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Synthesis of Novel 19-(Alkyloxycarbonylamino)bilanes.

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Abstract: α-Urethane-dipyrromethanes and -bilanes were synthesized for the first time and characterized by ^{1}H- and ^{13}C-NMR. Stability studies toward oxygen were also performed.

Keywords: *Pyrroles; urethanes; condensations; NMR.*

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, 1-hydroxymethylbilane (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] ^{13}C-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** ^{13}C-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-$^{13}CH_2OH$) 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**,

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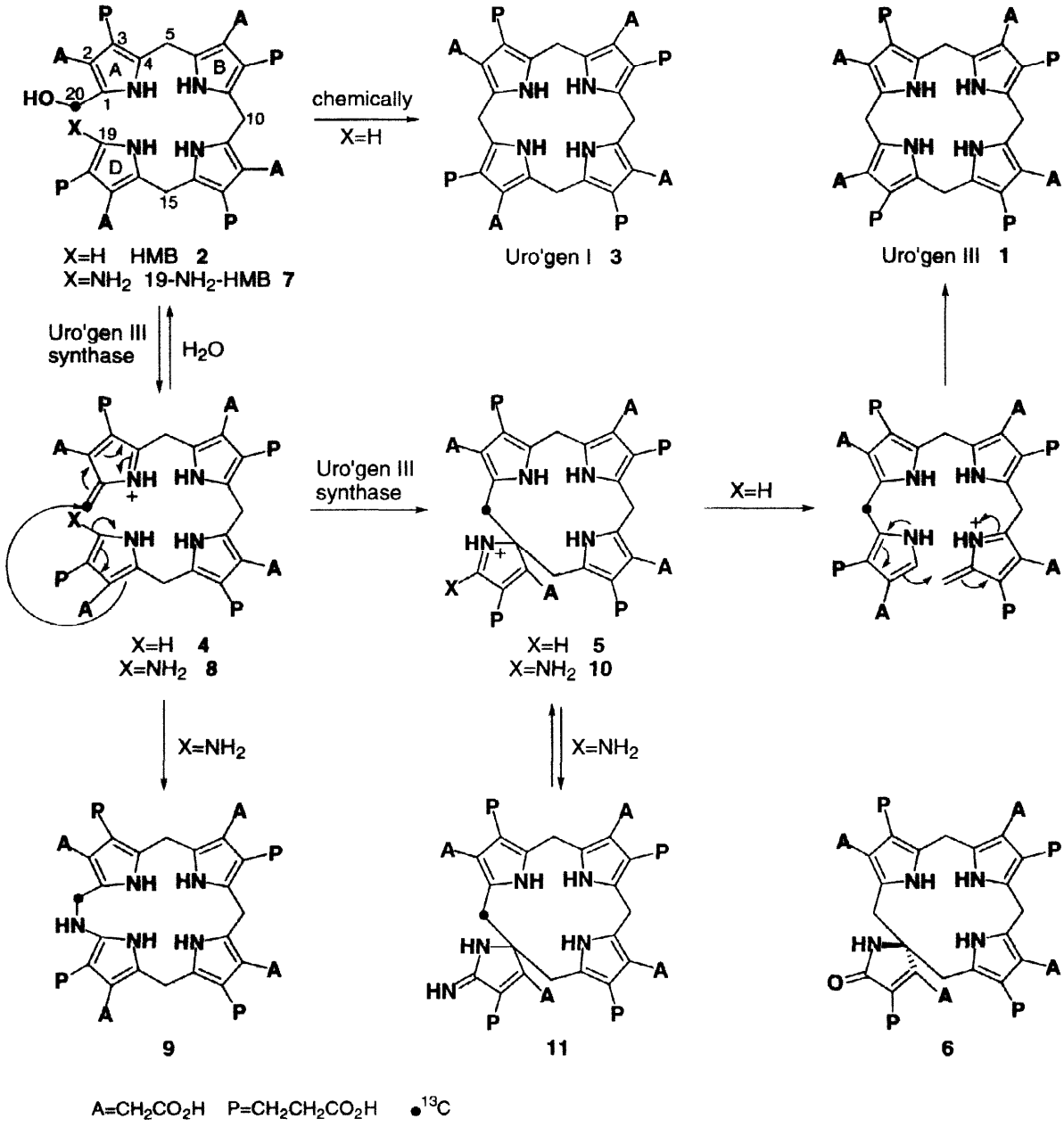
the reaction could proceed to the spiro intermediate **10** or its more stable form **11** (C-20 at ~30 ppm).

