

TETRAHEDRON

Synthesis of Novel 19-(Alkyloxycarbonylamino)bilanes.

Clotilde Pichon-Santander and A. Ian Scott.*

Center for Biological NMR, Department of Chemistry, Texas A&M University, P. O. Box 30012, College Station, TX 77842-3012, USA.

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Abstract: α -Urethane-dipyrromethanes and -bilanes were synthesized for the first time and characterized by ¹H- and ¹³C-NMR. Stability studies toward oxygen were also performed. © 1999 Elsevier Science Ltd. All rights reserved.

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In the biosynthesis of porphyrinoids, uroporphyrinogen III (uro'gen III, 1) is a key precursor of many vital pigments present in living systems (hemes, coenzyme F430, vitamin B_{12} , chlorophyll)¹ and is formed through enzymatic cyclization of the linear tetrapyrrole, 1hydroxymethylbilane (HMB, 2), by uroporphyrinogen III synthase (EC 4.2.1.75). A particular characteristic of this enzymatic reaction resides in the intramolecular ring D rearrangement, which occurs during cyclization. In the absence of enzyme, HMB ring-closes chemically to form uro'gen I (3) without ring inversion (scheme 1). On account of its importance and specificity, uro'gen III synthase has over the years generated extensive mechanistic studies.²⁻⁷ ¹³C-NMR evidence for the first azafulvene intermediate (4) was obtained after trapping experiments with nucleophilic salts.⁴ The next step is believed to involve the formation of a spiro intermediate (5), followed by fragmentation-recombination to uro'gen III (1), a mechanism which is supported by the strong enzyme inhibition exhibited by a synthetic tripyrrolic macrocyclic spiro-lactam (6), an analog of 5, suggesting that 6 is a transition-state analog.⁷

As a part of our continuing effort to probe the mechanism of uro'gen III synthase, a novel substrate analog, 19-amino-1-hydroxymethylbilane (7), has been designed. The 19-amino-HMB 7 ¹³C-labelled specifically at C-20 would allow NMR observation of its 3 possible interactions with the enzyme: 1) bilane 7 could act as a competitive inhibitor and the NMR signal at 55 ppm (pyrrole-¹³CH₂OH) would not change; 2) 7 could function as a substrate, form the azafulvene 8 and its amino substituent could then act as an intramolecular trap to give the azaporphyrinogen 9 (C-20 at ~35 ppm); or, 3) after formation of the azafulvene 8,

^{*} E-mail: scott@mail.chem.tamu.edu pichon@mail.chem.tamu.edu

the reaction could proceed to the spiro intermediate 10 or its more stable form 11 (C-20 at ~30 ppm).



Scheme 1: Proposed interactions of 19-amino-HMB with Uro'gen III synthase.

Our strategy for the synthesis of the 19-amino-HMB 7 followed the modified preparation of HMB: viz. condensation of an α -hydroxymethyldipyrromethane with an α -free α '-

formyldipyrromethane using Montmorillonite clay as acid catalyst.⁸ Several routes were explored to obtain the necessary α -urethane- α '-formyldipyrromethane.

From previous work, we were familiar with the chemistry of pyrrolylurethanes.⁹ They can be obtained by Curtius rearrangement of 2-azidocarbonylpyrroles in the presence of alcohol.¹⁰ Our first plan was to form the urethanedipyrromethane from the pyrrolylurethane bearing the required substituents. Preparation of the acylazide for the rearrangement reaction was straightforward (scheme 2). After hydrogenation of the 5-carbobenzoxypyrrole 12,^{11,12} the 5-carboxypyrrole 13 was treated with diphenyl-phosphorylazide (DPPA) in presence of triethylamine to afford the acylazide 14 in excellent yield. Pyrrolylurethanes bearing no electron-withdrawing substituent are known to auto-oxidize readily.^{9,10} Therefore, before the rearrangement reaction, the 2-methyl substituent was oxidized with sulfuryl chloride in presence of calcium carbonate (as the acylazide is acid sensitive) to give the 2-formylpyrrole 15 (scheme 2 - route 1). The rearrangement was then carried out in refluxing benzene in presence of benzyl alcohol to provide the stable 2-formylpyrrolylurethane 16. Dipyrromethanes are generally formed by condensation of an α -free pyrrole with an α acetoxymethylpyrrole in presence of an acid catalyst, such as Montmorillonite clay.¹³ This method has been successful for the synthesis of acid sensitive bilanes.⁸ Thus, the formyl group of pyrrole 16 was first reduced with sodium borohydride in presence of ammonium chloride to afford the 2-hydroxymethylpyrrolylurethane 17. This latest compound proves also to be oxygen sensitive and when attempting the coupling reaction with α -free pyrrole 18 in presence of Montmorillonite clay as catalyst, even under careful handling, only the 5-imino- Δ^3 -pyrrolin-2-one 19 could be isolated in low yield, as well as the starting α -free pyrrole 18.

