JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02067 • Publication Date (Web): 11 Sep 2019

Far away from flatland. Synthesis and molecular structure of di- and tri-hetera[3.3.n]propellanes – advanced analogues of morpholine/piperazine

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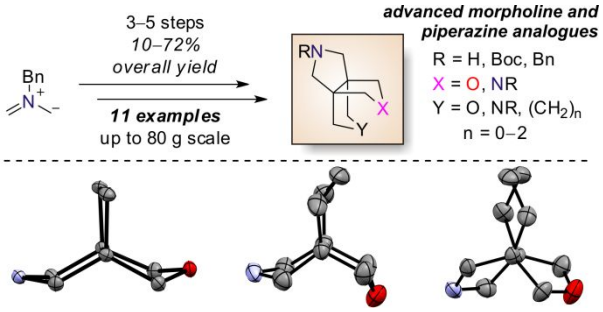
Abstract. An approach to di- and trihetera[3.3.n]propellanes (n = 2–4) – advanced morpholine and piperazine analogues – is developed. The key step of the reaction sequence included [3+2] cycloaddition reaction of unsaturated vicinal dicarboxylic acid derivatives and generated *in situ* azomethine ylide resulting in the formation of the pyrrolidine ring. One more heteroaliphatic ring (*i.e.* pyrrolidine or tetrahydrofuran) was annelated by nucleophilic cyclization of appropriate 1,4-dielectrophilic intermediates. 11 examples of title products were obtained in 3–5 steps on a multigram scale with 10–72% overall yield. In addition to that, molecular structures of homologous dihetera[3.3.n]propellanes – analogues of morpholine – were obtained from X-Ray diffraction studies and analyzed using exit vector plots (EVP). It was shown that the scaffolds obtained are somewhat larger as compared to the parent morpholine and bicyclic 3-oxa-7-azabicyclo[3.3.0]octane. Moreover, despite very similar chemical

structure, they provide very distinct spatial position of the heteroatoms, which is clearly seen from the conformation adopted by a formal eight membered ring including both N and O atoms (*i.e.* crown, boat-chair, twist chair-chair and boat-boat for the oxaza[3.3.2]-, -[3.3.3]-, -[4.3.3]propellanes and 3-oxa-7-azabicyclo[3.3.0]octane, respectively).



Introduction

Over the history of organic chemistry, molecules with unusual three-dimensional structures have always attracted attention of chemists as possible synthetic targets.[1–3] Among such structures, propellanes (tricyclo[m.n.p.$0^{x,y}$]alkanes) containing three rings fused by one C–C axis are one of the most recognizable.[4] The term "propellane" was coined by David Ginsburg in 1966; he had been the main contributor into the tricycloalkane chemistry with more than hundred publications and a monograph.[5,6] Since then, the smallest representative (tricyclo[1.1.1.$0^{1,3}$]pentane) became the objects of extensive study, while larger derivatives were scarcely reported.[7] This is especially the case with heterapropellanes, which are exotic in chemical and pharmaceutical practice to date, but extensively abundant in nature. In particular, propellanes were found in a large group of alkaloids, *i.e.* hasubanans **1**–**8** with aza[4.4.3]propellane framework, aza[4.3.3]propellanes represented by (-)-acutumines **9**–**11**, and fendleridines **12** and **13** bearing oxaza[4.4.3]propellane scaffold (Figure 1). However, the simplest representatives of oxa- / aza[3.3.n]propellanes (n = 2–4) were nor described in the literature, while being promising conformationally restricted analogues of widespread heteroaliphatic amines, *i.e.* morpholine and piperazine.[8,9] It should be outlined that such three-dimensional sp^3-enriched low-molecular weight building blocks are of high demand in drug discovery as a tool for improving physico-chemical properties, fine-tuning binding with biological targets, or reducing off-target activity.[10–13]

Known synthetic approaches to oxapropellanes relied on the construction of tetrahydrofuran ring *via* reduction of the corresponding bicyclic dicarboxylic acid derivatives, followed by intramolecular cyclization of the resulting diol (Scheme 1, Method **A**).[4,14,15] Meanwhile, amination of these starting derivatives with subsequent imide reduction was applied for the preparation of azapropellanes.[4,15–18]. The required starting materials were generally obtained by double alkylation,[19] the Weiss–Cook reaction (*i.e.* double condensation of 1,2-dicarbonyl compounds and acetone dicarboxylates)[20,21] or various rearrangements.[22,23] Alternative approaches included [2+2][24] or [4+2][25–28] cycloadditions (Method **B**),

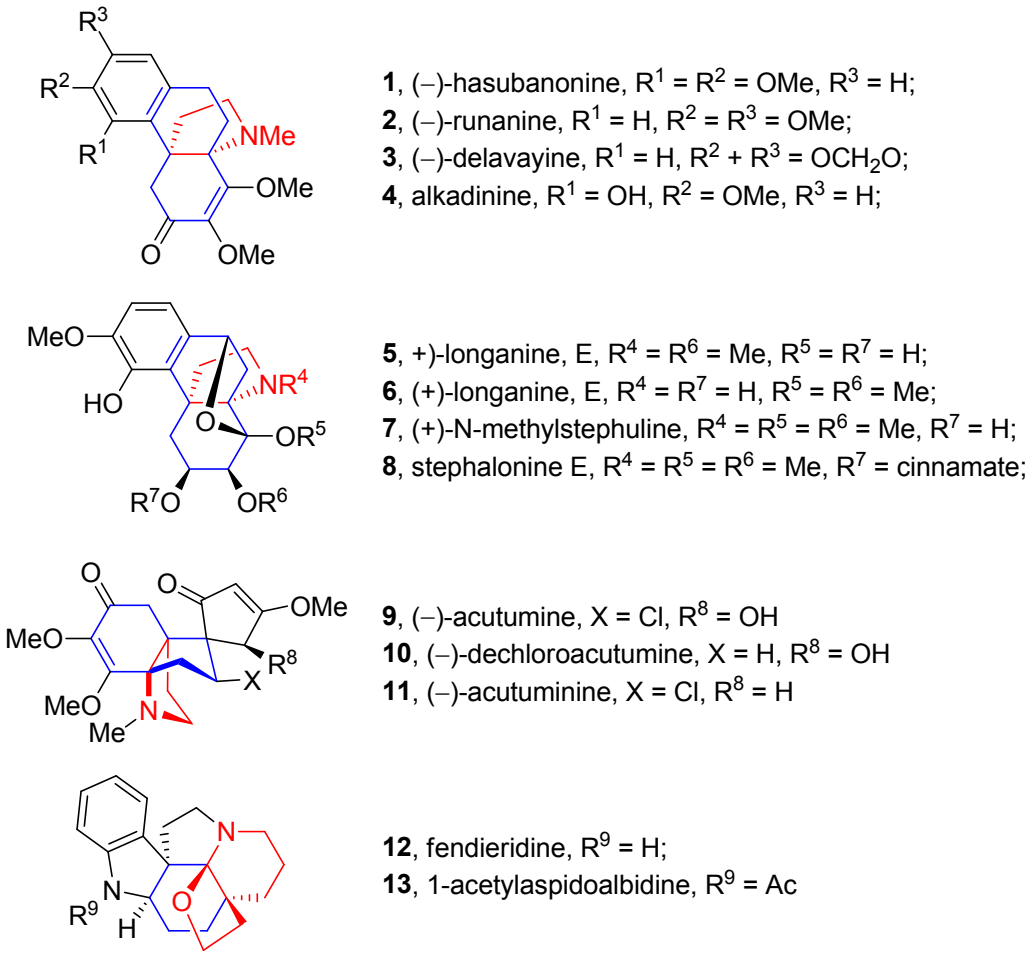
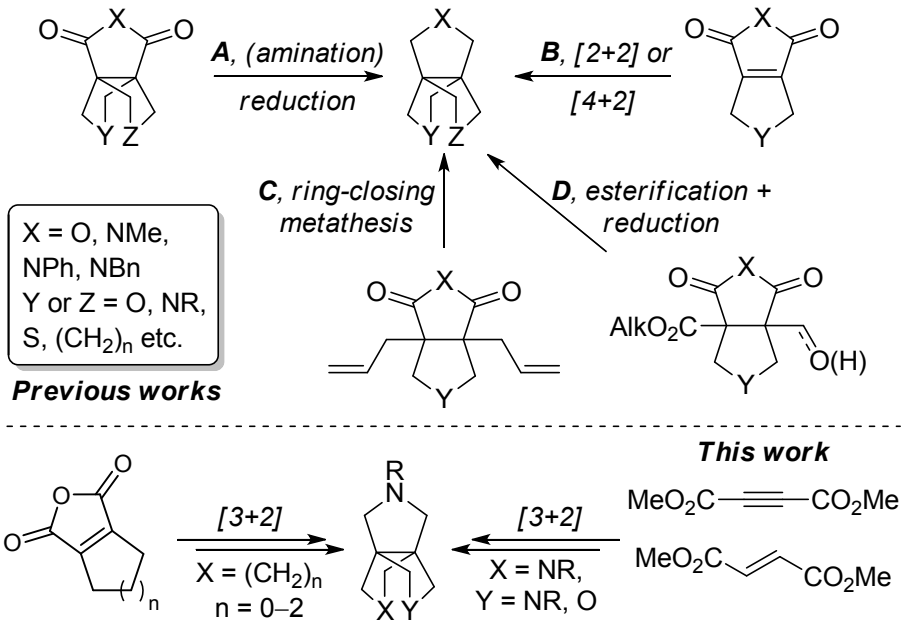


Figure 1. Several important alkaloids bearing aza- or oxazapropellane core



Scheme 1. Approaches to heterapropellane synthesis

ring-closing metathesis (Method **C**),[29–32] β-hydroxy-[33] or β-formylester[34] lactonization – reduction (Method **D**), and recyclizations of polycyclic derivatives.[35–40]

In this work, we have aimed at the preparation and structural characterization of di- and triheterapropellanes bearing pyrrolidine and tetrahydrofurane fragments *via* [3+2] cycloaddition of alkene dicarboxylates with azomethine ylide. In particular, five structural motifs were studied: oxaza[3.3.n]propellanes **14**–**16** and dioxaza[3.3.3]propellane **17** as morpholine analogues, oxadiaza[3.3.3]propellane **18** as dual morholine/piperazine mimetic, triaza[3.3.3]propellanes **19**–**21** and diaza[n.3.3]propellanes **22**–**24** as piperazine analogues (Figure 2). To the best of our knowledge, the only example of using the [3+2] cycloaddition reaction for the construction of heterapropellanes included synthesis of the compound **14** which was described in our preliminary report.[41] The methodology itself was based on the work by Achiwa and co-workers, where it was used for the construction of bicyclic systems.[42] Some other representatives of the series were also reported in the literature by Ginsburg and co-workers.[15,16]

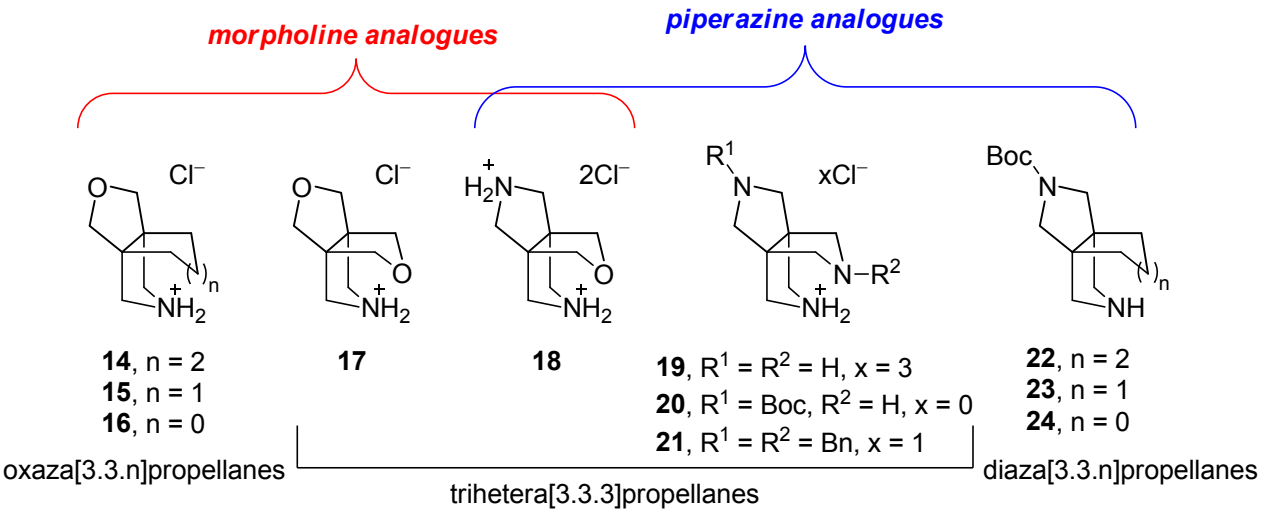
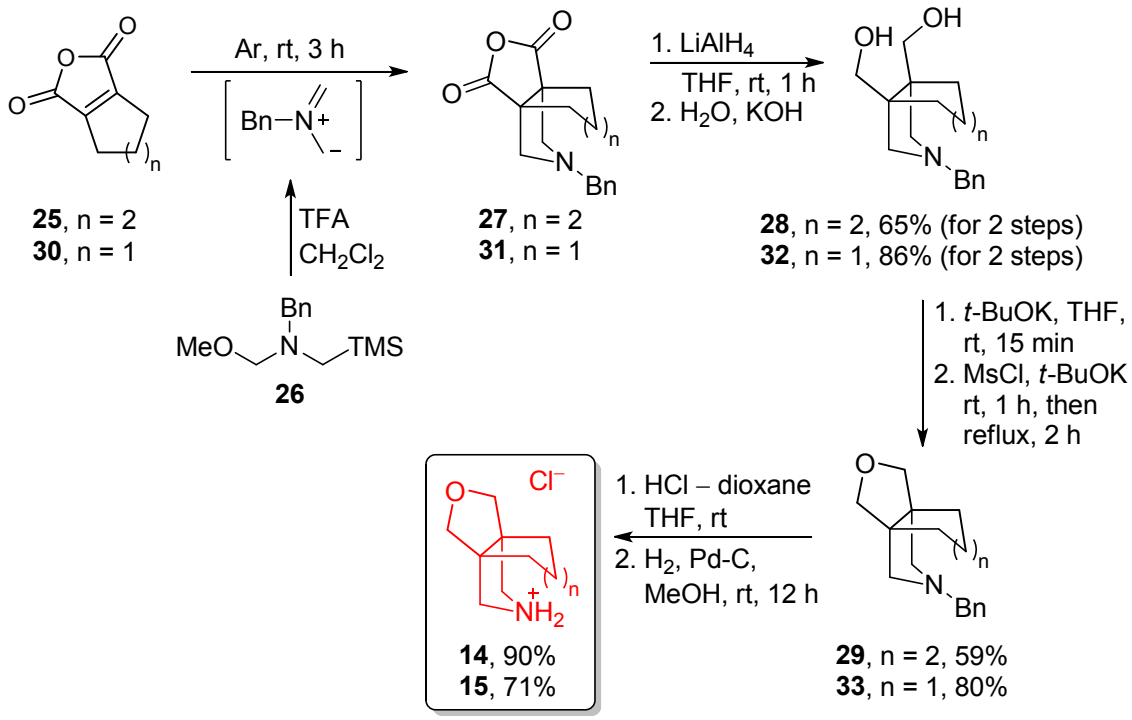


