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Barrelene Derivatives - Potential Modules for Assembly

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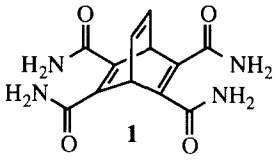
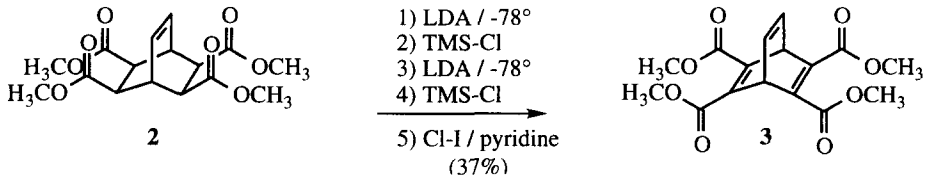
Abstract: Dihydrobarrelene tetraamide **8** was prepared by Diels-Alder reaction of **4** and **5** and indirect transformation of the ester into amide groups. The crystal structure of **8** showed an unpredicted conformation of the four amide groups.

Assemblies of molecules held together by hydrogen bonds are increasingly popular.[1] In this context, we are assessing small, convex compounds bearing divergent functionalities capable of hydrogen bonding. The dihydrobarrelene tetraamide[2] **1** is such a candidate. It has the potential of forming non-planar assemblies such as a cube-like hexamer by virtue of its skeletal curvature.



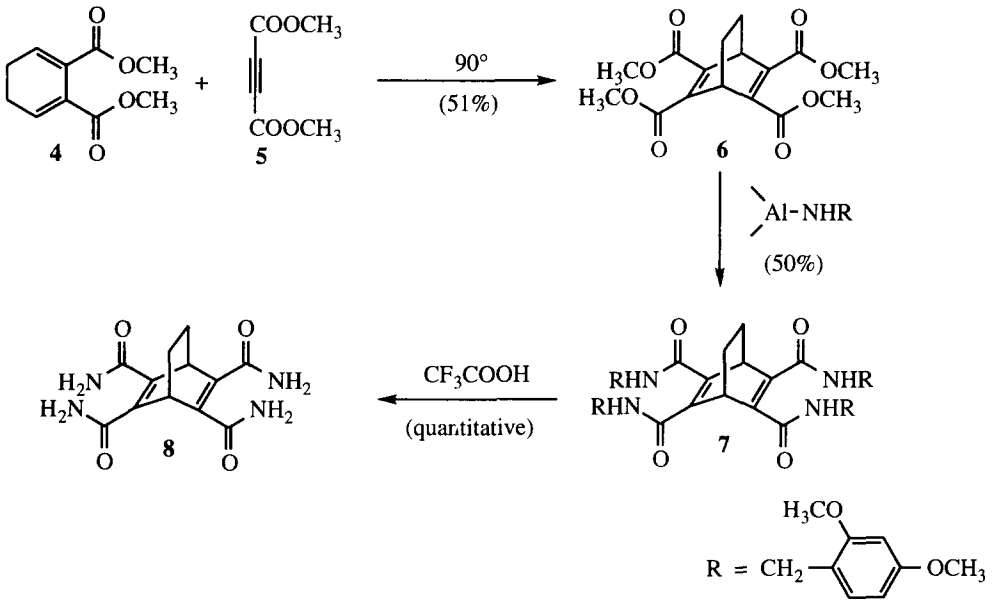
1

The synthesis of **1** was more complicated than first anticipated, given the known **2**. Conventional methods for introducing two new double bonds, e.g. quenching enolates of **2**[3] with halogenation or sulfination reagents failed, but sequential silylation was possible. This resulted in a mixture of regioisomers. Oxidative desilylation with Cl-I[4] followed by elimination of HI in the presence of pyridine afforded in one step the triene **3**. [5] The barrelene skeleton was in place and it remained only to convert the ester into amide groups. Unfortunately, at slightly elevated temperatures or upon treatment with bases or acids, **3** decomposes quite readily by *retro-Diels-Alder*-reaction to dimethyl phthalate and dimethyl acetylenedicarboxylate (**5**). This decomposition thwarted our efforts to use **3**.