However, this problem was overcome by inverting the reaction sequence to pyrrole coupling followed by Curtius rearrangement of the azidocarbonyldipyrromethane thus formed. Scheme 2 - route 2 presents the preparation of α -azido-carbonyldipyrromethane from α -azidocarbonylpyrrole 14. The condensation reaction is often carried out with an acetate function as leaving group. This was easily obtained by oxidation with sulfuryl chloride of the 2-methylpyrrole 14 to the 2-chloromethylpyrrole 20, followed by hydrolysis to the 2hydroxymethylpyrrole 21 and acetylation to the 2-acetoxymethylpyrrole 22 in good yields. The coupling of pyrrole 22 with the α -free pyrrole 18 over clay showed almost no formation of dipyrromethane after 2 days (usual reaction time). Addition of para-toluenesulfonic acid (pTsOH) allowed the condensation to take place in moderate yield (37%). However, 2 isomers 23a and 23b were present in a 3.5:1 ratio (determined by ¹H-NMR integration), the major one 23a being the desired product. Similar results have been reported elsewhere. 6,14,15 Presumably, the formation of 23b resulted from the attack of the azafulvene derived from 22 on the carbon bearing the formyl group in 18, followed by a series of spontaneous [1,5]signatropic rearrangements. Such a mechanism has been invoked to rationalize other rearrangements.¹⁰ The 2 isomers **23a** and **b** were difficult to separate by chromatography. Nevertheless, after Curtius rearrangement of the acylazide group, the separation of the isomeric 5-carbobenzoxyaminodipyrromethanes 26a and b became feasible.



Scheme 2: Preparation of the 5'-formyl-5-urethanedipyrromethane. Routes 1 and 2.

a) H₂/10% Pd-C, Et₃N, THF; b) DPPA, Et₃N, THF; c) 2 eq. SO₂Cl₂, CaCO₃, CH₂Cl₂, RT, 1 h; d) H₂O/acetone, RT, 2h; e) BzOH, PhH, reflux; f) NaBH₄, NH₄Cl, CH₂Cl₂/MeOH;

g) Montmorillonite clay, CH₂Cl₂; h) 1 eq. SO₂Cl₂, CH₂Cl₂, RT, 1 h; i) Ac₂O, pyridine; j) H⁺.

A^{Me}=CH₂CO₂Me P^{Me}=CH₂CH₂CO₂Me CBZ=CO₂CH₂Ph

Diverse attempts were made to optimize both yield and ratio of the desired compound 23a by modification of the pH of the reaction. This was accomplished using chloride (as in 20), hydroxide (as in 21) or acetate (as in 22) as leaving group in combination with addition of base [calcium carbonate (CaCO₃), triethylamine or basic alumina] or acid [clay, pTsOH, trifluoroacetic (TFA), chloroacetic, formic or oxalic acid]. With the 2-hydroxymethylpyrrole 21 and the 2-acetoxymethylpyrrole 22, addition of strong acids (pTsOH, TFA, oxalic acid)

was essential for the condensation to take place, but without improvement in yield or ratio. This was not necessary with the 2-chloromethylpyrrole 20, since it generated hydrochloric acid during reaction. Only with the pyrrole 20 did the coupling occur if some base was added, although at a slower rate. Yet, the isomeric ratio increased in favor of the desired product 23a. Thus, the best result was achieved by condensation of the 2-chloromethylpyrrole 20 and the α -free pyrrole 18 with addition of 0.25 equivalent of CaCO₃ at 8, 24 and 48 hours to give, after 5 days, 38% of the 5-azidocarbonyldipyrromethanes 23a and b in a 5.75:1 ratio.

At this point, it was found that the 5-azidocarbonyldipyrromethane 23a could be obtained as a single isomer in the same manner that 2-azidocarbonylpyrroles (ex: 14) are prepared: *i. e.*, hydrogenation of the 5-carbobenzoxydipyrromethane 24^{16} to give the 5-carboxydipyrromethane 25, followed by treatment with DPPA in presence of triethylamine to provide the 5-azidocarbonyldipyrromethane 23a in good yield (scheme 3). As mentioned above, Curtius rearrangement of dipyrrole 23a did not offer any difficulty. By changing the alcohol present in the reaction, a variety of carbamates can serve as protecting group for the amino function; two were chosen, the dipyrroles 26a (obtained from benzyl alcohol) and 30 (from trimethylsilylethanol), bearing in mind the mild conditions needed for their removal. With either dipyrrole, the formyl group was reduced to hydroxymethyl in the usual way to afford the 5'-hydroxymethyl-5-urethanedipyrromethanes 27 and 31. These compounds show more stability toward oxygen than the parent monopyrrole 17 and can be coupled to the α free α '-formyldipyrromethane 28¹⁶ using Montmorillonite clay as catalyst⁸ to provide the formylbilanes 29a and 32a in moderate yield.

Three steps remained in order to conduct biosynthetic studies with uro'gen III synthase: 1) reduction of the formyl group; 2) deprotection of the amine function; 3) hydrolysis of the methyl esters. The first one was accomplished as usual (with sodium borohydride) without any problem and cleanly gave the 19-urethane-HMB's **29b** and **32b**. As is usual with HMB's, the two bilanes are not very stable. The amine deprotection constituted the most critical step. The benzyl carbamate **29b** was hydrogenated over 10% palladium on carbon or palladium black. In absence of base, no reaction took place. In presence of triethylamine, ¹H-NMR showed the disappearance of the benzyl group, but also that of the hydroxymethyl function, and the formation of more than a single product, probably due to autoxidation. Additional precautions did not bring any improvement with the HMB derivative **29b** or with the formyl derivative **29a**. Similar results were observed for the trimethylsilylethyl carbamate **32b** when attempting removal of the protecting group with tetrabutylammonium fluoride.