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



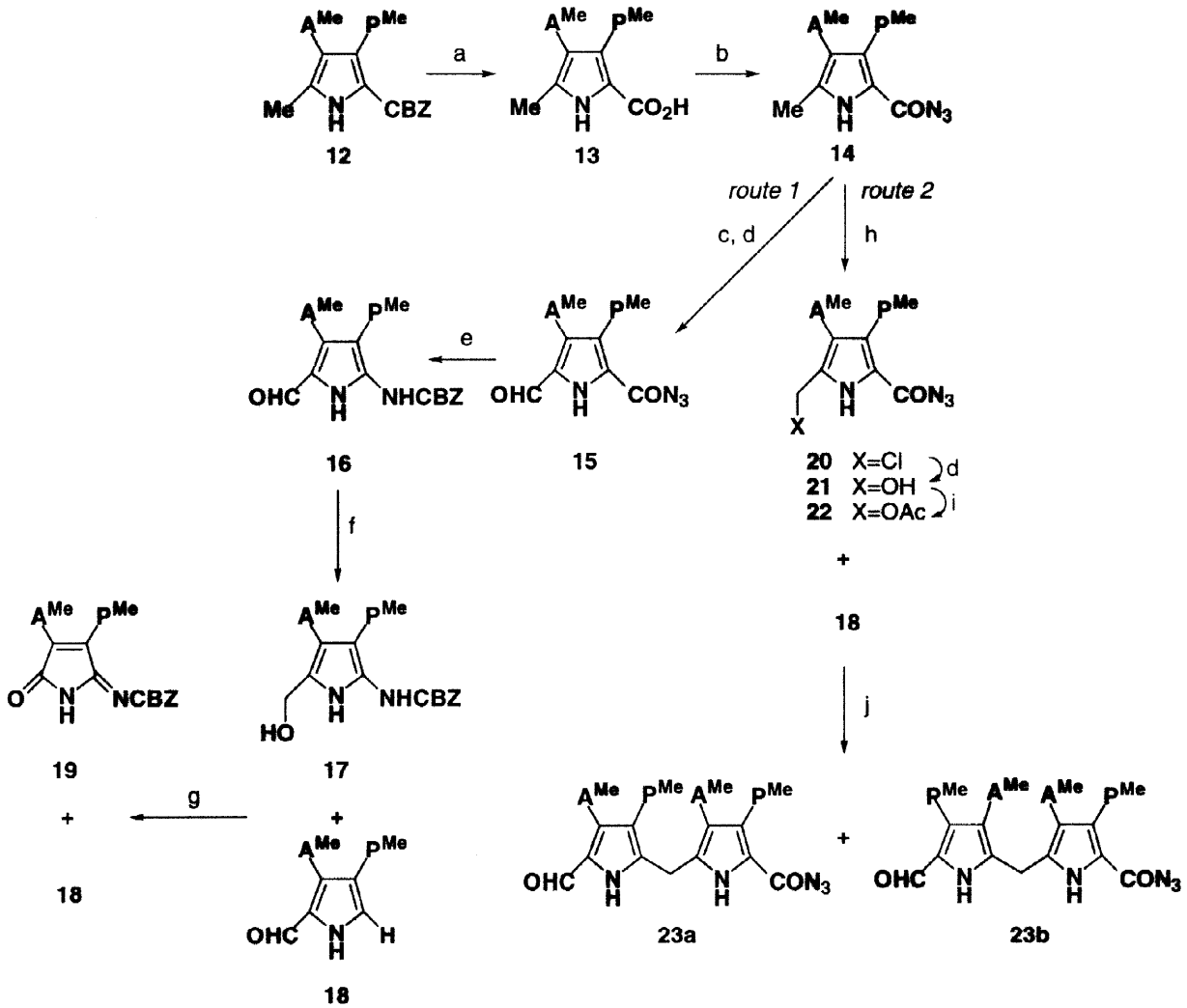
Our strategy for the synthesis of the 19-amino-HMB **7** followed the modified preparation of HMB: *viz.* condensation of an α-hydroxymethyldipyrromethane with an α-free α'-