Figure 2. Propellanes **14**–**24** – target molecules of this study

Results and discussion

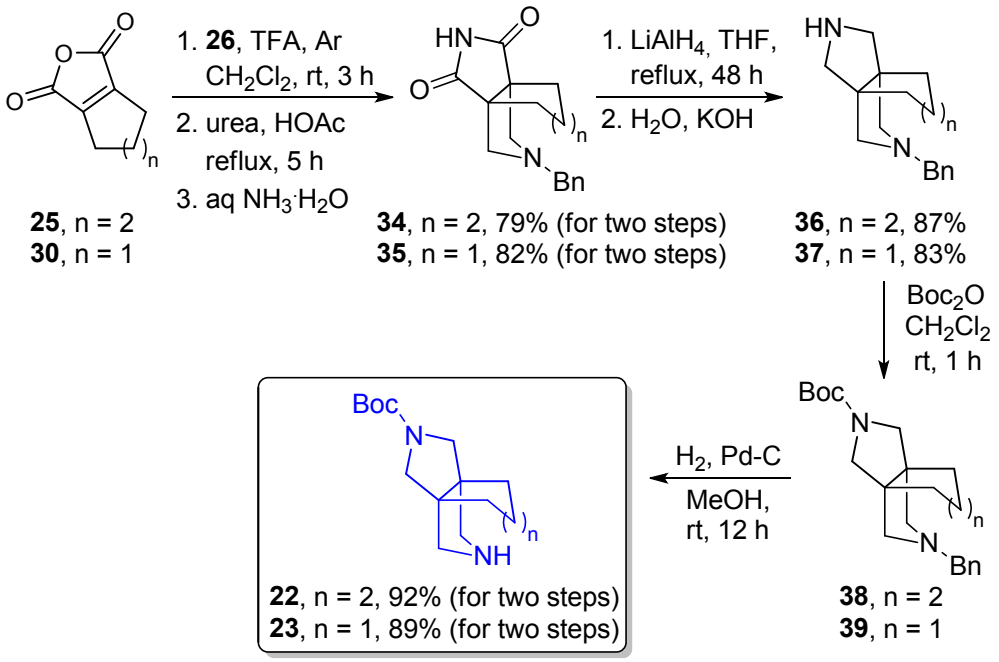
Synthesis. In our previous work cited above, preparation of the compound **14** relied on [3+2] cycloaddition of *cis*-1,2-cyclohexnedicarboxylic anhydride (**25**) and azomethine ylide generated *in situ* from the precursor **26**, which provided the tricyclic derivative **27** (Scheme 2).[41] Further steps of the

reaction sequence included reduction with $LiAlH_4$, intramolecular cyclization of diol **28** to the corresponding tetrahydrofurane **29**, treatment of amines **30** with HCl in 1,4-dioxane – THF followed by catalytic debenzylation leading to the target hydrochloride **14** in 34% overall yield. This method was extended successfully to the five-membered analogue **30** for the preparation of 3,7-oxaza[3.3.3]propellane **15**, which was prepared in 48% yield (over four steps) on up to 80 g scale.



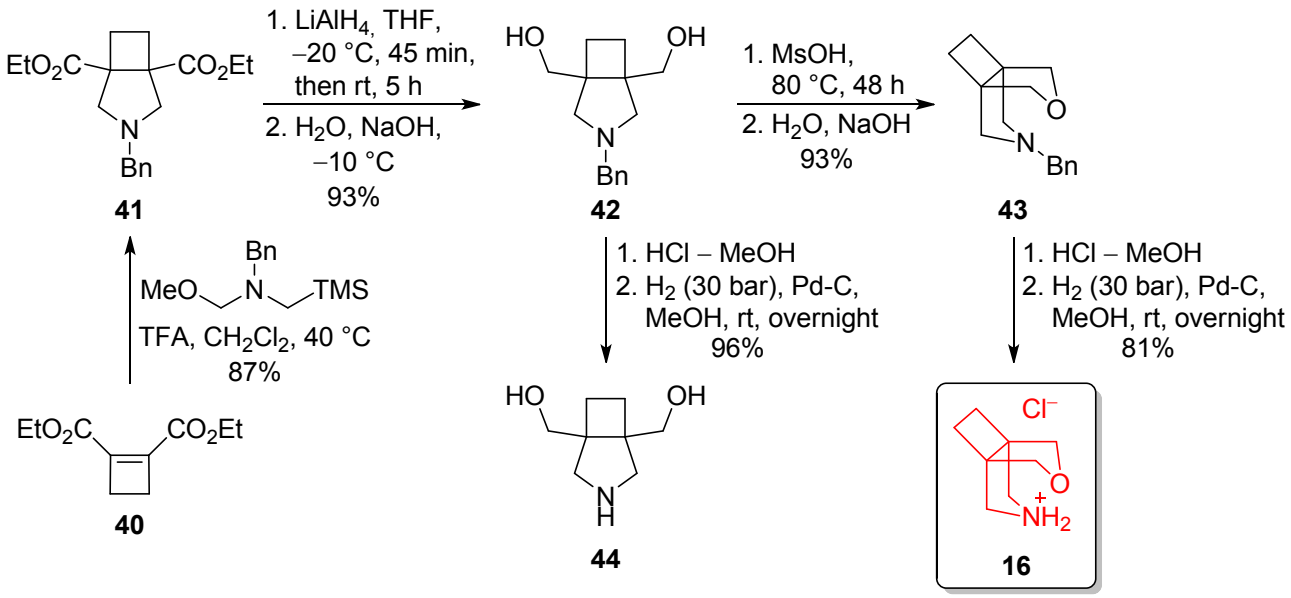
Scheme 2. Synthesis of oxaza[n.3.3]propellanes **14** and·**15**

In turn, reaction of anhydrides **27** and **31** (obtained from **25** and **30**, respectively) with urea in refluxing HOAc, followed by quenching with aq ammonia gave the corresponding imides **34** and **35** (79% and 82% yield for two steps, respectively) on up to 130 g scale (Scheme 3). Reduction of **34** and **35** with $LiAlH_4$ in refluxing THF resulted in the formation of monobenzyl-protected bispyrrolidines **36** and **37** in 87% and 83% yield, respectively. The orthogonally protected diamines **38** and **39** were obtained by the reaction of **36** and **37** with Boc_2O in CH_2Cl_2. The derivartives **38** and **39** were obtained in nearly quantitative yields and used in further debenzylation step (H_2, Pd-C, MeOH, rt) without additional purification, which gave the target mono-Boc-protected diaza[n.3.3]propellanes **22** and **23** in 92% and 89% yield, respectively.



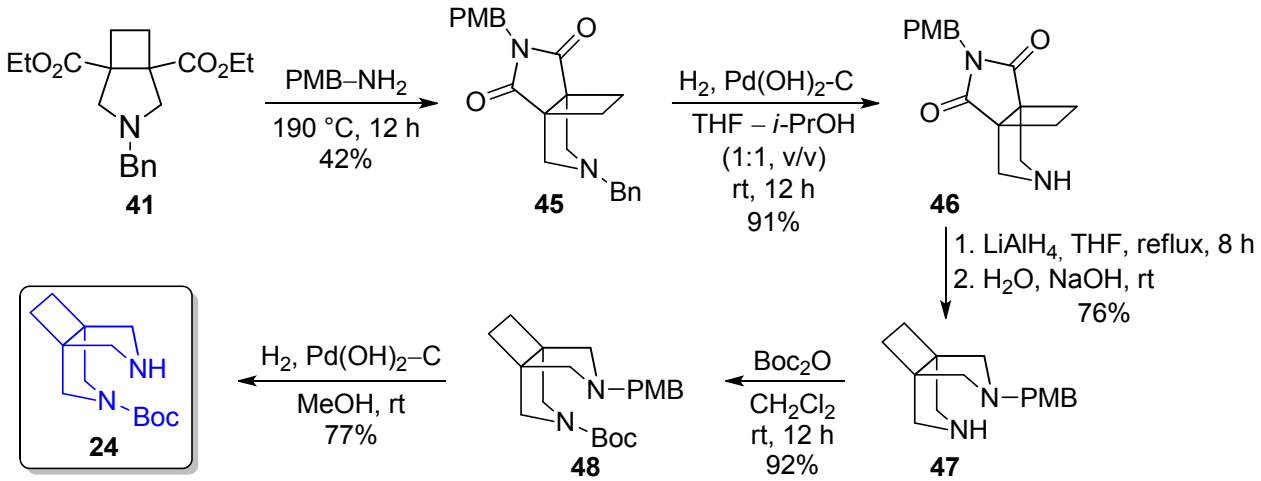
Scheme 3. Synthesis of diaza[n.3.3]propellanes **22** and **23**

A slightly different reaction was used for the preparation of a cyclobutane-derived analogue of **14** and **15**, *i.e.* oxaza[3.3.2]propellane (**16**). In particular, cyclobutene dicarboxylate **40** was involved in the [3+2] cycloaddition with azomethine ylide, which led to the corresponding vicinal diester **41** in 87% yield on up to 150 g scale (Scheme 4). Reduction of **41** was performed with $LiAlH_4$ in THF, which led to the corresponding diol **42** in 93% yield. In contract to transformations of **28** and **32** into the corresponding propellanes **29** and **33**, cyclization of **42** into **43** was challenging. Thus, reaction of **42** with TsCl led to *ca.* 1:1 mixture of the target tetrahydrofuran **43** and the corresponding ditosylate. Hence the cyclization was performed of **42** by treatment with 3-fold excess of methanesulfonic acid at 80 °C, which gave the corresponding *N*-benzyl oxaza[3.3.2]propellane **43** in 93% yield. The subsequent benzyl group cleavage was performed in an autoclave under 30 bar of H_2 in the presence of Pd-C, which gave the corresponding pyrrolidine **16** (81% yield, 61% overall yield for four steps). In turn, catalytic debenzylation of **42** gave the corresponding aminodiol **44** in 96% yield.



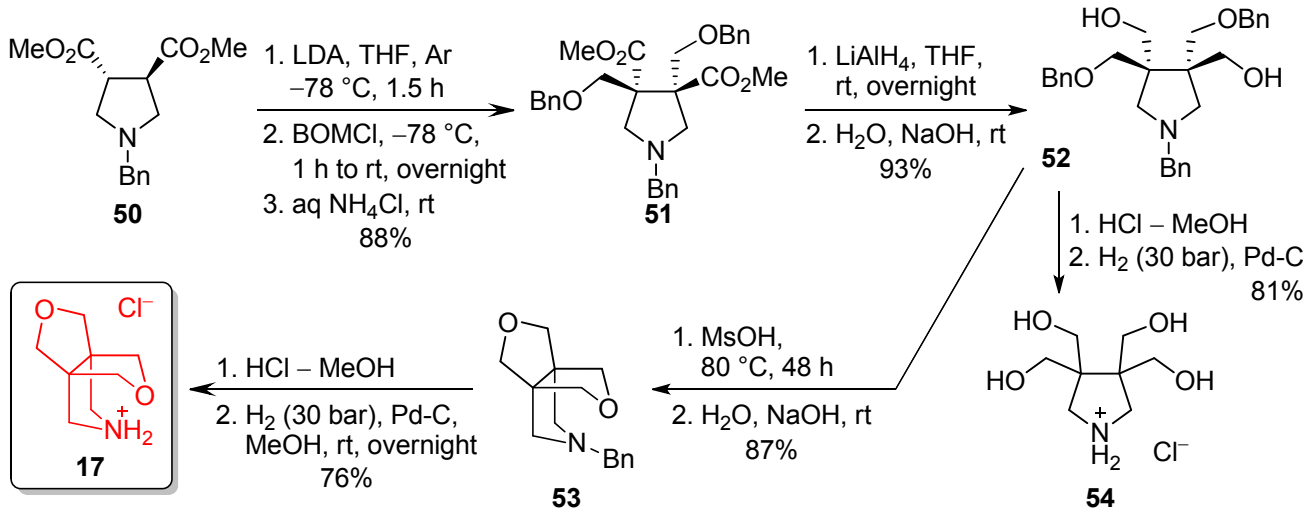
Scheme 4. Synthesis of oxaza[3.3.2]propellane **16**

To obtain the tricyclic piperazine analogue **24**, the diester **41** reacted with *p*-methoxybenzyl amine at 190 °C to give imide **45** (42% yield) (Scheme 5). Debenzylation of **45** was performed with $Pd(OH)_2$-C in THF – *i*-PrOH (1:1, v/v), which led to derivative **46** in 91% yield. Subsequnet reduction of imide **46** to the corresponding monoprotected bispyrrolidine **47** was performed with $LiAlH_4$ in refluxing THF. Further formation of carbamate **48** *via* the reaction of **47** with Boc_2O (92% yield), followed by catalytic cleavage of the PMB group (H_2, $Pd(OH)_2$-C in MeOH, rt) provided the target *N*-Boc derivative **24** in 77% yield.