Aminopyrroles and pyrrolylurethanes have been reported to be susceptible to autoxidation in the absence of any electron-withdrawing substituent,^{9,10} however very little is known about amino and urethane derivatives of di- or tetra-pyrroles. The α -formyl α '-urethane mono-, dior tetra-pyrroles (16, 26a or 29a) seem reasonably stable. If left under normal air atmosphere, no oxidation product was observed (¹H- and ¹³C-NMR) for the monopyrrole 16 after two weeks; the dipyrrole 26a was partially recovered (59%) and 2 oxidation products, the 5-imino- Δ^3 -pyrrolin-2-one 19 (16%) and the pyrrolyl-hydroxypyrrolinylurethane 33 (13%), reminiscent of the hydroxypyrrolinylurethane obtained by autoxidation of a pyrrolylurethane,⁹ were isolated after one week; the only compound isolable after one week in the aerial oxidation of the bilane **29a** was the iminopyrrolinone **19** (24%), no starting material being recovered. If the formyl is reduced to a hydroxymethyl group, the pyrrolylurethane **17** was completely oxidized after a few hours, the 5-imino- Δ^3 -pyrrolin-2-one **19** (15%) being the only product isolable. Similar results were obtained with the urethanehydroxymethyldipyrromethane **27**, however after a longer period of time (one week). For the 19-urethane-HMB **29b**, 2 oxidation products were separated from the crude reaction; the iminopyrrolinone **19** (23%) and a mixture of uro'gen I and III methyl esters (9%), presumably coming from fragmentation-recombination of the pyrrolic fragments. Similar behavior was observed for the amino derivatives, however with an increased sensitivity toward oxygen. No oxidation product could be isolated in the latter cases.



Scheme 3: Preparation of the 1-formyl-19-urethanebilane.

a) H₂/10% Pd-C, Et₃N, THF; b) DPPA, Et₃N, THF; c) ROH, PhH, reflux; d) NaBH₄, NH₄Cl, CH₂Cl₂/MeOH; e) Montmorillonite clay, CH₂Cl₂.

A^{Me}=CH₂CO₂Me P^{Me}=CH₂CH₂CO₂Me CBZ=CO₂CH₂Ph



From all these observations, we realized that the 19-amino-HMB 7 would be too unstable for mechanistic studies and any result of its interaction with uro'gen III synthase would thus become inconclusive. Therefore, we did not pursue the deprotection of the 1-formyl-19urethanebilane methyl ester.

In conclusion, α -urethane-dipyrromethanes and -bilanes were synthesized for the first time and characterized by ¹H- and ¹³C-NMR. Stability studies toward oxygen were also performed, demonstrating the greater susceptibility of these urethanes to autoxidation in absence of any electron-withdrawing substituent.

Experimental.

General procedures.

All solvents and reagents were purified and dried when necessary according to standard literature methods. All reactions were conducted in anhydrous solvents and under argon atmosphere, unless specified otherwise. Column chromatographies were carried out on E. Merck Kieselgel 60 (100-200 mesh), TLC and preparative TLC (PLC) on Analtech silica gel GF plates. ¹H- and ¹³C-NMR (500 MHz) were recorded in CDCl₃ on a Brüker AM-500. The coupling constants are expressed in Hz. Mass spectra were obtained on a VG analytical 70s high-resolution double-focussing magnetic-sector mass spectrometer.

5-Azidocarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-methylpyrrole (14).

A solution of the 5-carbobenzoxypyrrole $12^{11,12}$ (2.92 g, 7.8 mmol) in THF (10 mL) containing Et₃N (1 mL) was hydrogenated over 10% Pd-C (300 mg) at RT for 8 h. The solution was filtered through Celite and the solid washed with CH₂Cl₂. The solution was neutralized by washing with HCl 0.1N, dried over MgSO₄, filtered and evaporated to dryness to afford the 5-carboxypyrrole 13 (2.15 g, 7.6 mmol, 97%), which was used for the next step without further purification. ¹H-NMR δ 9.27 (s br, 1H, NH); 3.66, 3.64 (2 s, 6H, 2 CO₂CH₃); 3.43 (s, 2H, CH₂CO₂Me); 3.01 (t, J=7.8, 2H, CH₂CH₂CO₂Me); 2.60 (t, J=7.8, 2H, CH₂CH₂CO₂Me); 2.21 (s, 3H, CH₃). ¹³C-NMR δ 173.9, 172.2, 165.6, 133.0, 132.5, 116.0, 114.8, 52.0, 51.5, 34.6, 29.6, 20.5, 11.6.

Diphenylphosphorazide (1.8 mL, 8.36 mmol) was added to a solution of the 5-carboxypyrrole 13 prepared above (2.15 g, 7.6 mmol) and Et₃N (1.3 mL, 9.12 mmol) in THF (15 mL) and the reaction was stirred at RT overnight. After evaporation of the solvent, EtOAc (20 mL)

was added and the solution washed with aqueous NaHCO₃. The product **14** (2.02 g, 6.56 mmol, 86%) was purified by chromatography (CH₂Cl₂/EtOAc, 2/1). ¹H-NMR δ 9.80 (s br, 1H, NH); 3.60, 3.59 (2 s, 6H, 2 CO₂CH₃); 3.37 (s, 2H, CH₂CO₂Me); 2.96 (t, J=7.9, 2H, CH₂CH₂CO₂Me); 2.52 (t, J=7.9, 2H, CH₂CH₂CO₂Me); 2.17 (s, 3H, CH₃). ¹³C-NMR δ 173.5, 171.9, 163.1, 135.2, 133.0, 118.4, 115.7, 51.9, 51.4, 34.6, 29.4, 20.5, 11.5. MS(FAB) m/z 309 [M + H]⁺; 308 [M]⁺; 280 [M - N₂]⁺; 221 [M - N₂ - CO₂Me]⁺; 207 [M - N₂ - CH₂CO₂Me]⁺. HRMS(FAB) [C₁₃H₁₇N₄O₅]⁺, calcd.: 309.2305, found: 309.1184; [C₁₃H₁₆N₄O₅]⁺, calcd.: 308.2227, found: 308.1129.