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 2-hydroxymethylpyrrole **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 ^{1}H-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]-sigmatropic 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) H_2/10% Pd-C, Et_3N, THF; b) DPPA, Et_3N, THF; c) 2 eq. SO_2Cl_2, $CaCO_3$, CH_2Cl_2, RT, 1 h;
d) H_2O/acetone, RT, 2h; e) BzOH, PhH, reflux; f) $NaBH_4$, NH_4Cl, CH_2Cl_2/MeOH;
g) Montmorillonite clay, CH_2Cl_2; h) 1 eq. SO_2Cl_2, CH_2Cl_2, RT, 1 h; i) Ac_2O, pyridine; j) H^+.

A^{Me}=CH_2CO_2Me P^{Me}=$CH_2CH_2CO_2Me$ CBZ=CO_2CH_2Ph

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 ($CaCO_3$), 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 $CaCO_3$ 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.

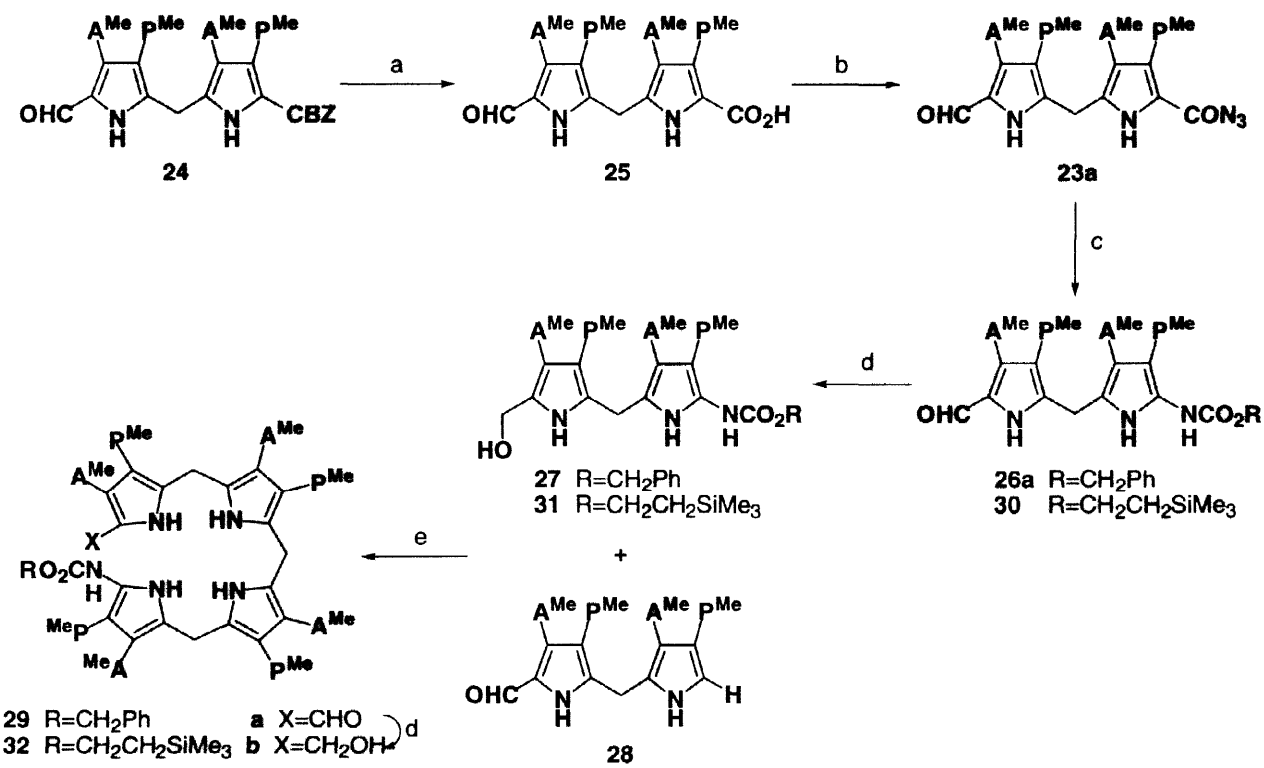
At this point, it was found that the 5-azidocarbonyldipyrromethane **23a** could be obtained as a single isomer in the same manner that 2-azidocarbonylpyrroles (ex: **14**) are prepared: *i. e.*, hydrogenation of the 5-carbobenzoxydipyrromethane **24**[16] to give the 5-carboxydipyrromethane **25**, 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 **28**[16] using Montmorillonite clay as catalyst[8] 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, ^{1}H-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-, di- or tetra-pyrroles (**16**, **26a** or **29a**) seem reasonably stable. If left under normal air atmosphere, no oxidation product was observed (^{1}H- and ^{13}C-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**