Scheme 5. Preparation of monoprotected diaza[3.3.2]propellane **24**

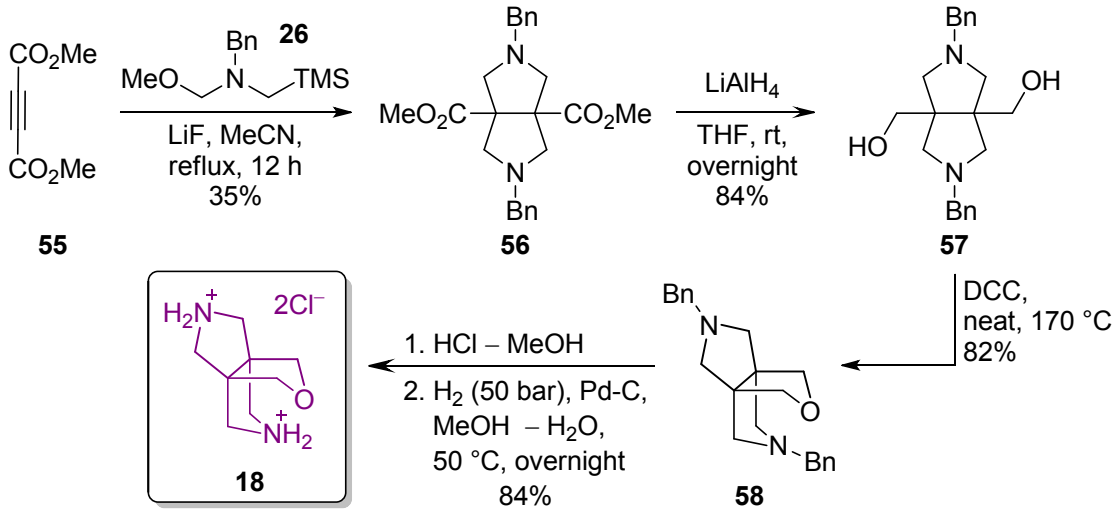
Further synthetic efforts were aimed at the preparation of triheterapropellanes **17**–**21**. The reaction sequence for the synthesis of dioxaza[3.3.3]propellane **17** commenced with metallation of the pyrrolidine diester **50** (prepared by the known [3+2] cycloaddition of dimethyl fumarate and azomethine ylide[42]) with LDA in THF at −78 °C, followed by reaction with 3-fold excess of BOM-Cl, which gave bis-(benzyloxy)methyl derivative **51** in 88% yield (Scheme 6). Subsequent reduction of **51** with $LiAlH_4$ in THF provided bis-hydroxymethyl derivative **52** (93% yield). As in the case of **42**, the TsCl-mediated cyclization of **52** to the corresponding tetrahydrofurane **53** was unfruitful. Nevertheless, reaction of **52** with methanesulfonic acid gave the target compound **53** in 87% yield. Catalytic debenzylation of **53** (as the hydrochloride) led to triheterapropellane **17** (76% yield, 54% overall yield for four steps). In turn, catalytic debenzylation of **52** gave polyfucntional derivative **54** (81% yield), which can be considered as an aminosugar mimetic.



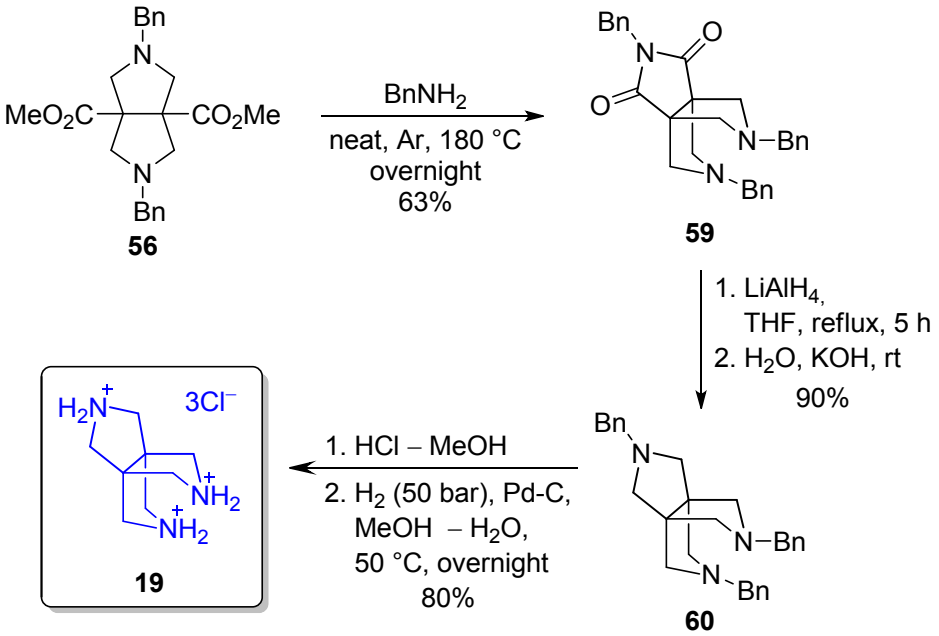
Scheme 6. Synthesis of dioxaza[3.3.3]propellane **17**

Preparation of oxadiaza[3.3.3]propellane **18** relied on the double [3+2] cycloaddition of dimethyl acetylene dicarboxylate (**55**) with the azomethine ylide generated from 2.8-fold excess of precursor **26** (Scheme 7). In contrast to the preparation of other bi- and tricyclic pyrrolidine derivatives performed in this work, in the case of **55**, the reaction was performed in the presence of LiF in refluxing MeCN. Althought the yield of the resulting bispyrrolidine diester **56** was moderate (35%), the product could be obtained on up to 400 g scale in a single run. Reduction of **56** with $LiAlH_4$ in THF gave the

corresponding diol **57** (84% yield). Cyclization of diol **57** into the target dibenzyl oxadiaza[3.3.3]propellane **58** was performed by heating of the neat starting material with DCC at 170 °C (82% yield, up to 100 g scale). Cleavage of the benzyl group from the hydrochloride **58**·HCl led to the title building block **18** (84% yield, up to 55 g scale).



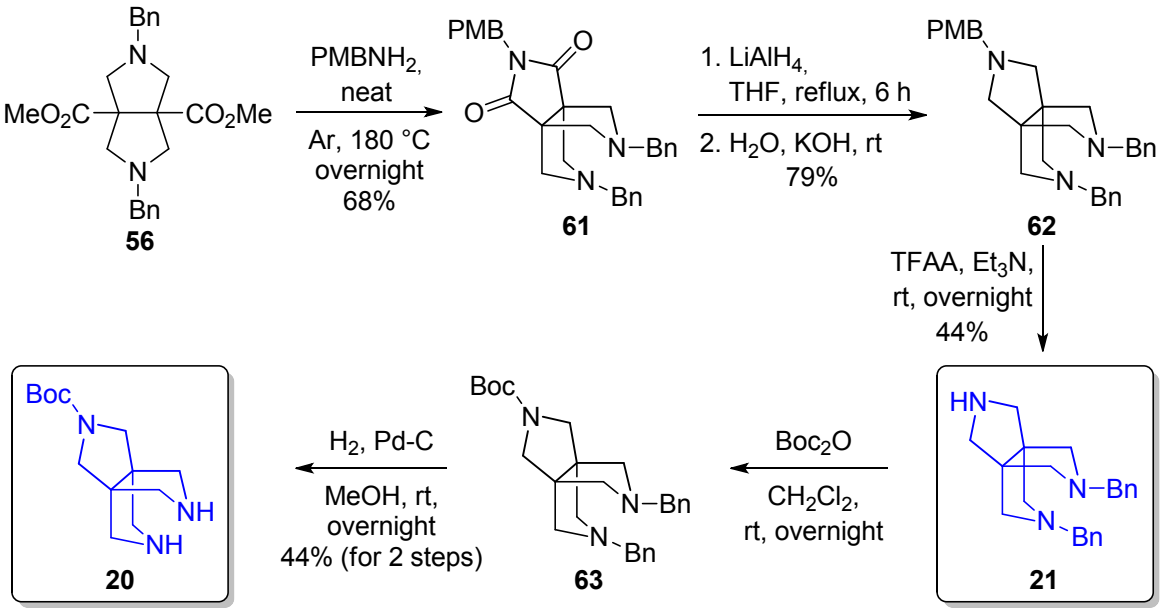
Scheme 7. Preparation of oxadiaza[3.3.3]propellane **18**



Scheme 8. Synthesis of triaza[3.3.3]propellane **19**·3HCl.

Synthesis of triaza[3.3.3]propellane **19** started with amination of the aforementioned diester **56** with benzylamine at 180 °C, which gave the corresponding tricyclic imide **59** in 63% yield on up to 100 g scale (Scheme 8). Reduction of the imide moiety with $LiAlH_4$ in refluxing THF resulted in the formation of protected trispyrrolidine **60** (90% yield). Exhaustive debenzylation of **60** gave the target C_3-symmetric trihydrochloride **18** in 80% yield on up to 40 g scale.

Preparation of mono- and bis-protected derivatives of the triamine **19** (compound **20** and **21**, respectively) appeared to be the most challenging part of this study. Our preliminary experiments commenced with amination of the diester **56** with urea, which was unfruitful in all applied conditions (*e.g.* heating on up to 240 °C). Thus, condensation of **56** with *p*-methoxybenzylamine at 180 °C under argon atmosphere was used for the preparation of tris-protected tricyclic derivative **61** in 68% yield (Scheme 9). The subsequent PMB group cleavage was unsuccessful (either by refluxing with TFA or TfOH in methoxybenzene or upon treatment with CAN in MeCN – H_2O). Thus, removal of the benzyl groups was performed (H_2, Pd-C in MeOH); however, further cleavage of the PMB fragment in the corresponding debenzylated derivative was also unfruitful in all attempts.



Scheme 9. Synthesis of mono- and bis-protected triaza[3.3.3]propellanes **20** and **21**

Finally, reduction of imide **61** with $LiAlH_4$ in THF gave fully protected tris-pyrrolidine **62** (79% yield). Selective removal of the *p*-methoxybenzyl group in **62** required tedious experimentations. In particular, using CAN in MeCN – H_2O, DDQ in CH_2Cl_2 – H_2O (10:1, v/v), as well as 1-chloroethyl chloroformate in THF at −78 °C and then – MeOH at 65 °C was unsuccessful. Fortunately, treatment of **62** with trifluoroacetic anhydride (TFAA) in Et_3N led to the target derivative **21** in 44% yield. Further *N*-Boc-protection of **21** followed by catalytic debenzylation gave the mono-*N*-Boc-triaza[3.3.3]propellane (**20**) in 44% yield in two steps.

Molecular structure. X-Ray diffraction studies were performed with single crystals of the morpholine analogues **14** – **16** (obtained by slow evaporation of their solutions in CH_2Cl_2 – hexanes or CH_2Cl_2 – Et_2O), **18**·H_2O (from *i*-PrOH – H_2O), and 3-oxa-7-azabicyclo[3.3.0]octane hydrochloride **64** (from MeOH). Crystals of **15**, **16**, **18**·H_2O, and **64** contained single type of the conformations in the unit cell, whereas for **14**, two very similar conformers (A and B) were observed (Table 1).