5-Azidocarbonyl-2-chloromethyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-pyrrole (20).

A solution of sulfuryl chloride (1.0 M in CH₂Cl₂, 3.9 mL, 3.9 mmol) was added dropwise to a solution of the 5-azidocarbonylpyrrole **14** (1.2 g, 3.88 mmol) in CH₂Cl₂ (10 mL) cooled in an ice-bath. At the end of the addition, the bath was removed and the reaction stirred at RT for 45 min. The solvent was then evaporated to dryness under vacuum at RT. More CH₂Cl₂ (5 mL) was added to the residue and evaporated again to dryness (repeat twice). The product was used for the next step without further purification. ¹H-NMR δ 10.20 (s br, 1H, NH); 4.58 (s, 2H, CH₂Cl); 3.62, 3.60 (2 s, 6H, 2 CO₂CH₃); 3.49 (s, 2H, CH₂CO₂Me); 2.97 (t, J=7.8, 2H, CH₂CH₂CO₂Me); 2.53 (t, J=7.8, 2H, CH₂CH₂CO₂Me). ¹³C-NMR δ 173.4, 171.4, 163.8, 132.4, 132.3, 120.4, 117.4, 52.1, 51.5, 35.8, 34.4, 29.1, 20.2.

5-Azidocarbonyl-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (23a) and 5-azidocarbonyl-5'-formyl-4,4'-di-(2-methoxycarbonyl-ethyl)-3,3'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (23b).

The 2-chloromethylpyrrole 20 prepared above (3.88 mmol) and α -free 5-formylpyrrole 18¹⁷ (981 mg, 3.88 mmol) were dissolved in CH_2Cl_2 (8 mL) and the solution stirred at RT for 5 days with addition of anhydrous solid CaCO₃ (3 x 100 mg, 3 x 1 mmol) at 8, 24 and 48 h. The solution was filtered through Celite, the solid washed with CH₂Cl₂/MeOH (95/5). The filtrate was washed with aqueous NaHCO3 and the products 23a and b isolated together (829 mg, 1.48 mmol, 38%) in a ratio of 5.75:1 by chromatography (hexanes/EtOAc, 1/1). The 2 isomers could not be totally separated. Major isomer 23a: ¹H-NMR δ 10.81, 10.43 (s + s br, 2H, 2 NH); 9.50 (s, 1H, CHO); 4.00 (s, 2H, CH2 meso); 3.73, 3.55 (2 s, 4H, 2 CH2CO2Me); 3.71, 3.69, 3.67, 3.63 (4 s, 12H, 4 CO_2CH_3); 2.99, 2.77 (2 t, J=7.8, 6.8, 4H, 2 CH₂CH₂CO₂Me); 2.53 (m, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 177.6, 173.9, 173.2, 172.8, 171.0, 162.9, 135.0, 133.6, 132.3, 129.0, 126.3, 121.0, 119.7, 115.9, 52.3, 52.1, 51.7, 51.3, 34.3, 33.9, 29.7, 29.2, 22.3, 20.3, 18.3. Minor isomer **23b**: ¹H-NMR δ 10.73, 10.43 (s + s br, 2H, 2 NH); 9.44 (s, 1H, CHO); 3.86 (s, 2H, CH₂ meso); 3.66, 3.44 (2 s, 4H, 2 CH₂CO₂Me); 3.62, 3.60, 3.58, 3.53 (4 s, 12H, 4 CO_2CH_3); 2.91, 2.68 (2 t, J=7.8, 6.9, 4H, 2 CH₂CH₂CO₂Me); 2.45 (m, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 177.5, 173.7, 173.1, 172.5, 170.9, 162.8, 135.8, 133.5, 132.2, 128.3, 126.3, 122.1, 115.5, 114.7, 52.1, 52.0, 51.3, 51.2, 35.4, 33.8, 29.0, 28.8, 22.5, 20.2, 18.7. MS(FAB) m/z 560 [M + H]+; 307 [M - PyrrCHO]+. HRMS(FAB) [C₂₅H₃₀N₅O₁₀]+, calcd.: 560.1993, found: 560.1992.

5-Benzyloxycarbonylamino-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (26a) and 5-benzyloxycarbonylamino-5'-formyl-4,4'-di-(2-methoxycarbonylethyl)-3,3'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (26b).