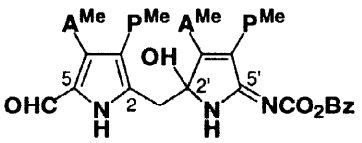
(13%), reminiscent of the hydroxypyrrolinylurethane obtained by autoxidation of a pyrrolylurethane,[9] were isolated after one week; the only compound isolable after one week in the aerial oxidation of the bilane **29a** was the iminopyrrolinone **19** (24%), no starting material being recovered. If 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) H_2/10% Pd-C, Et_3N, THF; b) DPPA, Et_3N, THF; c) ROH, PhH, reflux;
d) $NaBH_4$, NH_4Cl, CH_2Cl_2/MeOH; e) Montmorillonite clay, CH_2Cl_2.

A^{Me}=CH_2CO_2Me P^{Me}=$CH_2CH_2CO_2Me$ CBZ=CO_2CH_2Ph



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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-19-urethanebilane methyl ester.

In conclusion, α-urethane-dipyrromethanes and -bilanes were synthesized for the first time and characterized by ^{1}H- and ^{13}C-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. ^{1}H- and ^{13}C-NMR (500 MHz) were recorded in $CDCl_3$ 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 Et_3N (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 CH_2Cl_2. The solution was neutralized by washing with HCl 0.1N, dried over $MgSO_4$, 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. ^{1}H-NMR δ 9.27 (s br, 1H, N*H*); 3.66, 3.64 (2 s, 6H, 2 CO_2CH_3); 3.43 (s, 2H, CH_2CO_2Me); 3.01 (t, J=7.8, 2H, $CH_2CH_2CO_2Me$); 2.60 (t, J=7.8, 2H, $CH_2CH_2CO_2Me$); 2.21 (s, 3H, CH_3). ^{13}C-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 Et_3N (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 $NaHCO_3$. The product **14** (2.02 g, 6.56 mmol, 86%) was purified by chromatography (CH_2Cl_2/EtOAc, 2/1). ^{1}H-NMR δ 9.80 (s br, 1H, N*H*); 3.60, 3.59 (2 s, 6H, 2 CO_2CH_3); 3.37 (s, 2H, CH_2CO_2Me); 2.96 (t, J=7.9, 2H, $CH_2CH_2CO_2Me$); 2.52 (t, J=7.9, 2H, $CH_2CH_2CO_2Me$); 2.17 (s, 3H, CH_3). ^{13}C-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 $[M - N_2]^+$; 221 $[M - N_2 - CO_2Me]^+$; 207 $[M - N_2 - CH_2CO_2Me]^+$. HRMS(FAB) $[C_{13}H_{17}N_4O_5]^+$, calcd.: 309.2305, found: 309.1184; $[C_{13}H_{16}N_4O_5]^+$, 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 CH_2Cl_2, 3.9 mL, 3.9 mmol) was added dropwise to a solution of the 5-azidocarbonylpyrrole **14** (1.2 g, 3.88 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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. ^{1}H-NMR δ 10.20 (s br, 1H, N*H*); 4.58 (s, 2H, CH_2Cl); 3.62, 3.60 (2 s, 6H, 2 CO_2CH_3); 3.49 (s, 2H, CH_2CO_2Me); 2.97 (t, J=7.8, 2H, $CH_2CH_2CO_2Me$); 2.53 (t, J=7.8, 2H, $CH_2CH_2CO_2Me$). ^{13}C-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 **18**[17] (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 $CaCO_3$ (3 x 100 mg, 3 x 1 mmol) at 8, 24 and 48 h. The solution was filtered through Celite, the solid washed with CH_2Cl_2/MeOH (95/5). The filtrate was washed with aqueous $NaHCO_3$ 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**: ^{1}H-NMR δ 10.81, 10.43 (s + s br, 2H, 2 N*H*); 9.50 (s, 1H, C*H*O); 4.00 (s, 2H, CH_2 meso); 