To discuss their geometry, an exit vector plot (EVP)-based method was used,[43,44] which had been applied by our group for analysis of various cyclic systems previously.[45–51] The basic idea behind this methodology relies in simulating the functional groups mounted onto the ring system by so-called exit vectors. In the case of morpholine or piperazine analogues, the corresponding heteroatoms X^1 and X^2 are used as the starting points of these vectors, whereas their direction is defined by bisectors of the C–X^1–C and C–X^2–C angles (Figure 3a). Relative orientation of the exit vectors is described by four geometric parameters *r*, φ_1, φ_2, and θ defined in Figure 3b. Exit vector plots (EVP) are obtained by depicting valu-

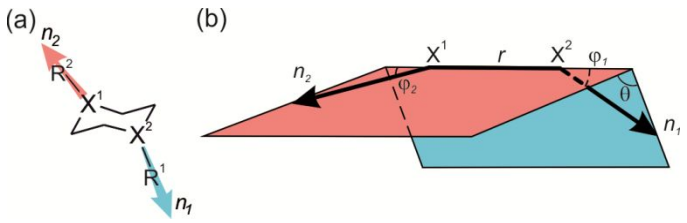
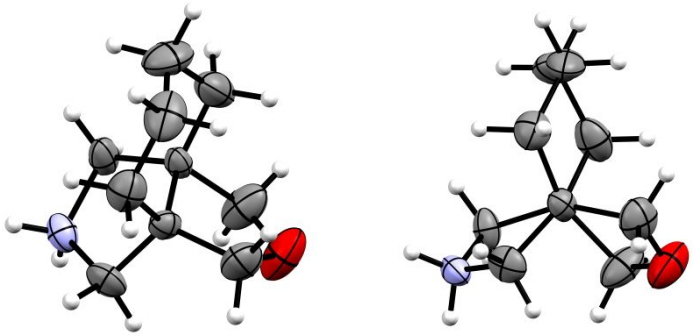
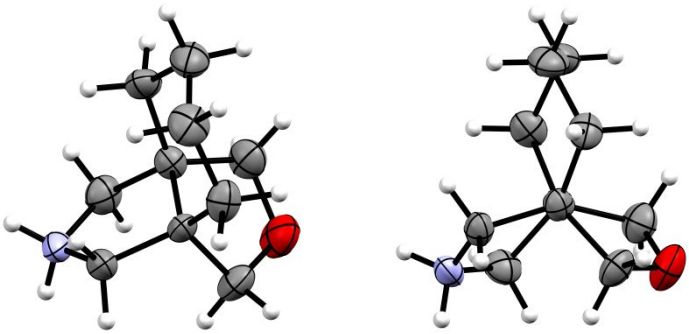


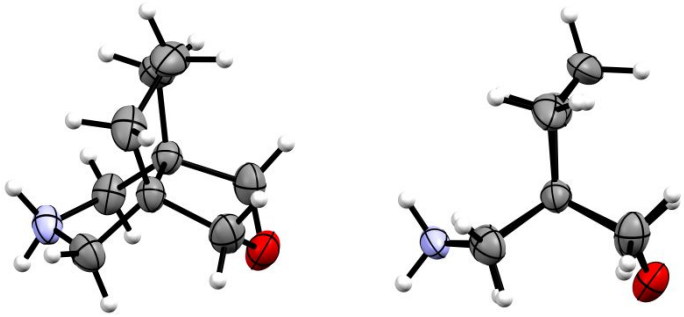
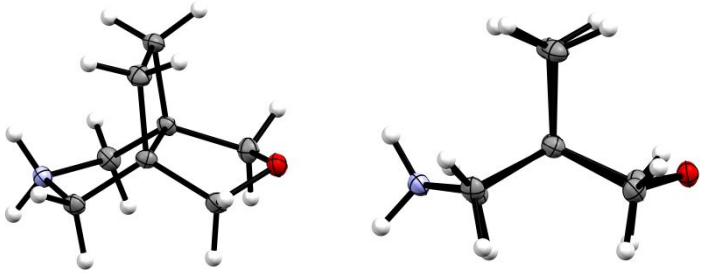
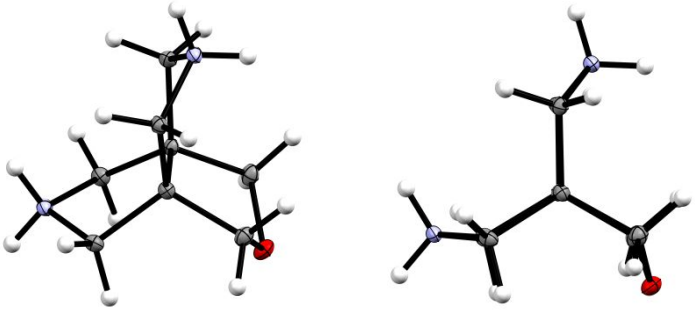
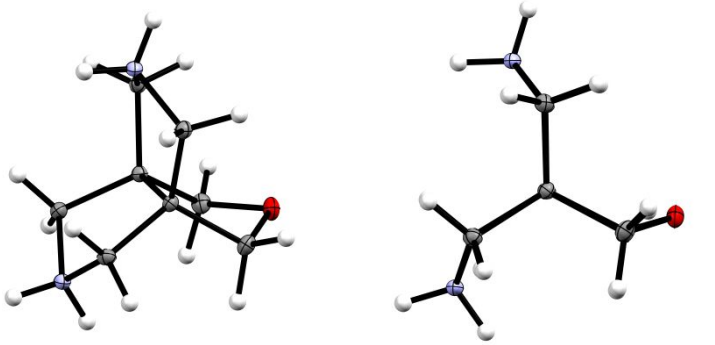
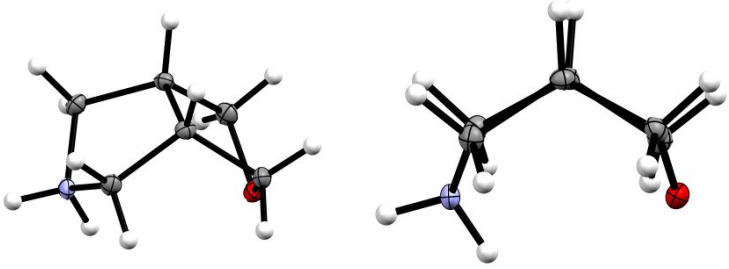
Figure 3. Definition of EVP parameters: (a) exit vectors; (b) *r*, φ_1, φ_2, and θ (reproduced with permission from ref. [48] Copyright (2019) American Chemical Society)

es of these parameters in $r - \theta$, $\theta - \varphi_1/\varphi_2$, and/or φ_1/φ_2 plots.

EVP analysis of the compounds **14–16** shows that although these tricyclic scaffolds are very close homologues, they provide distinct spatial arrangement of the corresponding heteroatoms (Table 1, Figure 4). In the $r - \theta$ plot, this difference is not clearly visible: all the compounds have r = 3.801–4.321 Å and θ = 7.1–9.5°. Therefore, they are expectedly larger than morpholine ($r \sim 2.85$ Å) and are found in the "extended" β region of the $r - \theta$ plot. This is not common for six-membered saturated heterocycles with two heteroatoms which typically occupy the γ_1 region of the plots with large θ values (that corresponds to the chair conformation).[44,48] Small θ values are possible for the energetically unfavorable boat conformation, which is not typically observed.

Table 1. Molecular geometry of the compounds **14–16**, **18**, and **64**

#	Compound	r, Å	φ_1,[a] deg	φ_2,[a] deg	$\lvert\theta\rvert$, deg[b]	ORTEP diagrams (two projections)[c]
1	**14** (A)[d]	3.836	31.9	29	8.7	
2	**14** (B)[d]	3.854	30.2	28.1	7.1	

3	**15**	3.801	57.2	8.4	9.5	
4	**16**	4.321	11.6	5.6	9.0	
5	**18** (A)[e]	3.802	60.3	9.0	2.0	
6	**18** (B)[e]	3.910	1.1	53.0	10.6	
7	**64**	3.136	72.4	69.2	4.8	

[a] According to Figure 3, X^1 = O, X^2 = N. [b] Since the signs of θ angle are opposite for different enantiomeric conformations, only absolute values of θ are considered. [c] Thermal ellipsoids are shown at 30% probability level. [d] Two slightly different conformers in the crystal unit. [e] Two ways to define the exit vectors are possible due to the presence of two nitrogen atoms

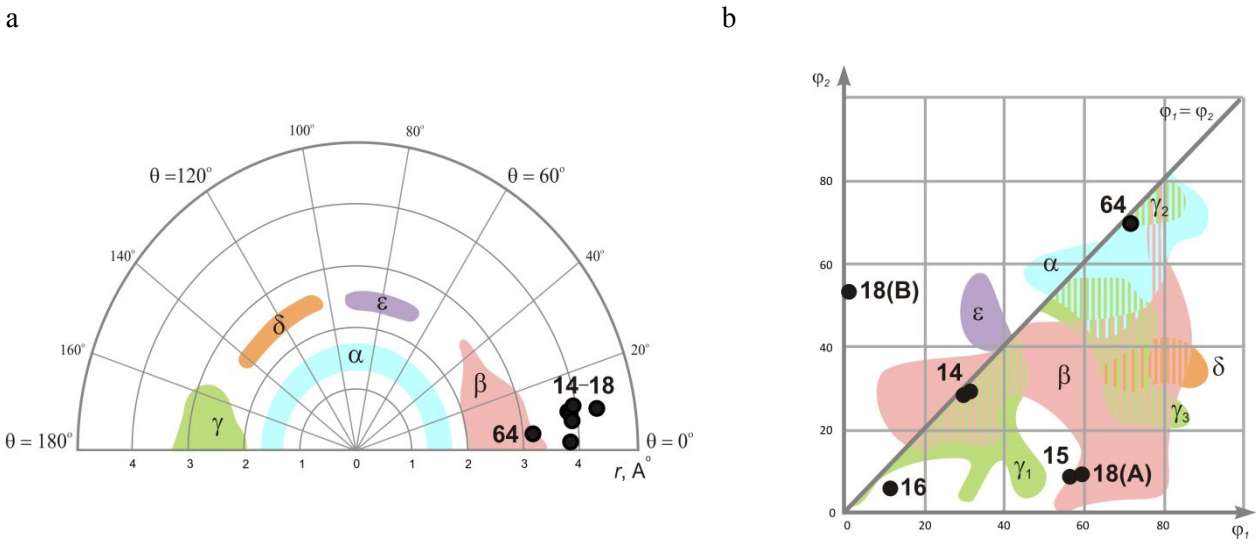


Figure 4. Geometric parameters of the compounds **14**–**16**, **18**, and **64** shown in (a) $r - \theta$ plot (polar coordinates); (b) $\varphi_1 - \varphi_2$ plot

On the contrary, compounds **14**–**16** are easily distinquished in the $\varphi_1 - \varphi_2$ plot. Whereas for **14** and **16**, the molecules adopt pseudosymmetric conformations with small (5.6–11.6°) and medium (*ca.* 30°) values of φ_1/φ_2, respectively, in the case of **15**, significant difference is observed betweem the φ_1 (57.2°) and φ_2 (8.4°) values. This behaviour can be easily rationalized by a closer conformational analysis. In particular, the cyclobutane ring of **16** adopts a non-common flattened conformation, whereas the pyrrolidine and tetrahydrofuran are found in envelope conformations with *exo* orientation of both heteroatoms with respect to the tricyclic system. For **15**, all the three five-membered ring are found in envelope conformations which are combined into a C_3-pseudosymmetric propeller-like structure, with opposite orientations of the heteroatoms redarding the scaffold. Finally, the chair conformation of the cyclohexane ring in the molecule of **14** together with increased steric repulsion force both the pyrrolidine and tetrahydrofuran rings to adopt the half-chair conformations. The difference is also clearly seen if the formal eight-membered rings which contain both the heteroatoms are considered: it is found in crown, boat-chair, and twisted conformations for **14**, **15**, and **16**, respectively.

Conformation of the compound **18** bearing an additional nitrogen atom is very similar to that of **15** (although formally, two ways to discuss it using EVP should be taken into account since two nitrogen

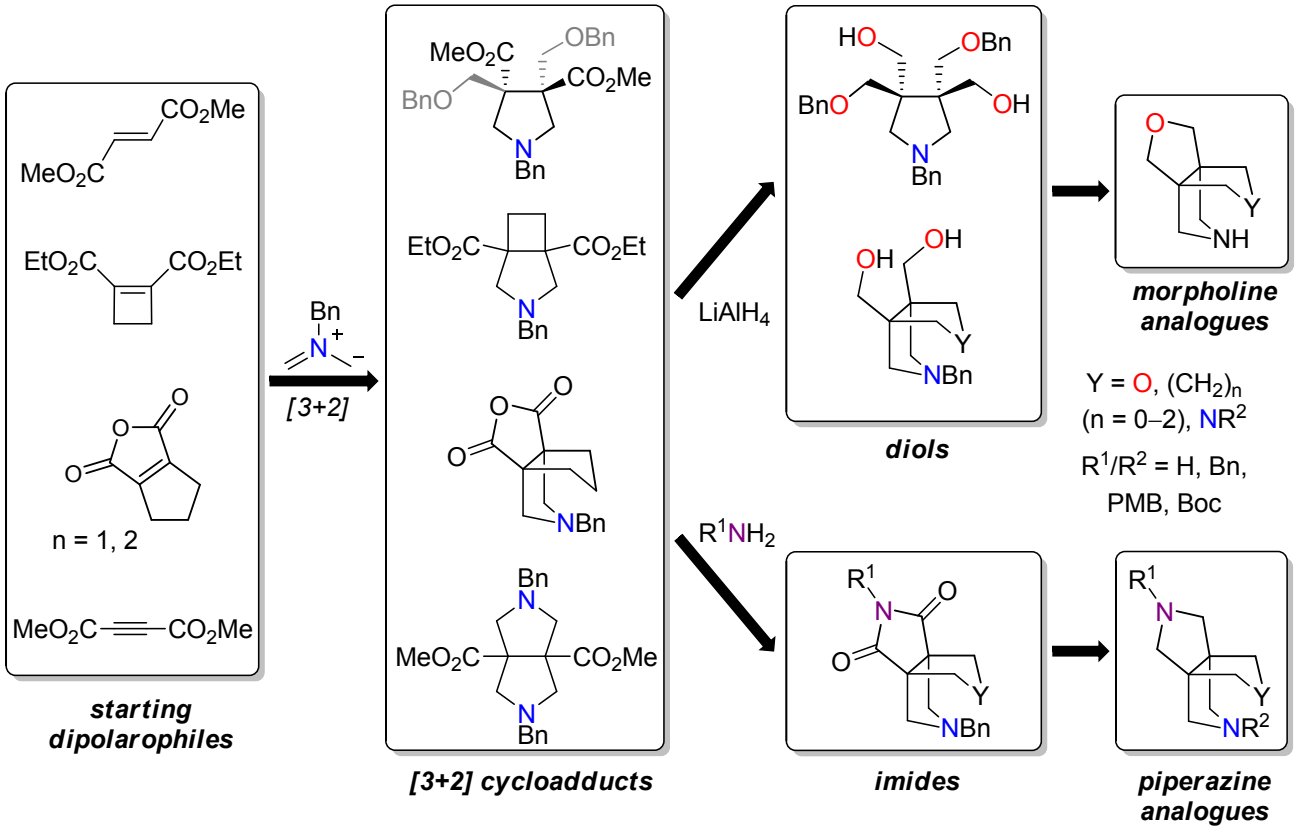
atoms are present – thus two different data points in the plots). One might expect that due to signidicant rigidity, conformational properties of other propellanes studied in this work should also resemple those discussed for the parent structures **14**–**16**.

