vis (chloroform): $\lambda_{max}(\varepsilon) = 250$ (2863); MS (70 eV): *m*/*z* (%): 458 (15) [M^+], 427 (4) [$M^+ - OCH_3$], 228 (35) [$M^+/2 - 1$], 214 (6) [$M^+/2 - CH_3$], 152 (100) [$M^+/2 - Ph$].

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Formation of a Novel Cage Compound with a Pentacyclo[6.3.0.1^{4,11}.0^{2,6}.0^{5,10}]dodecane Skeleton by Photolysis of [3$_4$](1,2,4,5)Cyclophane**

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Prismanes constitute a fascinating family of $(CH)_n$ polyhedra,[1] several members of which, namely, prismane,[2] cubane,[3] and pentaprismane,[4, 5] have been successfully synthesized. Recently, attention has focused on the challenging objective of synthesizing the higher prismanes, in particular, hexaprismanes **1**. Despite many efforts, they have so far eluded synthesis, mainly because of the lack of proper synthetic routes and the expected higher strain energies than the lower prismanes. In our approach to construct the hexaprismane skeleton by photolysis of multibridged [3$_n$]cyclophanes ($n = 3-6$) we first optimized the reaction conditions using the lowest homologue [3$_3$](1,3,5)cyclophane (**2**),

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[**] Multibridged [3$_n$]Cyclophanes. Part 8. For previous papers, see refs. [6 (Part 6) and 8 (Part 7)]. We gratefully acknowledge the financial support by the Grant-in-Aid for the Priority Area (A) of Creation of Delocalized Electronic Systems (no. 11133244) from the Ministry of Education, Science, Sports, and Culture, Japan.