3.73, 3.55 (2 s, 4H, 2 CH_2CO_2Me); 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 $CH_2CH_2CO_2Me$); 2.53 (m, 4H, 2 $CH_2CH_2CO_2Me$). ^{13}C-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**: ^{1}H-NMR δ 10.73, 10.43 (s + s br, 2H, 2 N*H*); 9.44 (s, 1H, C*H*O); 3.86 (s, 2H, CH_2 meso); 3.66, 3.44 (2 s, 4H, 2 CH_2CO_2Me); 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 $CH_2CH_2CO_2Me$); 2.45 (m, 4H, 2 $CH_2CH_2CO_2Me$). ^{13}C-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) $[C_{25}H_{30}N_5O_{10}]^+$, 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 µL, 7.4 mmol) was added and the reflux continued overnight. The solvent was evaporated and the 5-benzyloxycarbonylaminodipyrroles **26a** and **b** (813 mg, 1.27 mmol, 86%) isolated by chromatography (hexanes/EtOAc, 1/1). Another chromatography (CH_2Cl_2/EtOAc, 6/1) allowed separation of the 2 isomers **26a** and **b** in a 5.5:1 ratio. Major isomer **26a**: ^{1}H-NMR δ 10.25, 9.58 (2 s br, 2H, 2 N*H*); 9.47 (s, 1H, C*H*O); 8.19 (s, 1H, N*H*CO_2Bz); 7.34-7.28 (m, 5H, aro. H); 5.11 (s, 2H, C*H*$_2$Ph); 3.86 (s, 2H, C*H*$_2$ meso); 3.71, 3.42 (2 s, 4H, 2 C*H*$_2$$CO_2$Me); 3.72, 3.66, 3.61, 3.60 (4 s, 12H, 4 CO_2CH_3); 2.76, 2.61 (2 t, J=6.9, 6.2, 4H, 2 $CH_2CH_2CO_2$Me); 2.49 (m, 4H, 2 $CH_2CH_2CO_2$Me). ^{13}C-NMR δ 176.9, 175.1, 173.4, 173.1, 171.1, 154.1, 136.5, 136.0, 128.4, 128.1, 127.8, 127.6, 126.1, 123.4, 120.4, 119.5, 110.4, 106.4, 66.5, 52.1, 51.9, 51.6, 51.4, 34.0, 33.9, 29.8, 29.5, 22.0, 18.3, 17.6. MS(FAB) m/z 640 $[M + H]^+$; 639 $[M]^+$. HRMS(FAB) $[C_{32}H_{38}N_3O_{11}]^+$, calcd.: 640.2506, found: 640.2521; $[C_{32}H_{37}N_3O_{11}]^+$, calc.: 639.2428, found: 639.2456. Minor isomer **26b**: ^{1}H-NMR δ 9.95 (s br, 1H, N*H*); 9.53 (s, 1H, C*H*O); 9.38 (s br, 1H, N*H*); 8.02 (s br, 1H, N*H*CO_2Bz); 7.36-7.28 (m, 5H, aro. H); 5.15 (s, 2H, C*H*$_2$Ph); 3.81 (s, 2H, C*H*$_2$ meso); 3.77, 3.63, 3.62, 3.50 (4 s, 12H, 4 CO_2CH_3); 3.71, 3.40 (2 s, 4H, 2 C*H*$_2$$CO_2$Me); 3.00, 2.59 (2 t, J=7.6, 6.1, 4H, 2 $CH_2CH_2CO_2$Me); 2.55, 2.47 (2 t, J= 7.6, 6.1, 4H, 2 $CH_2CH_2CO_2$Me). ^{13}C-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 Et_3N (500 µL) was hydrogenated over 10% Pd-C (80 mg) at RT overnight. The solution was filtered through Celite, the catalyst washed with CH_2Cl_2 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. ^{1}H-NMR δ 11.40, 10.64 (2 s br, 2H, 2 N*H*); 9.30 (s, 1H, C*H*O); 3.96 (s, 2H, C*H*$_2$ meso); 3.68, 3.49 (2 s, 4H, 2 C*H*$_2$CO2Me); 3.64, 3.62, 3.58 (3 s, 12H, 4 CO_2CH_3); 2.97, 2.80 (2 t, J=7.7, 7.2, 4H, 2 $CH_2CH_2CO_2$Me); 2.54, 2.48 (2 t, J=7.7, 7.2, 4H, 2 C*H*$_2$$CH_2CO_2$Me). ^{13}C-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 µL, 1.32 mmol) in presence of Et_3N (200 µL, 1.44 mmol) at RT overnight. The solvent was evaporated, the residue rediluted in EtOAc and washed with aqueous $NaHCO_3$. The product **23a** (469 mg, 0.84 mmol, 71%) was obtained as a single isomer and purified by chromatography (CH_2Cl_2/EtOAc, 2/1).