2 **3**

Since the third double bond at the 'top' of the molecule has little influence on the shape of the molecule the dihydrocompound **8** was considered. The more stable ester **6** could be prepared surprisingly well by the *Diels-Alder*-reaction of the electron-poor diene **4**[6] with the electron-poor dienophile **5**.[7] Maintaining the reaction temperature at 90° is crucial since *retro-Diels-Alder*-reaction readily takes place at 110°, converting product **6** to tetramethyl benzene-1,2,4,5-tetracarboxylic acid and ethylene. Direct conversion of **6** to the corresponding tetraamide **8** by simple aminolysis failed. Rather, 1,4-attack of the nucleophile is favored which yields intermediates that unravel by *retro*-aldol-reactions. With dimethyl aluminum amides[8] the 1,4-reaction was avoided and the tetrabenzylamide **7** could be prepared.[9] The benzyl- and *p*-methoxybenzylamides could not be removed without destroying the molecule. Debenzylation of the 2,4-dimethoxybenzyl with CF_3COOH[10] then gave the desired tetraamide.[11]



The bicyclic tetraamide **8** was crystallized from water and single-crystal X-ray structure analysis[12] showed that all the amide groups are twisted out of the plane (see *figure*). This result is not anticipated by energy minimization calculations using *MacroModel*[13] and either the MM2 or Amber force fields. Such modeling suggested that the amide groups are oriented such that four intramolecular hydrogen bonds are formed around the bicyclo framework with hydrogen bond donors and acceptors radiating outward to find their complements on other molecules. In the solid state, however, no hydrogen bonds of a conventional sort can be found. Within the crystal lattice, C=O and NH_2 groups are often positioned nearby (see *figure*). However their spatial arrangement does not allow, for stereoelectronic reasons, other kinds of interaction than *Coulomb*-forces. A ^1H NMR spectrum of **8** in DMF, the least polar solvent with a sufficient solubility, gave no indication for intramolecular hydrogen bonds. The chemical shift of the N-H at 8.88 ppm in $CDCl_3$ of the more soluble benzyl derivative **7** showed a significant down field shift, compared to regular benzylamides.[14] This can be attributed to intramolecular hydrogen bonds in this apolar

solvent. It is our goal to increase the solubility of the tetraamide in apolar solvents, for example by attaching flexible, lipophilic substituents. We will report on the progress of the synthesis of such molecules in due course.

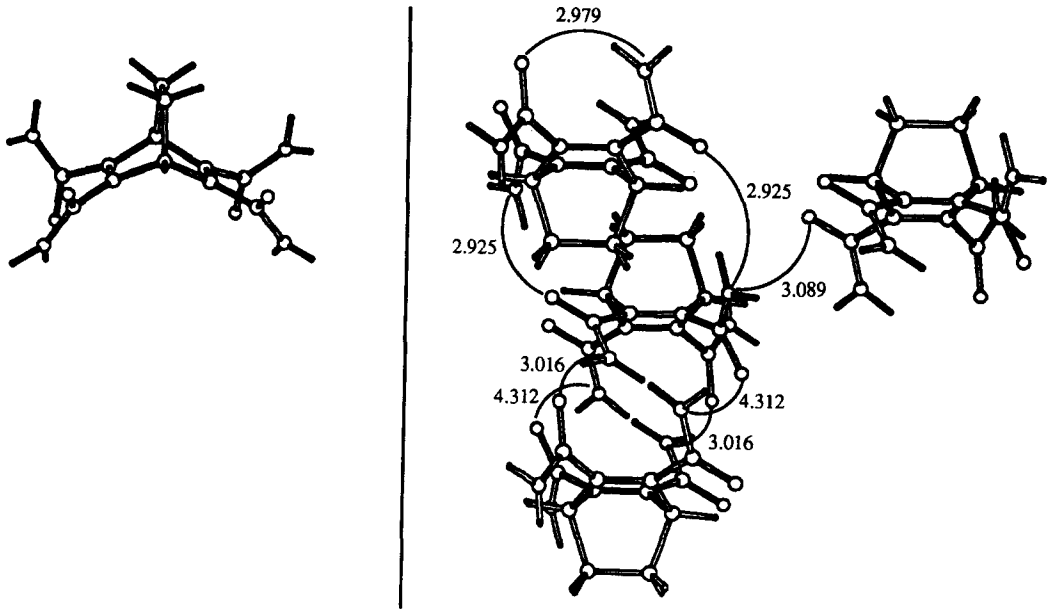


Figure: Single molecule 8 (left) and part of the crystal lattice with some selected nitrogen - oxygen distances in Å (right).

Acknowledgment

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5. A solution of 1.00 g (2.93 mmol) tetraester **2**, dissolved in 50 ml THF, was injected at -78° to 2.6 equivalents LDA in 10 ml THF. After 30 min. 1.86 ml TMS-Cl were injected and after further 30 min. the reaction was allowed to reach rt.. Work up with 100 ml sat. *aq.* $NaHCO_3$ soln. and extraction with ether gave the mono silylated product which was treated the same way again to give a mixture of bis(silylketeneacetals). These intermediates, dissolved in 40 ml pyridine, were treated dropwise with a solution of 1.27 g (7.84 mmol) Cl-I in 10 ml pyridine. The reaction took place instantly. Excess of Cl-I was reduced by *aq.* $Na_2S_2O_3$ soln.. CH_2Cl_2 (200 ml) was added and pyridine was removed by extrac tion versus diluted sulfuric acid and *aq.* $CuSO_4$. The evaporated raw product was chromatographed on silica (hexanes / ethyl acetate 2:1) to yield 368 mg (37%) **3**. (The main side product was the compound with only one new introduced double bond) ^1H NMR ($CDCl_3$): 7.00 (*dd, J* = 4.2, 3.1, 2H); 5.41 (*dd, J* = 4.2, 3.1, 2H); 3.80 (*s*, 12H). IR (KBr): 2956 (w), 1724 (s), 1712 (s), 1652 (m), 1628 (m), 1438 (m), 1330 (m), 1285 (s), 1258 (s), 1122 (m), 1106 (m), 1063 (m), 750 (m), 722 (m). UV (EtOH): 259 nm (ε = 1700), 206 nm (ε = 7400).