Notably, the conformations of **14** – **16** and **18** are rather different from that of **64**. In the latter case, smaller *r* value (3.136 Å) is observed; it is nonetheless accompanied by $\theta = 4.8°$, so that all the four compounds are located in the same region of the $r - \theta$ plot. Even so, much larger φ_1 and φ_2 (of ca. 70°) for **64** are indicative of considerably distinctive conformational behavior. In this case, the formal eight-membered ring (formed by the two five-membered "envelopes" of pyrrolidine and tetrahydrofuran rings) is found in non-typical boat-boat conformation. It should be noted that the conformation of **64** might be affected by packing of the ions in the crystal cell, which is stabilized by hydrogen bonds involving both nitrogen and oxygen atoms. No such effect is observed for **14**–**16**; in that case, only the N–H…Cl hydrogen bonds occur in the crystals.

Conclusions

In this work, several methods for preparation of hetera[3.3.n]propellanes (n = 2–4) which relied on [3+2] cycloaddition of unsaturated vicinal diesters or bicyclic anhydrides and *in situ* generated azomethine ylide, were developed. The aforementioned key step resulted in construction of the pyrrolidine ring of the target tricyclic system. In the case of oxaza[3.3.n]propellanes **14**–**16**, annelation of tetrahydrofuran ring was performed *via* reduction with $LiAlH_4$ of the cycloadducts thus obtained and cyclization of the resulting diols mediated by *t*-BuOK – MsCl. Diaza[3.3.n]propellanes **22**–**24** were obtained from the same cycloadducts, which were subjected to amination and subsequent imide reduction at the key steps (Scheme 10).

For the preparation of dioxaza[3.3.3]propellane **17**, the initial [3+2] cycloadduct obtained from dimethyl fumarate was bis-alkylated with BOMCl to introduce the two lacking carbon atoms of the target tricyclic system. After reduction of the ester groups, construction of both tetrahydrofuran rings was performed in one step by high-temperature MsOH-promoted cyclization.



Scheme 10. Approaches to hetera[3.3.n]propellane synthesis developed in this work

A common intermediate for the preparation of trihetera[3.3.3]propellanes **17-21** was obtained by [3+2] cycloaddition of dimethyl acetylene dicarboxylate with two equivalents of the azomethine ylide. To construct the tetrahydrofuran ring of the oxadiaza-derivative **18**, cyclization with DCC was applied after the reduction step. In turn, non-protected triazapropellane **19** was obtained *via* amination of the same cycloadduct with $BnNH_2$ and subsequent reduction of the intermediate imide. Finally, synthesis of mono- and bis-protected triaza[3.3.3]propellanes **20** and **21**, respectively, appeared to be the most challenging. Although the reaction sequence resembled that for **19**, it required carefully planned manipulations with protective groups.

The molecular structures of four representative heterapropellanes **14-16** and **18**, as well as 3-oxa-7-azabicyclo[3.3.0]octane derivative **64** were obtained from X-Ray diffraction studies and analyzed using exit vector plots (EVP). The *r* and θ parameters were similar for all the tricyclic compounds **14-16** and

18; they showed that these scaffolds can be considered as enlarged analogues of uncommon boat conformers of morpholine/piperazine. Notably, despite very close chemical structure of the aforementioned homologous heterapropellanes, they demonstrated very distinct conformational behavior in terms of φ_1/φ_2 angular parameters. It is particularly obvious from the conformation adopted by a formal eight membered ring including both N and O atoms (*i.e.* crown, boat-chair, twist chair-chair and boat-boat for the compounds **16**, **15**/**18**, **14**, and **64**, respectively).

Taking into account unusual conformational properties of di- and trihetera[3.3.n]propellanes obtained, as well their easy accessibility on a multigram scale (up to 80 g, 3–5 steps from common precursors, 10–72% overall yield), the title morpholine/piperazine analogues can be considered as extremely promising building blocks for drug discovery, as well as other areas such as supramolecular chemistry, which are now readily available to chemical community.

Experimental part

The solvents were purified according to the standard procedures.[52] The starting materials **25**, **30**, **40**, and **55** were purchased from commercial sources. The compound **50** was prepared according to the literature method.[42,53] Melting points were measured on an automated melting point system. Analytical TLC was performed using silica gel plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a NMR spectrometer at 500 MHz for Protons and 126 MHz for Carbon-13 or at 400 MHz for protons and 101 MHz for Carbon-13. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an LCMS instrument (chemical ionization (CI)) and GCMS instrument (electron impact ionization (EI)). Preparative flash chromatography was performed on chromatograph using 40 g columns. CCDC 1943266 (**18**), CCDC 1943267 (**16**), CCDC 1943268 (**15**), CCDC 1943269 (**14**) and CCDC 1943270 (**64**) contain the

supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***cis*-(2-Benzyloctahydrocyclopenta[*c*]pyrrole-3a,6a-diyl)dimethanol (32).** The compound **26** (244 g, 1.03 mol) was added to a solution of alkene **30** (141 g, 1.02 mol) in CH_2Cl_2 (700 mL). Then, a solution of TFA (7.79 mL, 11.6 g, 0.102 mol) in CH_2Cl_2 (20 mL) was added dropwise at 25 °C under an argon atmosphere. The mixture was stirred for 3 h, washed with H_2O (400 mL) and brine (400 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The resulting yellowish oil **31 (**246 g, *ca.* 89% yield) was used in the next step without purification. A suspension of $LiAlH_4$ (38.7 g, 1.02 mol) in THF (1200 mL) was added dropwise to the stirred solution of **31** (*ca.* 136 g, 0.503 mol) in THF (300 mL) at 25 °C. The resulting mixture was stirred at rt for 1 h. The reaction mixture was quenched with H_2O (100 mL) carefully added in portions, 10% aq KOH (200 mL) and additionally with H_2O (100 mL). The precipitate was filtered, washed with THF, and the combined filtrates were evaporated in *vacuo*. The compound was purified by HPLC (0.5–6.5 min; MeOH; flow rate: 30 mL / min). Yield 113 g (86%); colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 – 7.28 (m, 4H), 7.25 – 7.18 (m, 1H), 4.73 (s, 2H), 3.45 (s, 2H), 3.43 (d, J = 10.6 Hz, 2H), 3.39 (d, J = 10.6 Hz, 2H), 2.37 (dd, J = 14.6, 8.8 Hz, 4H), 1.73 – 1.63 (m, 3H), 1.54 – 1.47 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 140.0, 128.6, 128.6, 127.1, 65.8, 64.9, 60.0, 55.7, 38.1, 24.3. LC/MS (CI): m/z = 262 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{23}NO_2$: C 73.53; H 8.87; N 5.36. Found: C 73.67; H 8.87; N 5.26.

***cis*-2-Benzylhexahydro-3a,6a-(methanooxymethano)cyclopenta[*c*]pyrrole (33).** The diol **32** (107 g, 0.410 mol) was dissolved in THF (1000 mL), and *t*-BuOK (92.0 g, 0.820 mol) was added in portions. The mixture was stirred for 15 min; MsCl (47.0 g, 0.410 mol) was added dropwise, and then additional *t*-BuOK (46.0 g, 0.410 mol) was added at rt. The mixture was stirred at rt for 1 h, then refluxed for 2 h and cooled to rt. The solvent was evaporated in *vacuo*, the residue was diluted with H_2O (500 mL) and extracted with *t*-BuOMe (3×300 mL). The combined organic extracts were washed with H_2O and evaporated in *vacuo*. The product was purified by distillation in *vacuo*. Yield 79.8 g (80%); colorless liquid; bp 115–117 °C / 0.2 Torr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 3.66 (d, J = 8.7 Hz, 2H), 3.58 (d, J = 8.7 Hz, 2H), 3.58 (s, 2H), 2.54 (d, J = 9.2 Hz, 2H), 2.38 (d, J

= 9.2 Hz, 2H), 1.71 – 1.65 (m, 4H), 1.60 – 1.54 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 139.5, 128.4, 128.2, 126.8, 79.0, 64.4, 63.6, 59.1, 37.0, 26.5. LC/MS (CI): *m*/z = 244 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{21}NO$: C 78.97; H 8.70; N 5.76. Found: C 78.77; H 8.91; N 5.77.

***cis*-Hexahydro-3a,6a-(methanooxymethano)cyclopenta[*c*]pyrrol-2-ium chloride (15).** Compound **33** (61.2 g, 0.252 mol) was dissolved in THF (200 mL), and 10% HCl in dioxane (280 mL) was added. The mixture was evaporated in *vacuo*, and **33**·HCl thus obtained was dissolved in MeOH (500 mL). Then, 10% Pd-C (20.0 g) was added to this solution, and the resulting mixture was stirred under H_2 atmosphere at rt for 12 h. The catalyst was filtered off, and the filtrate was evaporated in *vacuo* to give the target compound **15**·HCl. Yield 33.9 g (71%); yellowish solid; mp 181–184 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 9.80 (br s, 2H), 3.81 (d, *J* = 9.2 Hz, 2H), 3.35 (d, *J* = 9.2 Hz, 2H), 3.16 (d, *J* = 12.0 Hz, 2H), 2.97 (d, *J* = 12.0 Hz, 2H), 1.79 – 1.72 (m, 2H), 1.66 – 1.59 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 77.4, 63.8, 54.7, 36.0, 26.2. LC/MS (CI): *m*/z = 154 $[M–HCl+H]^+$. Anal. Calcd. for $C_9H_{16}ClNO$: C 56.99; H 8.50; N 7.38; Cl 18.69. Found: C 56.69; H 8.90; N 7.27; Cl 18.37.

General procedure for the preparation of 34 and 35. The compound **26** (244 g, 1.03 mol) was added to the solution of alkene **25** or **30** (1.02 mol) in CH_2Cl_2 (700 mL). Then, the solution of TFA (11.6 g, 0.102 mol) in CH_2Cl_2 (20 mL) was added dropwise at 25 °C under an argon atmosphere. The mixture was stirred for 3 h, washed with H_2O (400 mL) and brine (400 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The resulting yellowish oil **27** or **31** was used in the next step without purification. The corresponding anhydride **27** or **31** (0.500 mol) and urea (60.1 g, 1.00 mol) were dissolved in glacial HOAc (500 mL) at rt. The reaction mixture was refluxed for 5 h; then, most of acetic acid was evaporated in *vacuo* and the residue was poured into conc. aq $NH_3·H_2O$ (1000 mL). The resulting solution was extracted with CH_2Cl_2 (300 mL), the organic phase was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

***cis*-9-Benzyltetrahydro-1*H*-3a,7a-(methanoiminomethano)isoindole-1,3(2*H*)-dione (34).** An analytical sample was obtained by HPLC (0.5–6.5 min; MeCN; flow rate: 30 mL / min). Yield 112 g (79% for two steps); yellowish oil. ^1H NMR (500 MHz, DMSO-d_6) δ 11.33 (br s, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.20 (m, 3H), 3.50 (s, 2H), 3.12 (d, *J* = 9.4 Hz, 2H), 2.14 (d, *J* = 9.4 Hz, 2H), 1.83 – 1.77

(m, 2H), 1.54 – 1.44 (m, 4H), 1.26 – 1.16 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 183.4, 138.6, 128.7, 128.7, 127.4, 62.9, 58.1, 53.7, 25.4, 17.4. LC/MS (CI): *m*/z = 285 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C 71.81; H 7.09; N 9.85. Found: C 72.09; H 7.08; N 9.84.

***cis*-8-Benzyldihydro-3a,6a-(methanoiminomethano)cyclopenta[*c*]pyrrole-1,3(2*H*,4*H*)-dione (35)**. An analytical sample was obtained by HPLC (0.5–6.5 min; MeOH; flow rate: 30 mL / min). Yield 111 g (82% for two steps); yellowish oil. ^1H NMR (500 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 7.32 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 3.53 (s, 2H), 3.15 (d, *J* = 9.6 Hz, 2H), 2.19 (d, *J* = 9.6 Hz, 2H), 1.81 – 1.66 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 182.3, 138.6, 128.8, 128.7, 127.5, 63.8, 62.0, 58.1, 33.3, 28.0. LC/MS (CI): *m*/z = 271 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C 71.09; H 6.71; N 10.36. Found: C 71.32; H 6.59; N 10.35.