*5-Benzyloxycarbonylamino-5'-formyl-3',4-di-(2-methoxycarbonylethyl)-3,4'-dimethoxycarbonylmethyl-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 µL, 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 NH_4Cl (50 mg) in CH_2Cl_2/MeOH (1/2, 3 mL) was reduced with $NaBH_4$ (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 H_2O (3 mL) and the 5'-hydroxymethyldipyrrole **27** (87 mg, 0.135 mmol, 97%) was extracted into CH_2Cl_2. The product was used as such for the next step. ^{1}H-NMR δ 9.27, 9.25 (2 s br, 2H, 2 N*H*); 7.94 (s br, 1H, N*H*CO_2Bz); 7.31-7.25 (m, 5H, H aro.); 5.09 (s, 2H, C*H*$_2$Ph); 4.35 (s, 2H, C*H*$_2$OH); 3.74 (s, 2H, C*H*$_2$ meso); 3.66, 3.63, 3.59, 3.56 (4 s, 12H, 4 CO_2CH_3); 3.40, 3.37 (2 s, 4H, 2 C*H*$_2CO_2$Me); 2.71, 2.57 (2 t, J=7.2, 6.4, 4H, 2 $CH_2CH_2CO_2$Me); 2.44 (m, 4H, 2 C*H*$_2CH_2CO_2$Me). ^{13}C-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 CH_2Cl_2 (2 mL) and the α-free dipyrromethane **28**[16] (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 CH_2Cl_2/MeOH (95/5) and the bilane **29a** (62 mg, 0.055 mmol, 36%) isolated by PLC (CH_2Cl_2/MeOH, 95/5, run