The isomeric mixture of 5-azidocarbonyldipyrroles 23a and b (829 mg, 1.48 mmol) was dissolved in PhH (5 mL) and heated at reflux for 1 h, then BzOH (770 μ L, 7.4 mmol) was added and the reflux continued overnight. The solvent was evaporated and the 5benzyloxycarbonylaminodipyrroles 26a and b (813 mg, 1.27 mmol, 86%) isolated by chromatography (hexanes/EtOAc, 1/1). Another chromatography (CH₂Cl₂/EtOAc, 6/1) allowed separation of the 2 isomers 26a and b in a 5.5:1 ratio. Major isomer 26a: ¹H-NMR δ 10.25, 9.58 (2 s br, 2H, 2 NH); 9.47 (s, 1H, CHO); 8.19 (s, 1H, NHCO₂Bz); 7.34-7.28 (m, 5H, aro. H); 5.11 (s, 2H, CH₂Ph); 3.86 (s, 2H, CH₂ meso); 3.71, 3.42 (2 s, 4H, 2 CH₂CO₂Me); 3.72, 3.66, 3.61, 3.60 (4 s, 12H, 4 CO_2CH_3); 2.76, 2.61 (2 t, J=6.9, 6.2, 4H, 2 CH₂CH₂CO₂Me); 2.49 (m, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 176.9, 175.1, 173.4, 173.1, 171.1, 154.1, 136.5, 136.0, 128.4, 128.1, 127.8, 127.6, 126.1, 123.4, 120.4, 119.5, 110.4, 106.4, 66.5, 52.1, 51.9, 51.6, 51.4, 34.0, 33.9, 29.8, 29.5, 22.0, 18.3, 17.6. MS(FAB) m/z 640 $[M + H]^+$; 639 $[M]^+$. HRMS(FAB) $[C_{32}H_{38}N_3O_{11}]^+$, calcd.: 640.2506, found: 640.2521; $[C_{32}H_{37}N_{3}O_{11}]^+$, calc.: 639.2428, found: 639.2456. Minor isomer **26b**: ¹H-NMR δ 9.95 (s br, 1H, NH); 9.53 (s, 1H, CHO); 9.38 (s br, 1H, NH); 8.02 (s br, 1H, NHCO₂Bz); 7.36-7.28 (m, 5H, aro. H); 5.15 (s, 2H, CH₂Ph); 3.81 (s, 2H, CH₂ meso); 3.77, 3.63, 3.62, 3.50 (4 s, 12H, 4 CO₂CH₃); 3.71, 3.40 (2 s, 4H, 2 CH₂CO₂Me); 3.00, 2.59 (2 t, J=7.6, 6.1, 4H, 2 CH₂CH₂CO₂Me); 2.55, 2.47 (2 t, J= 7.6, 6.1, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 177.0, 175.4, 173.3, 172.9, 172.6, 154.2, 137.2, 136.3, 133.1, 128.4, 128.3, 128.1, 128.0, 124.1, 119.7, 114.0, 110.5, 106.1, 66.9, 52.6, 52.4, 51.9, 51.7, 35.9, 34.2, 30.1, 29.3, 22.5, 19.1, 17.8.

5-Carboxy-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'methylenedipyrrole (25).

A solution of the 5-carbobenzoxydipyrromethane (24,¹⁶ synthesized as described in ref. 4) (785 mg, 1.26 mmol) in THF (8 mL) containing Et₃N (500 µL) was hydrogenated over 10% Pd-C (80 mg) at RT overnight. The solution was filtered through Celite, the catalyst washed with CH₂Cl₂ and the filtrate neutralized by washing with 0.1 N HCl. The compound **25** (630 mg, 1.18 mmol, 94 %) was used in the next step without further purification. ¹H-NMR δ 11.40, 10.64 (2 s br, 2H, 2 NH); 9.30 (s, 1H, CHO); 3.96 (s, 2H, CH₂ meso); 3.68, 3.49 (2 s, 4H, 2 CH₂CO₂Me); 3.64, 3.62, 3.58 (3 s, 12H, 4 CO₂CH₃); 2.97, 2.80 (2 t, J=7.7, 7.2, 4H, 2 CH₂CH₂CO₂Me); 2.54, 2.48 (2 t, J=7.7, 7.2, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 177.4,

173.5, 173.3, 172.5, 170.9, 164.8, 136.2, 131.7, 131.5, 129.0, 128.0, 121.5, 117.8, 114.8, 52.2, 52.1, 51.6, 51.3, 34.5, 34.4, 29.7, 29.4, 22.5, 20.3, 18.6.

5-Azidocarbonyl-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-di-(methoxycarbonylmethyl)-2,2'-methylenedipyrrole (23a).

The 5-carboxydipyrromethane (25) (630 mg, 1.18 mmol) was dissolved in THF (30 mL) and treated with diphenylphosphorazide (285 μ L, 1.32 mmol) in presence of Et₃N (200 μ L, 1.44 mmol) at RT overnight. The solvent was evaporated, the residue rediluted in EtOAc and washed with aqueous NaHCO₃. The product 23a (469 mg, 0.84 mmol, 71%) was obtained as a single isomer and purified by chromatography (CH₂Cl₂/EtOAc, 2/1).

5-Benzyloxycarbonylamino-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxy-carbonylmethyl-2,2'-methylenedipyrrole (26a).

A solution of the 5-azidocarbonyldipyrromethane **23a** (469 mg, 0.84 mmol) in PhH (5 mL) was heated at reflux for 1 h, then BzOH (435 μ L, 4.2 mmol) was added and the heating continued overnight. After evaporation of the solvent, the crude product was chromatographied (hexanes, hexanes/EtOAc 1/1, hexanes/EtOAc 2/1) and gave the compound **26a** (494 mg, 0.77 mmol, 92%).

5-Benzyloxycarbonylamino-5'-hydroxymethyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (27).