General procedure for the preparation of 36 and 37. A solution of the corresponding imide **34** or **35** (0.440 mol) in THF (500 mL) was added dropwise to the stirred suspension of $LiAlH_4$ (66.8 g, 1.76 mol) in THF (1000 mL) at 25 °C and the resulting mixture was refluxed for 48 h. The reaction mixture was quenched with H_2O (100 mL) added carefully in portions, 10% aq KOH (2×200 mL), and additionally with H_2O (100 mL). The precipitate was filtered, washed with THF, and the combined filtrates were evaporated in *vacuo.*

***cis*-2-benzylhexahydro-1*H*-3a,7a-(methanoiminomethano)isoindole dihydrochloride (36).** The compound (as a base) was purified by distillation in *vacuo*. Yield 98.1 g (87%); colorless liquid; bp 132–134 °C / 0.1 mmHg. The analytical sample was obtained as dihydrochloride **36**·2HCl: 2 M HCl solution in Et_2O (7.5 mL) was added to the diamine **36** (1.00 g, 3.90 mmol) at rt. The resulting mixture was stirred for 1 h, then filtered, and dried in *vacuo*. ^1H NMR (500 MHz, D_2O) δ 7.50 – 7.44 (m, 5H), 4.45 (s, 2H), 3.66 – 3.47 (m, 4H), 3.42 – 3.39 (m, 4H), 1.66 – 1.53 (m, 4H), 1.47 – 1.39 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) δ 130.9, 130.4, 129.4, 129.2, 60.4, 59.8, 52.5, 49.8, 27.5, 19.3. LC/MS (CI): *m*/z = 257 $[M–2HCl+H]^+$. Anal. Calcd. for $C_{17}H_{26}Cl_2N_2$: C 62.00; H 7.96; N 8.51; Cl 21.53. Found: C 62.18; H 8.12; N 8.31; Cl 21.55.

***cis*-2-Benzylhexahydro-3a,6a-(methanoiminomethano)cyclopenta[*c*]pyrrole (37).** The compound was purified by distillation in *vacuo*; bp 121–123 °C / 0.1 mmHg. Yield 88.5 g (83%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 4H), 7.22 – 7.17 (m, 1H), 3.52 (s, 2H), 2.81 (d, *J* = 10.7 Hz, 2H), 2.65 (d, *J* = 10.7 Hz, 2H), 2.42 (d, *J* = 8.8 Hz, 2H), 2.35 (d, *J* = 8.8 Hz, 2H), 2.07 (s, 1H), 1.65 – 1.58 (m, 4H), 1.47 – 1.40 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.6, 128.4, 128.1, 126.7, 65.6, 63.2, 59.5, 59.3, 37.5, 26.2. LC/MS (CI): *m*/z = 243 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{22}N_2$: C 79.29; H 9.15; N 11.56. Found: C 79.36; H 9.32; N 11.29.

General procedure for the preparation of monoprotected diamines 22 and 23. The corresponding *N*-benzyl amine **36** or **37** (0.382 mol) was dissolved in CH_2Cl_2 (300 mL) and Boc_2O (87.8 mL, 83.4 g, 0.382 mol) was added dropwise ar rt. The resulting mixture was stirred for additional 1 h and evaporated in *vacuo*. The resulting colorless liquids **38** or **39** were obtained in nearly quantitative yield and used in the next step without additional purification. Next, 10% Pd-C (20.0 g) was added to a solution of **38** or **39** (*ca.* 0.382 mol) in MeOH (500 mL), and the resulting mixture was stirred under H_2 atmosphere at rt for 12 h. The catalyst was filtered off, and the filtrate was evaporated in *vacuo*.

***tert*-Butyl tetrahydro-1*H*-3a,7a-(methanoiminomethano)isoindole-2(3*H*)-carboxylate (22).** The compound existed as a mixture of *ca.* 1:1 of rotamers. Yellowish oil; yield: 93.6 g (92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.18 (s, 4H), 2.77 (d, *J* = 10.6 Hz, 2H), 2.71 (d, *J* = 10.6 Hz, 2H), 1.55 – 1.42 (m, 2H), 1.38 (s, 4.5H), 1.38 – 1.34 (m, 9.5H), 1.11 – 1.08 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 154.5, 78.6, 56.0 and 55.8, 55.4 and 54.9, 49.9 and 49.0, 29.4, 28.7, 22.1. GC/MS (EI): *m/z* = 193 [M–O*t*-Bu]$^+$, 210 $[M–H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{15}H_{26}N_2O_2$: C 67.63; H 9.84; N 10.52. Found: C 67.77; H 9.84; N 10.14.

***tert*-Butyl tetrahydro-3a,6a-(methanoiminomethano)cyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (23).** Yield 85.8 g (89%); colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.33 (d, *J* = 11.3 Hz, 2H), 3.18 (d, *J* = 11.3 Hz, 2H), 2.79 (d, *J* = 2.3 Hz, 4H), 1.69 – 1.47 (m, 7H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 154.2, 79.0, 62.6, 57.4, 57.0, 37.8, 28.6, 26.1. GC/MS (EI): *m/z* = 179 [M–O*t*-Bu]$^+$, 196 $[M–H_2C=C(CH_3)_2]^+$, 237 $[M–CH_3]^+$, 252 $[M]^+$. Anal. Calcd. for $C_{14}H_{24}N_2O_2$: C 66.63; H 9.59; N 11.10. Found: C 66.95; H 9.47; N 11.01.

Diethyl 3-benzyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylate (41). The diester **40** (100 g, 0.504 mol) was dissolved in CH_2Cl_2 (2000 mL), and TFA (5.75 g, 3.74 mL, 50.4 mmol) was added to the

stirred solution, then warmed up to 50 °C. A solution of compound **26** (240 g, 1.01 mol) in CH_2Cl_2 (2000 mL) was added dropwise, and the resulting mixture was stirred at 50 °C overnight. Then, the solution was washed with saturated aq $NaHCO_3$ (1000 mL), H_2O (2×1000 mL), organic layer was separated, dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient $CHCl_3$ – MeCN as eluent. Yield 145 g (87%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.17 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 4H), 3.71 (s, 2H), 2.96 (d, *J* = 9.3 Hz, 2H), 2.59 (d, *J* = 9.3 Hz, 2H), 2.50 (dt, *J* = 6.2, 5.7 Hz, 2H), 2.01 (dt, *J* = 6.2, 5.7 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.2, 139.2, 128.5, 128.3, 127.0, 62.3, 60.6, 59.3, 55.6, 25.4, 14.1. LC/MS (CI): *m*/z = 332 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{25}NO_4$: C 68.86; H 7.6; N 4.23. Found: C 68.81; H 7.39; N 4.10.

(3-Benzyl-3-azabicyclo[3.2.0]heptane-1,5-diyl)dimethanol (42). THF (1500 mL) was cooled to –20 °C, and $LiAlH_4$ (34.4 g, 0.906 mol) was added in portions under argon over 15 min. Then, a solution of diester **41** (100 g, 0.302 mol) in THF (500 mL) was added dropwise at –20 °C for 45 min. The resulting mixture was warmed up to rt and stirred for 5 h. The reaction completion was monitored by TLC using $CHCl_3$ – *i*-PrOH (19:1, v/v) as eluent. Then, the reaction mixture was cooled to –10 °C, and H_2O (35.0 mL), 15% aq NaOH (35.0 mL), and then H_2O (105 mL) were slowly added dropwise at –10 °C. The resulting mixture was warmed up to rt and stirred overnight, the precipitate was filtered off, washed with THF (2×100 mL). The combined filtrates were evaporated in *vacuo*, the residue was dissolved in CH_2Cl_2 (500 mL). The solution was dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by HPLC (0.5–6.5 min; H_2O - MeCN; flow rate: 30 mL / min). Yield 69.5 g (93%); beige powder; mp 104-105 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.23 (m, 1H), 3.77 (br s, 2H), 3.74 (d, *J* = 11.7 Hz, 2H), 3.69 (s, 2H), 3.52 (d, *J* = 11.7 Hz, 2H), 2.68 (d, *J* = 9.0 Hz, 2H), 2.46 (d, *J* = 9.0 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.76 – 1.69 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.5, 128.6, 128.2, 126.8, 63.6, 62.5, 60.1, 50.2, 24.2. LC/MS (CI): *m*/z = 248 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{21}NO_2$: C 72.84; H 8.56; N 5.66. Found: C 72.5; H 8.68; N 5.55.

5-Benzyltetrahydro-1*H*-3a,6a-ethanofuro[3,4-*c*]pyrrole (43). MsOH (35.0 g, 0.384 mol) was added to diol **42** (30.0 g, 0.121 mol), and the resulting mixture was stirred at 80 °C for 48 h. The resulting mixture was evaporated in *vacuo*, diluted with H_2O (100 mL), and 10% aq NaOH (16.0 g, 0.400 mol) was added in portions. The aqueous solution was extracted with CH_2Cl_2 (2×100 mL), combined organic layer was dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient *t*-BuOMe – MeOH as eluent. Yield 25.8 g (93%); yellowish powder, mp 47-49 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.29 (m, 4H), 7.26 – 7.20 (m, 1H), 3.72 (d, J = 8.9 Hz, 2H), 3.65 (s, 2H), 3.37 (d, J = 8.9 Hz, 2H), 2.72 (d, J = 9.2 Hz, 2H), 2.24 (d, J = 9.2 Hz, 2H), 1.94 – 1.87 (m, 2H), 1.87 – 1.80 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 139.7, 128.7, 128.6, 127.2, 77.4, 63.0, 58.9, 56.0, 26.5. LC/MS (CI): m/z = 230 [M+H]$^+$. Anal. Calcd. for $C_{15}H_{19}NO$: C 78.56; H 8.35; N 6.11. Found: C 78.23; H 8.18; N 5.88.

Tetrahydro-1*H*-3a,6a-ethanofuro[3,4-*c*]pyrrol-5-ium chloride (16). The *N*-benzyl amine **43** (25.0 g, 0.109 mol) was dissolved in 2 M HCl in MeOH (250 mL), the resulting solution was evaporated in *vacuo*. The crystalline **43**·HCl was dissolved in MeOH (600 mL), and 10% Pd-C (5.63 g) was added. The resulting mixture was hydrogenated with H_2 (30 bar) in autoclave at rt overnight, the catalyst was filtered off, and washed with MeOH (2×100 mL). Combined filtrates were evaporated in *vacuo*, the residue was dried in *vacuo* (1 mmHg). Yield 15.5 g (81%); colorless powder; mp 214-217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (br d, J = 77.6 Hz, 2H), 3.76 (d, J = 9.2 Hz, 2H), 3.56 (d, J = 9.2 Hz, 2H), 3.34 (d, J = 11.8 Hz, 2H), 3.09 – 3.02 (m, 2H), 2.11 (dt, J = 6.4, 5.8 Hz, 2H), 1.88 (dt, J = 6.4, 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 76.9, 56.7, 53.1, 25.0. LC/MS (CI): m/z = 140 [M–HCl+H]$^+$. Anal. Calcd. for $C_8H_{14}ClNO$: C 54.70; H 8.03; N 7.97; Cl 20.18. Found: C 54.69; H 7.95; N 8.19; Cl 19.89.

3-Azabicyclo[3.2.0]heptane-1,5-diyldimethanol (44). The *N*-benzyl amine **42** (18.0 g, 72.8 mmol) was dissolved in MeOH (500 mL), and 10% Pd-C (4.03 g) was added. The resulting mixture was hydrogenated with H_2 (30 bar) in autoclave at rt overnight, the catalyst was filtered off, and washed with MeOH (2×100 mL). Combined filtrates were evaporated in *vacuo*, and the residue was dried in *vacuo*

(1 mmHg). Yield 11.0 g (96%); colorless powder; mp = 214-217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.71 (s, 2H), 3.49 (d, J = 10.8 Hz, 2H), 3.44 (d, J = 10.8 Hz, 2H), 3.17 (s, 1H), 2.62 (d, J = 11.3 Hz, 2H), 2.58 (d, J = 11.3 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.53 – 1.43 (m, 2H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, J = 11.8 Hz, 2H), 3.55 (d, J = 11.8 Hz, 2H), 2.99 (d, J = 11.2 Hz, 2H), 2.89 – 2.64 (m, 5H), 1.78 – 1.70 (m, 2H), 1.62 – 1.50 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 62.8, 55.9, 51.6, 23.5. LC/MS (CI): m/z = 158 $[M+H]^+$. Anal. Calcd. for $C_8H_{15}NO_2$: C 61.12; H 9.62; N 8.91. Found: C 61.07; H 9.58; N 9.20.

5-Benzyl-2-(4-methoxybenzyl)dihydro-3a,6a-ethanopyrrolo[3,4-*c*]pyrrole-1,3(2*H*,4*H*)-dione (45). *p*-Methoxybenzylamine (34.7 mL, 36.4 g, 0.266 mol) was added to the diester **41** (20.0 g, 53.1 mmol), and the resulting mixture was heated at 180 °C for 12 h. The product was separated by column chromatography on silica gel using gradient hexanes – *t*-BuOMe as eluent. Analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeCN; flow rate: 30 mL / min). Yield 8.40 g (42%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 (t, J = 7.3 Hz, 2H), 7.26 – 7.20 (m, 3H), 7.14 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.51 (s, 2H), 3.73 (s, 3H), 3.64 (s, 2H), 2.78 (d, J = 9.7 Hz, 2H), 2.71 (d, J = 9.7 Hz, 2H), 2.35 – 2.26 (m, 2H), 2.26 – 2.17 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 179.3, 159.0, 138.7, 128.9, 128.7, 128.7, 128.6, 127.5, 114.4, 59.5, 57.6, 55.5, 51.4, 41.6, 24.6. LC/MS (CI): m/z = 377 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{24}N_2O_3$: C 73.38; H 6.43; N 7.44. Found: C 73.38; H 6.54; N 7.43.