twice). ^{1}H-NMR δ 9.95, 9.21, 9.13, 9.01 (4 s br, 4H, 4 N*H*); 9.44 (s, 1H, C*H*O); 7.90 (s br, 1H, N*H*CO_2Bz); 7.31-7.27 (m, 5H, H aro.); 5.10 (s, 2H, CH_2Ph); 3.77, 3.70, 3.69 (3 s, 6H, 3 CH_2 meso); 3.66, 3.65, 3.62, 3.60, 3.58, 3.57, 3.56 (7 s, 24H, 8 CO_2CH_3); 3.64, 3.35, 3.33, 3.32 (4 s, 8H, 4 CH_2CO_2Me); 2.75, 2.71, 2.65, 2.56 (4 t, J=7.8, 7.8, 7.3, 6.3, 8H, 4 $CH_2CH_2CO_2$Me); 2.41 (m, 8H, 4 C$H_2CH_2CO_2$Me). ^{13}C-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 $[CHO(CH_2Pyrr)_3]^+$. HRMS(FAB) $[C_{56}H_{67}N_5O_{19}]^+$, calcd.: 1113.4430, found: 1113.4485; $[C_{56}H_{67}N_5NaO_{19}]^+$, 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 NH_4Cl (30 mg) in CH_2Cl_2/MeOH (1/1, 2 mL) was reduced with $NaBH_4$ (40 mg) at 0 °C for 5 min, then at RT for 30 min. The reaction was quenched with H_2O, the HMB **29b** extracted into CH_2Cl_2 and used as such for further experiments. ^{1}H-NMR δ 9.21, 9.16, 8.88 (3 s br, 4H, 4 N*H*); 7.86 (s br, 1H, N*H*CO_2Bz); 7.33-7.28 (m, 5H, H aro.); 5.12 (s, 2H, CH_2Ph); 4.39 (s, 2H, CH_2OH); 3.71, 3.69, 3.66 (3 s, 6H, 3 CH_2 meso); 3.66, 3.65, 3.60, 3.59, 3.56, 3.54 (6 s, 24H, 8 CO_2CH_3); 3.57, 3.40, 3.37, 3.33 (4 s, 8H, 4 C$H_2CO_2CH_3$); 2.72, 2.66, 2.56 (t + m + t, J=7.4, 6.2, 12H, 4 $CH_2CH_2CO_2$Me); 2.41, 2.35 (m + t, J=7.4, 12H, 4 C$H_2CH_2CO_2$Me).^{13}C-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 2-trimethylsilylethanol (500 μL, 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%). ^{1}H-NMR δ 10.03, 9.43 (2 s br, 2H, 2 N*H*); 9.44 (s, 1H, C*H*O); 8.03 (s br, 1H, N*H*$CO_2CH_2CH_2SiMe_3$); 4.13 (t, J=8.3, 2H, $CO_2CH_2CH_2SiMe_3$); 3.83 (s, 2H, CH_2 meso); 3.70, 3.64, 3.61, 3.60 (4 s, 12H, 4 CO_2CH_3); 3.69, 3.36 (2 s, 4H, 2 CH_2CO_2Me); 2.72, 2.55 (2 t, J=6.8, 6.5, 4H, 2 $CH_2CH_2CO_2$Me); 2.47, 2.42 (2 t, J=6.8, 6.5, 4H, 2 C$H_2CH_2CO_2$Me); 0.96 (t, J=8.3, 2H, CH_2SiMe_3); -0.04 (s, 9H, Si(CH_3)$_3$). ^{13}C-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 NH_4Cl (80 mg) in CH_2Cl_2/MeOH (1/2, 4.5 mL) was reduced with $NaBH_4$ (120 mg) at 0 °C for 5 min, then at RT for 20 min. The reaction was quenched with H_2O, the 5'-hydroxymethyldipyrromethane **31** (102 mg, 0.157 mmol, 98%) was extracted into CH_2Cl_2 and, after evaporation of the solvent to dryness, used without purification in the next step. ^{1}H-NMR δ 9.25, 9.19 (2 s br, 2H, 2 N*H*); 7.87 (s br, 1H, N*H*$CO_2CH_2CH_2SiMe_3$); 4.39 (s, 2H, C*H*$_2$OH); 4.13 (t, J=8.4, 2H, $CO_2CH_2CH_2SiMe_3$); 3.74 (s, 2H, C*H*$_2$ meso); 3.65, 3.63, 3.60, 3.59 (4 s, 12H, 4 CO_2CH_3); 3.40, 3.39 (2 s, 4H, 2 C*H*$_2CO_2$Me); 2.71, 2.56 (2 t, J=7.2, 6.2, 4H, 2 $CH_2CH_2CO_2$Me); 2.44 (m, 4H, 2 C*H*$_2CH_2CO_2$Me); 0.97 (t, J=8.2, 2H, C*H*$_2SiMe_3$); 0.01 (s, 9H, Si(C*H*$_3$)$_3$).