A solution of the 5'-formyldipyrrole **26a** (89 mg, 0.14 mmol) and NH₄Cl (50 mg) in CH₂Cl₂/MeOH (1/2, 3 mL) was reduced with NaBH₄ (2 x 30 mg) at 0 °C. After 5 min, the cool-bath was removed and the reaction stirred another 15 min. The reaction was quenched with H₂O (3 mL) and the 5'-hydroxymethyldipyrrole **27** (87 mg, 0.135 mmol, 97%) was extracted into CH₂Cl₂. The product was used as such for the next step. ¹H-NMR δ 9.27, 9.25 (2 s br, 2H, 2 NH); 7.94 (s br, 1H, NHCO₂Bz); 7.31-7.25 (m, 5H, H aro.); 5.09 (s, 2H, CH₂Ph); 4.35 (s, 2H, CH₂OH); 3.74 (s, 2H, CH₂ meso); 3.66, 3.63, 3.59, 3.56 (4 s, 12H, 4 CO₂CH₃); 3.40, 3.37 (2 s, 4H, 2 CH₂CO₂Me); 2.71, 2.57 (2 t, J=7.2, 6.4, 4H, 2 CH₂CH₂CO₂Me); 2.44 (m, 4H, 2 CH₂CH₂CO₂Me). ¹³C-NMR δ 175.1, 173.9, 173.8, 173.7, 154.3, 136.1, 128.3, 128.1, 127.9, 127.7, 125.6, 122.7, 121.9, 116.1, 111.5, 109.6, 106.9, 66.7, 55.6, 52.1, 52.0, 51.7, 51.4, 34.9, 34.1, 29.9, 29.8, 21.8, 19.0, 17.8.

19-Benzyloxycarbonylamino-1-formyl-3,8,13,18-tetra-(2-methoxycarbonylethyl)-2,7,12,17-tetra-(methoxycarbonylmethyl)-bilane (29a).

The 5'-hydroxymethyldipyrrole 27 (87 mg, 0.135 mmol) was dissolved into CH₂Cl₂ (2 mL) and the α -free dipyrromethane 28¹⁶ (102 mg, 0.209 mmol) was added, then Montmorillonite clay (prepared as in ref. 8, 700 mg). The flask was wrapped in aluminium foil and stirred for 2 days. The solution was filtered through Celite, the solid washed with CH₂Cl₂/MeOH (95/5) and the bilane 29a (62 mg, 0.055 mmol, 36%) isolated by PLC (CH₂Cl₂/MeOH, 95/5, run

twice). ¹H-NMR δ 9.95, 9.21, 9.13, 9.01 (4 s br, 4H, 4 NH); 9.44 (s, 1H, CHO); 7.90 (s br, 1H, NHCO₂Bz); 7.31-7.27 (m, 5H, H aro.); 5.10 (s, 2H, CH₂Ph); 3.77, 3.70, 3.69 (3 s, 6H, 3 CH₂ meso); 3.66, 3.65, 3.62, 3.60, 3.58, 3.57, 3.56 (7 s, 24H, 8 CO₂CH₃); 3.64, 3.35, 3.33, 3.32 (4 s, 8H, 4 CH₂CO₂Me); 2.75, 2.71, 2.65, 2.56 (4 t, J=7.8, 7.8, 7.3, 6.3, 8H, 4 CH₂CH₂CO₂Me); 2.41 (m, 8H, 4 CH₂CH₂CO₂Me). ¹³C-NMR δ 177.0, 175.2, 174.6, 173.9, 173.8, 173.4, 171.3, 154.3, 136.4, 136.2, 128.5, 128.4, 128.3, 128.0, 127.8, 125.8, 125.7, 124.9, 122.9, 122.6, 122.3, 120.6, 116.0, 115.9, 111.1, 110.3, 109.5, 107.1, 66.7, 52.2, 52.1, 51.7, 51.5, 51.3, 35.2, 35.0, 34.5, 34.2, 30.1, 30.0, 29.8, 29.6, 22.6, 22.2, 22.0, 19.4, 19.3, 18.7, 17.8. MS(FAB) m/z 1114 [M + H]+; 1113 [M]+; 1130 [M + OH]+; 740 [CHO(CH₂Pyrr)₃]+. HRMS(FAB) [C₅₆H₆₇N₅O₁₉]+, calcd.: 1113.4430, found: 1113.4485; [C₅₆H₆₇N₅NaO₁₉]+, calc.: 1136.4228, found: 1136.4403.

19-Benzyloxycarbonylamino-1-hydroxymethyl-3,8,13,18-tetra-(2-methoxycarbonylethyl)-2,7,12,17-tetra-(methoxycarbonylmethyl)-bilane (29b).

A solution of the 1-formylbilane **29a** (28 mg, 0.025 mmol) and NH₄Cl (30 mg) in CH₂Cl₂/MeOH (1/1, 2 mL) was reduced with NaBH₄ (40 mg) at 0 °C for 5 min, then at RT for 30 min. The reaction was quenched with H₂O, the HMB **29b** extracted into CH₂Cl₂ and used as such for further experiments. ¹H-NMR δ 9.21, 9.16, 8.88 (3 s br, 4H, 4 NH); 7.86 (s br, 1H, NHCO₂Bz); 7.33-7.28 (m, 5H, H aro.); 5.12 (s, 2H, CH₂Ph); 4.39 (s, 2H, CH₂OH); 3.71, 3.69, 3.66 (3 s, 6H, 3 CH₂ meso); 3.66, 3.65, 3.60, 3.59, 3.56, 3.54 (6 s, 24H, 8 CO₂CH₃); 3.57, 3.40, 3.37, 3.33 (4 s, 8H, 4 CH₂CO₂CH₃); 2.72, 2.66, 2.56 (t + m + t, J=7.4, 6.2, 12H, 4 CH₂CH₂CO₂Me); 2.41, 2.35 (m + t, J=7.4, 12H, 4 CH₂CH₂CO₂Me).¹³C-NMR δ 175.3, 174.4, 174.3, 174.0, 173.9, 154.5, 136.3, 128.4, 128.1, 127.9, 125.8, 125.3, 125.0, 124.8, 122.6, 122.4, 116.1, 111.7, 110.5, 110.3, 109.6, 107.4, 66.8, 55.8, 52.1, 51.8, 51.5, 51.4, 35.4, 35.3, 35.1, 34.3, 30.0, 29.8, 22.4, 22.2, 19.6, 19.4, 19.3, 17.9.