2-(4-Methoxybenzyl)dihydro-3a,6a-ethanopyrrolo[3,4-*c*]pyrrole-1,3(2*H*,4*H*)-dione hydrocloride (46). $Pd(OH)_2$-C (2.07 g) was added to the solution of *N*-benzyl amine **45** (7.95 g, 21.1 mmol) in THF – *i*-PrOH (120 mL, 1:1, v/v), the resulting mixture was degased, refilled with H_2, and stirred at rt for 12 h. The catalyst was filtered off, washed with THF (2×30 mL), and combined filtrates were evaporated in *vacuo*. The analytical sample was obtained as hydrochloride **46**·HCl: 2 M HCl in Et_2O (3.5 mL) was added to the diamine **36** (1.00 g, 3.49 mmol) at rt. The resulting mixture was stirred for 1 h, then filtered, and dried in *vacuo*. Yield 5.50 g (91% as a base); colorless powder; mp 244–247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (br s, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.49 (s, 2H), 3.73 (s, 3H), 3.62 (d, J = 12.1 Hz, 2H), 3.45 (d, J = 12.1 Hz, 2H), 2.58 (dd, J = 6.9, 5.9 Hz, 2H),

2.22 (dd, J = 6.9, 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 176.8, 159.1, 129.3, 128.3, 114.5, 55.5, 51.9, 49.8, 42.1, 24.4. LC/MS (CI): m/z = 287 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{19}ClN_2O_3$: C 59.54; H 5.93; N 8.68; Cl 10.98. Found: C 59.68; H 5.89; N 8.53; Cl 11.38.

2-(4-Methoxybenzyl)hexahydro-3a,6a-ethanopyrrolo[3,4-*c*]pyrrole (47). To a suspension of $LiAlH_4$ (1.46 g, 38.4 mmol) in THF (100 mL), the imide **46** (5.50 g, 19.2 mmol) was added in portions at rt. The resulting mixture was refluxed for 8 h, then H_2O (1.20 mL), 20% aq NaOH (1.20 mL), and H_2O (3.60 mL) were added. The precipitate was filtered off, washed with THF (2×20 mL), combined filtrates were evaporated in *vacuo*. The residue was diluted with toluene – CCl_4 (50 mL, 1:1, v/v) and evaporated in *vacuo*. The compound was purified by HPLC (0.5-6.5 min; MeOH – NH_3; flow rate: 30 mL / min). Yield 3.77 g (76%); colorless powder; mp 80–81 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 3.81 (s, 3H), 3.62 (s, 2H), 2.89 (d, J = 11.2 Hz, 2H), 2.80 (d, J = 9.2 Hz, 2H), 2.68 (d, J = 11.2 Hz, 2H), 2.65 (s, 1H), 2.16 (d, J = 9.2 Hz, 2H), 2.00 (dd, J = 6.5, 5.7 Hz, 2H), 1.76 (dd, J = 6.5, 5.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.4, 131.7, 129.6, 113.5, 64.1, 58.7, 57.9, 55.9, 55.2, 26.9. LC/MS (CI): m/z = 259 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{22}N_2O$: C 74.38; H 8.58; N 10.84. Found: C 74.59; H 8.37; N 10.65.

***tert*-Butyl 5-(4-methoxybenzyl)tetrahydro-3a,6a-ethanopyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (48).** Boc_2O (3.27 mL, 3.10 g, 14.2 mmol) was added dropwise to a solution of amine **47** (3.50 g, 13.5 mmol) in CH_2Cl_2 (50 mL) at rt. The resulting mixture was stirred at rt for 12 h, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient hexanes – *t*-BuOMe as eluent. Yield 4.45 g (92%); yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.73 (s, 3H), 3.57 (s, 2H), 3.49 (d, J = 11.3 Hz, 2H), 3.12 – 3.05 (m, 2H), 2.77 (d, J = 9.2 Hz, 2H), 2.11 (d, J = 9.2 Hz, 2H), 1.97 – 1.88 (m, 2H), 1.88 – 1.79 (m, 2H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 158.6, 154.2, 131.4, 129.9, 114.0, 79.7, 78.9, 64.2, 58.2, 56.9, 55.4, 28.6, 27.5. LC/MS (CI): m/z = 359 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{30}N_2O_3$: C 70.36; H 8.44; N 7.81. Found: C 70.33; H 8.60; N 7.81.

***tert*-Butyl tetrahydro-3a,6a-ethanopyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (24).** $Pd(OH)_2$-C (1.20 g) was added to the solution of *p*-methoxybenzylamine **48** (4.30 g, 12.0 mmol) in MeOH (100

mL), the resulting mixture was degased, refilled with H_2, and stirred at rt for 12 h. The catalyst was filtered off, washed with MeOH (2×25 mL), and combined filtrates were evaporated in *vacuo*. The compound was purified by column chromatography using gradient *t*-BuOMe – MeOH as eluent. Yield 2.20 g (77%); white powder; mp 204–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.58 (d, J = 11.4 Hz, 2H), 3.30 (d, J = 11.9 Hz, 2H), 3.22 (d, J = 11.4 Hz, 2H), 3.03 (d, J = 11.9 Hz, 2H), 2.50 – 2.48 (m, 1H), 2.13 (dd, J = 6.9, 5.8 Hz, 2H), 1.86 (dd, J = 6.9, 5.8 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 154.2, 79.2, 56.5, 54.3, 53.7, 28.6, 26.1. LC/MS (CI): m/z = 165 [M–O*t*-Bu]$^+$, 183 [M-H_2C=C$(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C 65.52; H 9.30; N 11.75. Found: C 65.62; H 9.01; N 12.12.

Dimethyl 1-benzyl-3,4-bis((benzyloxy)methyl)pyrrolidine-3,4-dicarboxylate (51). Diisopropylamine (63.2 mL, 45.3 g, 0.448 mol) was dissolved in THF (750 mL) under argon atmosphere, and the resulting solution was cooled to –40 °C. *n*-BuLi (180 mL, 2.5 M in hexanes, 0.448 mol) was added dropwise at –40 °C. The resulting mixture was cooled to –78 °C, and a solution of diester **50** (50.0 g, 0.180 mol) in THF (250 mL) was slowly added dropwise for 30 min. After 1 h, a solution of BOMCl (84.7 g, 0.540 mol) in THF (250 mL) was added dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 1 h, then warmed up to rt overnight. Then, saturated aq NH_4Cl (1000 mL) was added in portions at rt. Organic layer was separated, evaporated in *vacuo*, the residue was dissolved in CH_2Cl_2 (500 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient $CHCl_3$ – MeCN as eluent. Yield 82.0 g (88%); yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.26 (m, 11H), 7.21 – 7.17 (m, 4H), 4.40 (s, 4H), 3.59 (s, 6H), 3.59 – 3.56 (m, 4H), 3.50 (d, J = 8.1 Hz, 2H), 3.08 (d, J = 9.4 Hz, 2H), 2.70 (d, J = 9.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.7, 139.2, 138.3, 128.7, 128.6, 128.0, 127.9, 127.3, 73.0, 72.0, 59.0, 58.9, 57.1, 52.3. LC/MS (CI): *m/z* = 518 [M+H]$^+$. Anal. Calcd. for $C_{31}H_{35}NO_6$: C 71.93; H 6.82; N 2.71. Found: C 71.85; H 6.54; N 3.10.

(1-Benzyl-3,4-bis((benzyloxy)methyl)pyrrolidine-3,4-diyl)dimethanol (52). THF (1500 mL) was cooled to –20 °C, and $LiAlH_4$ (22.2 g, 0.585 mol) was added in portions for 15 min under argon. Then, a solution of diester **51** (101 g, 0.195 mol) in THF (500 mL) was added dropwise at –20 °C for 45 min.

The resulting mixture was warmed up to rt and stirred for 5 h. The reaction completion was monitored by TLC using $CHCl_3$ – *i*-PrOH (19:1, v/v) as eluent. The reaction mixture was cooled to –10 °C, and H_2O (23.0 mL), 15% aq NaOH (23.0 mL), and H_2O (69.0 mL) were added slowly dropwise. The resulting mixture was warmed up to rt and stirred overnight, the precipitate was filtered off, washed with (2×300 mL), and combined filtrated were evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (500 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient $CHCl_3$ – MeCN as eluent. Yield 83.7 g (93%); yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.23 (m, 15H), 4.89 (s, 2H), 4.50 (d, J = 12.3 Hz, 2H), 4.45 (d, J = 12.3 Hz, 2H), 3.65 – 3.52 (m, 6H), 3.49 (d, J = 10.6 Hz, 2H), 3.40 (d, J = 10.6 Hz, 2H), 2.66 (d, J = 9.4 Hz, 2H), 2.48 (d, J = 9.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 139.9, 139.2, 128.7, 128.6, 128.6, 127.7, 127.7, 127.1, 73.0, 70.5, 60.9, 60.0, 59.2, 51.4. LC/MS (CI): *m/z* = 462 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{35}NO_4$: C 75.46; H 7.64; N 3.03. Found: C 75.64; H 7.73; N 3.19.

5-Benzyltetrahydro-1*H*-3a,6a-(methanooxymethano)furo[3,4-*c*]pyrrole (53). A mixture of the bis-benzyloxydiol **52** (80.0 g, 0.173 mol) and MsOH (66.6 g, 0.693 mol) was heated at 80 °C for 48 h. The mixture was evaporated in *vacuo*, the residue was diluted with H_2O (200 mL), and 10% aq NaOH (27.7 g, 0.693 mol) was added in portions at rt. The reaction mixture was extracted with CH_2Cl_2 (2×200 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography on silica gel using gradient $CHCl_3$ - MeCN as eluent. The analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeCN; flow rate: 30 mL / min). Yield 36.9 g (87%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 3.60 – 3.55 (m, 6H), 3.51 (d, J = 8.8 Hz, 4H), 2.45 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 139.3, 128.7, 128.7, 127.3, 76.4, 66.3, 62.1, 58.3. LC/MS (CI): *m/z* = 246 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{19}NO_2$: C 73.44; H 7.81; N 5.71. Found: C 73.23; H 7.56; N 5.97.

Tetrahydro-1*H*-3a,6a-(methanooxymethano)furo[3,4-*c*]pyrrol-5-ium chloride (17). The *N*-benzyl amine **53** (20.0 g, 81.5 mmol) was dissolved in 2 M HCl in MeOH (200 mL), the resulting solution was evaporated in *vacuo*. The crystalline **53**·HCl was dissolved in MeOH (600 mL), and 10% Pd-C (4.00 g)

was added. The resulting mixture was hydrogenated with H_2 (30 bar) in autoclave at rt overnight, the catalyst was filtered off, and washed with MeOH (2×100 mL). Combined filtrates were evaporated in *vacuo*, the residue was dried in *vacuo* (1 mmHg). Yield 11.9 g (76%); yellowish crystals; mp 234–236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (br s, 2H), 3.84 (d, J = 9.3 Hz, 4H), 3.55 (d, J = 9.3 Hz, 4H), 3.17 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 75.9, 66.7, 52.5. LC/MS (CI): m/z = 156 [M–HCl+H]$^+$. Anal. Calcd. for $C_8H_{14}ClNO_2$: C 50.13; H 7.36; N 7.31; Cl 18.50. Found: C 49.91; H 7.32; N 6.94; Cl 18.42.

Pyrrolidine-3,3,4,4-tetrayltetramethanol hydrochloride (54). Amine **52** (27.5 g, 59.6 mmol) was dissolved in 2 M HCl in MeOH (300 mL), the resulting solution was evaporated in *vacuo*. The crystalline **52**·HCl was dissolved in MeOH (700 mL), and 10% Pd-C (5.44 g) was added. The resulting mixture was hydrogenated with H_2 (30 bar) in autoclave at rt overnight, the catalyst was filtered off, and washed with MeOH (2×150 mL). Combined filtrates were evaporated in *vacuo*, the residue was dried in *vacuo* (1 mmHg). Yield 11.0 g (81%); yellow crystals; mp 203–206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (br s, 2H), 5.00 (br s, 4H), 3.50 (s, 8H), 3.14 (t, J = 6.1 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 60.8, 52.3, 50.5. GC/MS (EI): m/z = 227 [M]$^+$. Anal. Calcd. for $C_8H_{18}ClNO_4$: C 42.20; H 7.97; N 6.15; Cl 15.57. Found: C 42.47; H 8.23; N 5.97; Cl 15.31.

Dimethyl 2,5-dibenzyloctahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxylate (56). Dimethyl acetylenedicarboxylate (**55**, 100 g, 0.704 mol) and the compound **26** (468 g, 1.97 mol) were dissolved in MeCN (2500 mL), and LiF (91.3 g, 3.52 mol) was added. The resulting suspension was refluxed for 12 h, then evaporated in *vacuo*. The residue was diluted with H_2O (1000 mL), and extracted with EtOAc (2×1000 mL). Combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*. The analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeCN; flow rate: 30 mL / min). Yield 101 g (35%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 8H), 7.28 – 7.24 (m, 2H), 3.70 – 3.65 (m, 10H), 3.10 (d, J = 9.1 Hz, 4H), 2.73 (d, J = 9.1 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.9, 138.7, 128.4, 128.2, 126.9, 62.9, 62.8, 58.7, 52.1. LC/MS (CI): m/z = 409 [M+H]$^+$. Anal. Calcd. for $C_{24}H_{28}N_2O_4$: C 70.57; H 6.91; N 6.86. Found: C 70.92; H 7.04; N 6.56.