*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 CH_2Cl_2 (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 CH_2Cl_2/MeOH (95/5). The bilane **32a** was isolated (37 mg, 0.033 mmol, 21%) by PLC (CH_2Cl_2/MeOH, 95/5, run twice). ^{1}H-NMR δ 9.95, 9.19, 9.14, 8.99 (4 s br, 4H, 4 N*H*); 9.45 (s, 1H, C*H*O); 7.81 (s br, 1H, N*H*$CO_2CH_2CH_2SiMe_3$); 4.16 (t, J=8.2, 2H, $CO_2CH_2CH_2SiMe_3$); 3.78, 3.70, 3.69 (3 s, 6H, 3 C*H*$_2$ meso); 3.66, 3.65, 3.64, 3.62, 3.61, 3.59, 3.56 (7 s, 24H, 8 CO_2CH_3); 3.63, 3.35, 3.33, 3.32 (4 s, 8H, 4 C*H*$_2CO_2$Me); 2.75, 2.71, 2.66, 2.55 (4 t, J=7.6, 7.8, 7.8, 6.1, 8H, 4 $CH_2CH_2CO_2$Me); 2.41 (m, 8H, 4 C*H*$_2CH_2CO_2$Me); 0.98 (t, J=8.2, 2H, C*H*$_2SiMe_3$); 0.01 (s, 9H, Si(C*H*$_3$)$_3$). ^{13}C-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-methoxycarbonylethyl)-2,7,12,17-tetra-(methoxycarbonylmethyl)-bilane (**32b**).*
A solution of the 1-formylbilane **32a** (26.7 mg, 0.238 mmol) and NH_4Cl (25 mg) in CH_2Cl_2/MeOH (1/2 mL) was reduced with $NaBH_4$ (40 mg) at 0 °C for 5 min, then at RT for 30 min. The reaction was quenched with H_2O (4 mL) and the 1-hydroxymethylbilane **32b** extracted into CH_2Cl_2. The bilane **32b** was used directly as such for further experiments. ^{1}H-NMR δ 9.18, 8.93, 8.90 (3 s br, 4H, 4 N*H*); 7.72 (s br, 1H, N*H*$CO_2CH_2CH_2SiMe_3$); 4.40 (s, 2H, C*H*$_2$OH); 4.15 (t, J=8.4, 2H, NHCO$_2$C*H*$_2CH_2SiMe_3$); 3.71, 3.70, 3.68 (3 s, 6H, 3 C*H*$_2$ meso); 3.67, 3.66, 3.61, 3.60, 3.55 (5 s, 24H, 8 CO_2CH_3); 3.58, 3.41, 3.36, 3.33 (4 s, 8H, 4 C*H*$_2CO_2$Me); 2.70, 2.67, 2.56 (t + m + t, J=8.1, 7.8, 8H, 4 $CH_2CH_2CO_2$Me); 2.40, 2.35 (m + t, J=8.1, 8H, 4 C*H*$_2CH_2CO_2$Me); 0.98 (t, J=8.4, 2H, C*H*$_2SiMe_3$); 0.01 (s, 9H, Si(C*H*$_3$)$_3$).

*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 $CHCl_3$ (5 mL) was left on the bench under normal air atmosphere and light for 1 week. After evaporation, 3 compounds were isolated by PLC (CH_2Cl_2/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%). ^{1}H-NMR δ 9.30 (s br, 1H, N*H*); 7.41-7.32 (m, 5H, H aro.); 5.22 (s, 2H, C*H*$_2$Ph); 3.69, 3.62 (2 s, 6H, 2 CO_2CH_3); 3.53 (s, 2H, C*H*$_2$CO$_2$Me); 2.78 (t, J=7.0, 2H, $CH_2CH_2CO_2Me$); 2.66 (t, J=7.0, 2H, C*H*$_2$$CH_2CO_2Me$). ^{13}C-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 - $NHCO_2Bz$ - 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%). ^{1}H-NMR δ 9.99 (s br, 1H, N*H*); 9.49 (s, 1H, C*H*O); 9.10 (s br, 1H, N*H*); 7.35-7.25 (m, 5H, aro. H); 5.10, 5.05 (AB syst., J=12.3, 2H, C*H*$_2$Ph); 4.84 (m, 1H, O*H*); 3.68 (s, 2H, C*H*$_2$ meso); 3.67, 3.65, 3.60, 3.58 (4 s, 12H, 4 CO_2CH_3); 3.63, 3.16, 3.11, 2.97 (2 AB syst., J=17.0, 14.7, 4H, 2 C*H*$_2$CO$_2$Me); 2.67, 2.60, 2.41 (t + m + t, J=7.4, 7.6, 8H, 2 C*H*$_2$C*H*$_2$CO$_2$Me). ^{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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