6. Huang, N. Z.; Xing, Y. D.; Ye, D. Y. *Synthesis* **1982**, 1041.

7. A mixture of 2.2g (11.2 mmol) **4** and 1.44 ml (11.2 mmol) **5** was heated at 90° for at first 44 h. More **5** (0.7 ml (5.7 mmol)) was added and heating was continued for further 22 h. Chromatography (hexanes / ethyl acetate 2:1) yielded 1.94 g (51%) **6** as white crystals melting at 106.0° - 106.6°. ^1H NMR ($CDCl_3$): 4.43 (*s, br*, 2H); 3.78 (*s*, 12H); 1.62 (*s, br*, 4H). ^{13}C NMR: 165.2; 141.1; 52.4; 40.8; 24.4. IR (KBr): 2955 (w), 1711 (s), 1646 (m), 1434 (m), 1284 (s), 1263 (s), 1127 (m), 1079 (m), 1069 (m), 950 (m), 748 (m). MS (EI, 70 eV): 339 (0.35), 338 (2.4, M^+), 310 (14), 307 (8), 280 (20), 279 (100).

8. Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383.

9. To 1.24 g (7.4 mmol) 2,4-dimethoxybenzylamine in 15 ml CH_2Cl_2 were added 3.7 ml (7.4 mmol) trimethylaluminium solution (2 M in hexanes). After 5 min. a soln. of 500 mg (1.48 mmol) **6**, dissolved in 10 ml CH_2Cl_2, was injected. After 3 d stirring at rt. 10 ml 1 M *aq.* HCl were carefully added while cooling with an ice bath. The organic layer was separated, evaporated and chromatographed (hexanes / ethyl acetate 1:1) to yield 653.3 mg (50%) **7** as white foam melting at 69°. ^1H NMR ($CDCl_3$): 8.88 (*t, J* = 5.8, 4H); 7.10 (*d, J* = 8.2, 4H); 6.43 (*d, J* = 2.2, 4H); 6.38 (*dd, J* = 8.2, 2.2, 4H); 4.57 (*s, br*, 2H); 4.40 (*d, J* = 5.8, 8H); 3.82 (*s*, 12H); 3.79 (*s*, 12H); 1.58 (*s, br*, 4H). IR (KBr): 3288 (w, br), 2936 (w), 1641 (s), 1617 (s), 1546 (m), 1507 (s), 1458 (m), 1288 (m), 1263 (m), 1209 (s), 1157 (m), 1130 (m), 1038 (m). MS (FAB, 3-NBA): 881 (15), 880 (52), 879 (100, M^++1), 878 (37, M^+).

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11. A mixture of 460.2 mg (0.524 mmol) **7** and 13 ml CF_3COOH was stirred for 5 d. The solvent was evaporated and the residue taken into 10 ml CH_2Cl_2 and 30 ml water and stirred vigorously for 90 min. The aqueous layer was evaporated to give 191.6 mg **8** as a white powder which even after prolonged drying in high vacuo still contained *ca.* 30% water. M.p.: >400°(probably decomposes before). ^1H NMR (DMF): 8.11 (*s, br*, 4H); 7.56 (*s, br*, 4H); 4.60 (*s, br*, 2H); 1.59 (*s, br*, 4H). ^{13}C NMR: 168.6; 143.6; 44.2; 25.0. IR (KBr): 3555 (m), 3349 (m), 3183 (m), 1675 (s), 1649 (s), 1618 (m), 1602 (m), 1386 (w), 1210 (w), 1177 (m). MS (EI, 70 eV): 279 (10), 278 (63, M^+), 250 (10), 244 (24), 234 (100), 217 (30), 216 (23). HRMS: calculated for $C_{12}H_{14}N_4O_4$: 278.1012; found: 278.1014.

12. Space group: P1(Nr. 2); a = 8.923 Å; b = 8.332 Å; c = 9.591 Å; α = 103.1°; β = 95.01°; γ = 109.51°; one molecule per unit cell; R = 0.048.

13. Still, W. C. 'Macromodel v3.5', Columbia University, New York.

14. Typical value for N-H of benzylamides: 7 ppm.

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