(2,5-Dibenzyloctahydropyrrolo[3,4-*c*]pyrrole-3a,6a-diyl)dimethanol (57).[16] To a suspension of $LiAlH_4$ (41.8 g, 1.10 mol) in THF (2500 mL), a solution of diester **56** (180 g, 0.441 mol) in THF (200 mL) was added dropwise at rt. The resulting mixture was stirred at rt overnight, then H_2O (100 mL) was added dripwise at rt. KOH (64.8 g) was added until the precipitate was dissolved, the resulting solution was extracted with Et_2O (3×500 mL), combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*. The analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeOH; flow rate: 30 mL / min). Yield 131 g (84%); beige oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 8H), 7.28 – 7.22 (m, 2H), 4.36 (s, 2H), 3.65 (s, 4H), 3.59 (s, 4H), 2.58 (dd, J = 9.3, 2.1 Hz, 8H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.5, 128.5, 128.4, 127.2, 65.3, 62.6, 59.5, 55.1. LC/MS (CI): *m/z* = 353 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C 74.97; H 8.01; N 7.95. Found: C 74.59; H 8.38; N 7.72.

2,5-Dibenzylhexahydro-3a,6a-(methanooxymethano)pyrrolo[3,4-*c*]pyrrole (58).[16] DCC (95.1 g, 0.461 mol) was added to diol **57** (125 g, 0.355 mol) under argon atmosphere, and the mixture was heated at 170 °C for 3 h. Then, the reaction mixture was diluted with CH_2Cl_2 (500 mL) and extracted with 1 M aq HCl (4×100 mL). Aqueous phase was separated, and 1 M aq NaOH (500 mL) was added in portions. The resulting solution was extracted with Et_2O, (3×200 mL), combined organic layers were dried over Na_2SO_4, dried over Na_2SO_4, and evaporated in *vacuo*. The analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeCN; flow rate: 30 mL / min). Yield 97.4 g (82%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 8H), 7.27 – 7.24 (m, 2H), 3.68 (s, 4H), 3.62 (s, 4H), 2.60 (d, J = 8.9 Hz, 4H), 2.49 (d, J = 8.9 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.5, 128.4, 128.2, 126.8, 77.5, 63.4, 62.9, 58.8. LC/MS (CI): *m/z* = 335 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{26}N_2O$: C 79.00; H 7.84; N 8.38. Found: C 79.33; H 8.05; N 8.60.

Hexahydro-3a,6a-(methanooxymethano)pyrrolo[3,4-*c*]pyrrole-2,5-diium chloride (18). Amine **58** (97.0 g, 0.290 mol) was dissolved in 1 M HCl in MeOH (1000 mL), the resulting solution was evaporated in *vacuo*. The crystalline **58**·HCl was dissolved in MeOH - H_2O (1200 mL, 5:1, v/v), and 10% Pd-C (15.1 g) was added. The resulting mixture was hydrogenated with H_2 (50 bar) in autoclave at 50 °C overnight, the catalyst was filtered off, and washed with H_2O) (100 mL). Combined filtrates were

evaporated in *vacuo*, the residue was dissolved in hot H_2O (100 mL) and poured into *i*-PrOH (600 mL). The precipitate formed was filtered and dried in *vacuo* (1 mmHg). Yield 55.3 g (84%); colorless powder; the compound decomposed upon heating on up to 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (br s, 4H), 3.84 (s, 4H), 3.56 (d, J = 12.3 Hz, 4H), 3.17 (d, J = 12.3 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 76.1, 63.7, 52.7. LC/MS (CI): *m/z* = 155 $[M–HCl+H]^+$. Anal. Calcd. for $C_8H_{18}Cl_2N_2O_2$: C 39.20; H 7.40; N 11.43; Cl 28.92. Found: C 39.23; H 7.22; N 11.47; Cl 28.92.

2,5,8-Tribenzyldihydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole-1,3(2*H*,4*H*)-dione (59). Benzylamine (63.0 g, 0.588 mol) was added to the diester **56** (200 g, 0.490 mol) under argon atmosphere, and the resulting mixture was heated at 180 °C overnight. The compound was purified by column chromatography using hexanes – *t*-BuOMe (3:2) as eluent. Yield 139 g (63%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.6 Hz, 5H), 7.25 – 7.18 (m, 8H), 4.62 (s, 2H), 3.58 (s, 4H), 3.01 (d, J = 9.5 Hz, 4H), 2.53 (d, J = 9.5 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 179.8, 138.5, 136.2, 128.9, 128.8, 128.7, 127.8, 127.5, 127.1, 62.1, 59.8, 57.9, 42.1. LC/MS (CI): *m/z* = 452 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{29}N_3O_2$: C 77.14; H 6.47; N 9.31. Found: C 76.87; H 6.57; N 9.08.

2,5,8-Tribenzylhexahydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole (60). Imide **59** (100 g, 0.221 mol) was dissolved in THF (100 mL), and a suspension of $LiAlH_4$ (25.2 g, 0.664 mol) in THF (1300 mL) was added dropwise at rt for 30 min. The resulting mixture was refluxed for 6 h, then H_2O (25.0 mL) was added until the H_2 evolution ceased. KOH (39.1 g, 0.692 mol) was added until the precipitate was dissolved, and the reaction mixture was extracted with Et_2O (3×500 mL), combined organic phases were washed with brine (2×250 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The analytical sample was obtained by HPLC (0.5–6.5 min; H_2O – MeOH; flow rate: 30 mL / min). Yield 86.0 g (90%); brownish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.27 (m, 12H), 7.23 – 7.20 (m, 3H), 3.54 (s, 6H), 2.40 (s, 12H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 139.7, 128.6, 128.6, 127.1, 63.8, 60.4, 58.7. LC/MS (CI): *m/z* = 424 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{33}N_3$: C 82.23; H 7.85; N 9.92. Found: C 82.08; H 8.08; N 10.21.

Hexahydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole-2,5-diium chloride (19). The tribenzyl amine **60** (85.5 g, 0.202 mol) was dissolved in 1 M HCl in MeOH (1000 mL), the resulting solution was evaporated in *vacuo*. The crystalline **60**·3HCl was dissolved in MeOH – H_2O (1200 mL, 5:1, v/v), and 10% Pd-C (15.5 g) was added. The resulting mixture was hydrogenated with H_2 (50 bar) in autoclave at 50 °C overnight, the catalyst was filtered off, and washed with H_2) (100 mL). Combined filtrates were evaporated in *vacuo*, the residue was dissolved in hot H_2O (100 mL) and poured into *i*-PrOH (600 mL). The precipitate formed was filtered and dried in *vacuo* (1 mmHg). Yield 42.4 g (80%); white solid; mp 301–303 °C. ^{1}H NMR (400 MHz, D_2O) δ 3.53 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 60.6, 53.6. LC/MS (CI): *m/z* = 154 $[M–3HCl+H]^+$. Anal. Calcd. for $C_8H_{18}Cl_3N_3$: C 36.59; H 6.91; N 16.00; Cl 40.50. Found: C 36.83; H 6.51; N 15.81; Cl 40.83.

5,8-Dibenzyl-2-(4-methoxybenzyl)dihydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole-1,3(2*H*,4*H*)-dione (61). *p*-Methoxybenzylamine (6.71 mL, 7.05 g, 51.4 mmol) was added to the diester **56** (10.0 g, 24.5 mmol) under argon atmosphere, and the resulting mixture was heated at 180 °C overnight. The compound was purified by column chromatography using hexanes – *t*-BuOMe (3:1) as eluent. Yield 8.02 g (68%); yellow solid; mp 107–109 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 – 7.26 (m, 4H), 7.25 – 7.21 (m, 2H), 7.19 – 7.14 (m, 6H), 6.89 (d, *J* = 8.3 Hz, 2H), 4.54 (s, 2H), 3.75 (s, 3H), 3.56 (s, 4H), 2.98 (d, *J* = 9.6 Hz, 4H), 2.51 (d, *J* = 9.6 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 179.7, 159.0, 138.5, 128.7, 128.7, 128.7, 128.3, 127.5, 114.3, 62.0, 59.7, 57.8, 55.6, 41.6. LC/MS (CI): *m/z* = 482 $[M+H]^+$. Anal. Calcd. for $C_{30}H_{31}N_3O_3$: C 74.82; H 6.49; N 8.73. Found: C 74.59; H 6.55; N 9.13.

2,5-dibenzyl-8-(4-methoxybenzyl)hexahydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-c]pyrrole (62). Imide **59** (7.95 g, 16.5 mmol) was dissolved in THF (10 mL), and a suspension of $LiAlH_4$ (1.25 g, 33.0 mmol) in THF (130 mL) was added dropwise at rt for 30 min. The resulting mixture was refluxed for 6 h, then H_2O (5.0 mL) was added dropwise until H_2 evolution ceased. KOH (1.94 g, 34.7 mmol) was added until the precipitate was dissolved, and the reaction mixture was extracted with Et_2O (3×50 mL), combined organic phases were washed with brine (2×25 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using

hexanes – EtOAc (3:1) as eluent. Yield 5.91 g (79%); colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 – 7.27 (m, 8H), 7.23 – 7.18 (m, 4H), 6.86 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.53 (s, 4H), 3.46 (s, 2H), 2.39 (s, 8H), 2.38 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.5, 139.8, 131.6, 129.7, 128.6, 128.6, 127.1, 114.0, 63.8, 63.7, 60.4, 58.7, 58.1, 55.4. LC/MS (CI): *m/z* = 454 [M+H]$^+$. Anal. Calcd. for $C_{30}H_{35}N_3O$: C 79.43; H 7.78; N 9.26. Found: C 79.63; H 7.96; N 9.38.

2,5-Dibenzylhexahydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole (21).[17] To a solution of *p*-methoxybenzylamine **62** (7.31 g, 16.1 mmol) in Et_3N (20.0 mL), TFAA (5.00 mL) was added dropwise ar rt. The resulting mixture was stirred overnight and evaporated in *vacuo*. The residue was diluted with MeOH (25 mL), and 10% aq NaOH (10 mL) was added. The mixture was stirred for 30 min, most of MeOH was evaporated in *vacuo*, and the residue was diluted with H_2O (25 mL) and aqueous mixture was extracted with CH_2Cl_2 (2×20 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound was purified by column chromatography using gradient MeOH – MeCN as eluent. Yield 2.36 g (44%); colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 – 7.21 (m, 10H), 3.53 (s, 4H), 2.72 (s, 4H), 2.48 – 2.41 (m, 5H), 2.39 (d, J = 8.8 Hz, 4H). LC/MS (CI): *m/z* = 334 [M+H]$^+$. Anal. Calcd. for $C_{22}H_{27}N_3$: C 79.24; H 8.16; N 12.60. Found: C 79.37; H 8.31; N 12.71.

***tert*-Butyl tetrahydro-3a,6a-(methanoiminomethano)pyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (20).** Boc_2O (1.52 mL, 1.44 g, 6.61 mmol) was added dropwise to a solution of amine **21** (2.10 g, 6.30 mmol) in CH_2Cl_2 (50 mL) at rt. The resulting mixture was stirred overnight at rt, then evaporated in *vacuo*. The corresponding *N*-Boc amine **63** was obtained as colorless oil and used in the next step without additional purification. The compound **63** was dissolved in MeOH (10 mL), 20% $Pd(OH)_2$-C (110 mg) was added under argon atmosphere. The reaction mixture was stirred overnight, the catalyst was filtered off, washed with MeOH (2×3 mL), and combined filtrates were evaporated in *vacuo*. The compound was purified by column chromatography using gradient MeOH – MeCN as eluent. The compound existed as a mixture of *ca.* 1:1 of rotamers. Yield 702 mg (44%); mp 174–176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.22 (s, 4H), 3.19 (s, 2H), 2.66 (d, J = 11.1 Hz, 4H), 2.61 (d, J = 11.1 Hz, 4H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 154.2, 78.8, 66.7 and 65.8, 58.1, 56.1 and 56.0,

28.6. LC/MS (CI): *m/z* = 198 $[M–H_2C=C(CH_3)_2+H]^+$, 254 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{23}N_3O_2$: C 61.63; H 9.15; N 16.59. Found: C 61.31; H 9.29; N 16.35.

X-Ray diffraction studies of 14–16, 18 and 64. The crystals for X-ray diffraction studies were obtained by slow evaporation of their solutions in CH_2Cl_2 – hexanes or CH_2Cl_2 – Et_2O (**14** – **16**), slow crystallization from *i*-PrOH – H_2O (**18**·H_2O) or MeOH (**64**).

X-Ray diffraction studies were performed on an automatic diffractometer (graphite monochromated MoK_α radiation, CCD-detector, ω-scanning, $2\theta_{max}$ = 60°). The structure was solved by direct method using SHELXTL package. The crystallographic data and experimental parameters are listed in Table S1 in the Supporting Information. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The deposition numbers are CCDC 1943266 (**18**), CCDC 1943267 (**16**), CCDC 1943268 (**15**), CCDC 1943269 (**14**), and CCDC 1943270 (**64**).

Supporting Information: copies of ^1H and ^{13}C NMR spectra, ORTEP diagrams, and Table S1 containing crystallographic data and experimental parameters for the compounds **14**–**16**, **18**, and **64**. This material is available free of charge at http://pubs.acs.org.

Acknowledgements

The work was funded by Enamine Ldt. O.O.G. was also funded by Ministry of Education and Science of Ukraine (Grant No. 19BF037-03). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support, and Mrs. Vladyslava Prykhodko for her help with cover picture preparation.

References and notes

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