5-(2-Trimethylsilylethoxycarbonylamino)-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (30).

A solution of the 5-azidocarbonyldipyrromethane **23a** (379 mg, 0.68 mmol) and 2trimethylsilylethanol (500 μ L, 3.4 mmol) in PhH (2 mL) was heated at reflux overnight. The solvent was evaporated and the product purified by chromatography (hexanes, hexanes/EtOAc 1/1, hexanes/EtOAc 2/1) to give the 5-(2-trimethylsilylethoxycarbonylamino)dipyrromethane **30** (410 mg, 0.63 mmol, 93%). ¹H-NMR δ 10.03, 9.43 (2 s br, 2H, 2 NH); 9.44 (s, 1H, CHO); 8.03 (s br, 1H, NHCO₂CH₂CH₂SiMe₃); 4.13 (t, J=8.3, 2H, CO₂CH₂CH₂SiMe₃); 3.83 (s, 2H, CH₂ meso); 3.70, 3.64, 3.61, 3.60 (4 s, 12H, 4 CO₂CH₃); 3.69, 3.36 (2 s, 4H, 2 CH₂CO₂Me); 2.72, 2.55 (2 t, J=6.8, 6.5, 4H, 2 CH₂CH₂CO₂Me); 2.47, 2.42 (2 t, J=6.8, 6.5, 4H, 2 CH₂CH₂CO₂Me); 0.96 (t, J=8.3, 2H, CH₂SiMe₃); -0.04 (s, 9H, Si(CH₃)₃). ¹³C-NMR δ 177.1, 175.4, 173.5, 171.2, 154.4, 136.5, 128.6, 125.8, 124.2, 120.4, 119.1, 110.6, 105.6, 63.4, 52.3, 52.1, 51.8, 51.6, 34.2, 34.1, 30.0, 29.7, 22.2, 18.5, 17.6, 17.5, -1.7.

5-(2-Trimethylsilylethoxycarbonylamino)-5'-hydroxymethyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (31).

A solution of the 5'-formyldipyrromethane **30** (104 mg, 0.16 mmol) and NH₄Cl (80 mg) in CH₂Cl₂/MeOH (1/2, 4.5 mL) was reduced with NaBH₄ (120 mg) at 0 °C for 5 min, then at RT for 20 min. The reaction was quenched with H₂O, the 5'-hydroxymethyldipyrromethane **31** (102 mg, 0.157 mmol, 98%) was extracted into CH₂Cl₂ and, after evaporation of the solvent to dryness, used without purification in the next step. ¹H-NMR δ 9.25, 9.19 (2 s br, 2H, 2 NH); 7.87 (s br, 1H, NHCO₂CH₂CH₂SiMe₃); 4.39 (s, 2H, CH₂OH); 4.13 (t, J=8.4, 2H, CO₂CH₂CH₂SiMe₃); 3.74 (s, 2H, CH₂ meso); 3.65, 3.63, 3.60, 3.59 (4 s, 12H, 4 CO₂CH₃); 3.40, 3.39 (2 s, 4H, 2 CH₂CO₂Me); 2.71, 2.56 (2 t, J=7.2, 6.2, 4H, 2 CH₂CH₂CO₂Me); 2.44 (m, 4H, 2 CH₂CH₂CO₂Me); 0.97 (t, J=8.2, 2H, CH₂SiMe₃); 0.01 (s, 9H, Si(CH₃)₃).

19-(2-Trimethylsilylethoxycarbonylamino)-1-formyl-3,8,13,18-tetra-(2-methoxycarbonylethyl)-2,7,12,17-tetra-(methoxycarbonylmethyl)-bilane (32a).

To the 5'-hydroxymethyldipyrromethane **31** prepared above was added to the α -free formyl dipyrromethane **28**¹⁶ (118 mg, 0.241 mmol) and both were dissolved in CH₂Cl₂ (2 mL) and stirred over Montmorillonite clay (500 mg, prepared as in ref. 8) in the dark for 2 days. The solution was filtered through Celite and the solid washed with CH₂Cl₂/MeOH (95/5). The bilane **32a** was isolated (37 mg, 0.033 mmol, 21%) by PLC (CH₂Cl₂/MeOH, 95/5, run twice). ¹H-NMR δ 9.95, 9.19, 9.14, 8.99 (4 s br, 4H, 4 NH); 9.45 (s, 1H, CHO); 7.81 (s br, 1H, NHCO₂CH₂CH₂CH₂SiMe₃); 4.16 (t, J=8.2, 2H, CO₂CH₂CH₂SiMe₃); 3.78, 3.70, 3.69 (3 s, 6H, 3 CH₂ meso); 3.66, 3.65, 3.64, 3.62, 3.61, 3.59, 3.56 (7 s, 24H, 8 CO₂CH₃); 3.63, 3.35, 3.33, 3.32 (4 s, 8H, 4 CH₂CO₂Me); 2.75, 2.71, 2.66, 2.55 (4 t, J=7.6, 7.8, 7.8, 6.1, 8H, 4 CH₂CH₂CO₂Me); 2.41 (m, 8H, 4 CH₂CH₂CO₂Me); 0.98 (t, J=8.2, 2H, CH₂SiMe₃); 0.01 (s, 9H, Si(CH₃)₃). ¹³C-NMR δ 177.0, 175.3, 174.7, 174.0, 173.4, 171.3, 154.7, 136.4, 128.5, 125.9, 125.7, 124.9, 123.1, 123.0, 121.9, 120.6, 116.1, 116.0, 111.2, 110.4, 109.5, 106.5, 63.4, 52.2, 51.8, 51.5, 51.4, 35.3, 35.1, 34.6, 34.3, 30.2, 30.0, 29.8, 29.7, 22.6, 22.3, 22.1, 19.4, 18.8, 17.6, -1.6.

19-(2-Trimethylsilylethoxycarbonylamino)-1-hydroxymethyl-3,8,13,18-tetra-(2-methoxy-carbonylethyl)-2,7,12,17-tetra-(methoxycarbonylmethyl)-bilane (32b).

A solution of the 1-formylbilane **32a** (26.7 mg, 0.238 mmol) and NH₄Cl (25 mg) in CH₂Cl₂/MeOH (1/2 mL) was reduced with NaBH₄ (40 mg) at 0 °C for 5 min, then at RT for 30 min. The reaction was quenched with H₂O (4 mL) and the 1-hydroxymethylbilane **32b** extracted into CH₂Cl₂. The bilane **32b** was used directly as such for further experiments. ¹H-NMR δ 9.18, 8.93, 8.90 (3 s br, 4H, 4 NH); 7.72 (s br, 1H, NHCO₂CH₂CH₂SiMe₃); 4.40 (s, 2H, CH₂OH); 4.15 (t, J=8.4, 2H, NHCO₂CH₂CH₂SiMe₃); 3.71, 3.70, 3.68 (3 s, 6H, 3 CH₂ meso); 3.67, 3.66, 3.61, 3.60, 3.55 (5 s, 24H, 8 CO₂CH₃); 3.58, 3.41, 3.36, 3.33 (4 s, 8H, 4 CH₂CO₂Me); 2.70, 2.67, 2.56 (t + m + t, J=8.1, 7.8, 8H, 4 CH₂CH₂CO₂Me); 2.40, 2.35 (m + t, J=8.1, 8H, 4 CH₂CH₂CO₂Me); 0.98 (t, J=8.4, 2H, CH₂SiMe₃); 0.01 (s, 9H, Si(CH₃)₃).

Aerial oxidation of the 5-benzyloxycarbonylamino-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-2,2'-methylenedipyrrole (**26a**).

A solution of dipyrromethane 26a (143 mg, 0.224 mmol) in CHCl₃ (5 mL) was left on the bench under normal air atmosphere and light for 1 week. After evaporation, 3 compounds were isolated by PLC (CH₂Cl₂/MeOH, 95/5, run twice). The first one was the 5-imino- Δ^3 pyrrolin-2-one **19** (14.5 mg, 0.037 mmol, 16%). ¹H-NMR δ 9.30 (s br, 1H, NH); 7.41-7.32 (m, 5H, H aro.); 5.22 (s, 2H, CH₂Ph); 3.69, 3.62 (2 s, 6H, 2 CO₂CH₃); 3.53 (s, 2H, CH₂CO₂Me); 2.78 (t, J=7.0, 2H, CH₂CH₂CO₂Me); 2.66 (t, J=7.0, 2H, CH₂CH₂CO₂Me). ¹³C-NMR δ 172.5, 170.1, 168.9, 163.9, 162.1, 147.5, 135.1, 133.5, 128.6, 68.8, 52.5, 51.7, 32.1, 28.7, 19.7. MS(FAB) m/z 389 [M + H]+; 388 [M]+; 282 [M - OBz + H]+; 222 [M - NHCO₂Bz - OH]⁺. The second compound was the starting material 26a (85 mg, 0.133 mmol, 59%) and the last product the pyrrolyl-hydroxypyrroline-urethane 33 (19.6 mg, 0.03 mmol, 13%). ¹H-NMR δ 9.99 (s br, 1H, NH); 9.49 (s, 1H, CHO); 9.10 (s br, 1H, NH); 7.35-7.25 (m, 5H, aro. H); 5.10, 5.05 (AB syst., J=12.3, 2H, CH_2Ph); 4.84 (m, 1H, OH); 3.68 (s, 2H, CH_2 meso); 3.67, 3.65, 3.60, 3.58 (4 s, 12H, 4 CO₂CH₃); 3.63, 3.16, 3.11, 2.97 (2 AB syst., J=17.0, 14.7, 4H, 2 CH₂CO₂Me); 2.67, 2.60, 2.41 (t + m + t, J=7.4, 7.6, 8H, 2 CH₂CH₂CO₂Me). 13 C-NMR δ 177.4, 173.4, 173.2, 171.3, 171.2, 167.3, 164.3, 148.0, 137.4, 136.3, 131.6, 129.3, 128.4, 128.2, 128.0, 125.9, 123.9, 92.1, 67.4, 52.9, 52.3, 51.6, 34.6, 33.9, 31.8, 30.5, 29.7, 19.1, 18.6.

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