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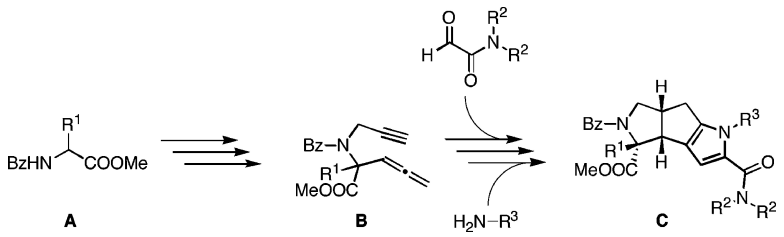

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Solution-Phase Synthesis of a Tricyclic Pyrrole-2-Carboxamide Discovery Library Applying a Stetter−Paal−Knorr Reaction Sequence

Stefan Werner,*,† Pravin S. Iyer,† Matthew D. Fodor,† Claire M. Coleman,†,‡ Leslie A. Twining,† Branko Mitasev,‡ and Kay M. Brummond*,‡

University of Pittsburgh Center for Chemical Methodologies and Library Development, Pittsburgh, Pennsylvania 15260, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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The solution-phase synthesis of a discovery library of 178 tricyclic pyrrole-2-carboxamides was accomplished in nine steps and seven purifications starting with three benzoyl-protected amino acid methyl esters. Further diversity was introduced by two glyoxaldehydes and 41 primary amines. The combination of Pauson−Khand, Stetter, and microwave-assisted Paal−Knorr reactions was applied as a key sequence. The discovery library was designed with the help of QikProp 2.1, and physicochemical data are presented for all pyrroles. Library members were synthesized and purified in parallel and analyzed by LC/MS. Selected compounds were fully characterized.

Introduction

Currently, medicinal chemists rely largely on the notion of "druglike" space[1,2] and chemical intuition as a basis for preselecting compounds to be screened as potential drug candidates. This established approach will certainly lead to the development of new drug candidates. However, arguments are being made that "druglike" space is limiting, and opportunities are being missed by not venturing outside this area. Drugs such as nitrous oxide, lithium, and insulin, which do not fall into the realm of "druglike" space support the premise that expanding drug discovery space may be valuable. A potential solution to this drug discovery limitation is the preparation and assaying of "discovery libraries". A discovery library is defined as compounds that occupy a heretofore poorly populated chemical space. There are many compounds that fall into this category; however, when a discovery library is designed, there are a few criteria that should be considered: (1) the number of synthetic steps should be minimized while structural and functional diversity is maximized; (2) the amount of each compound synthesized should be adequate so that numerous biological evaluations can be performed; (3) properties, such as lipophilicity and solubility,[3] should be taken into consideration, since this is an issue for most of the assays; (4) and finally, precautions should be taken in the design phase so that very reactive functional groups that covalently bind to the targets are avoided.[4] These guidelines will then lead to compounds that will function as tools[1,5] for probing biological activity.

The synthesis of compounds that occupy new chemical space depends on new method development to access these unique chemical structures.[6] Recently, protocols have been developed by Brummond and Mitasev that demonstrate that structurally unique scaffolds can be generated by subjecting a common intermediate to different transition-metal-catalyzed conditions.[7] The compounds that have been synthesized using this diverging strategy are new and are being evaluated for interesting bioactivity; however, it is the unique reactivity profile of each scaffold and its potential to be differentially functionalized that is deemed the most useful feature of this approach. Thus far, most of our efforts have been devoted to *back-end* diversifications of these scaffolds.

A discovery library of pyrrolecarboxamides[8] is of special interest because of the pharmacological activity of this unit. The pyrrolecarboxamide skeleton is a core unit in many marine natural products[9] (Figure 1), such as agelastatin A (**1**, antitumor activity),[10] dispacamide A (**2**, antihistaminic activity),[11] hymenialdisine (**3**, kinase inhibitor),[12] sceptrin (**4**, antiviral activity),[13] or storniamide A (**5**, antibacterial activity).[14] One of the most important natural products with a pyrrolecarboxamide unit is distamycin (**6**), a well-established DNA minor groove binder.[15] Synthetic pyrrolecarboxamides exert a wide range of pharmacological activities; for example, they show antimalarial activity,[16] bind to dopamine-D2-like receptors,[17] inhibit the enzymes MAO-A and MAO-B,[18] inhibit tyrosine kinase,[19] or show growth hormone secretagogue agonist activity[20] or modulate protein kinase activity.[21] The calcium salt of atorvastatin (**7**, Lipitor, Pfizer, 1997, hypolipidemic activity) became a blockbuster drug.

Results and Discussion

Library Design. To obtain a defined skeleton in a few steps, a complexity generating reaction or reaction sequence

* To whom correspondence should be addressed. E-mails: stw15@pitt.edu, kbrummon@pitt.edu.

† University of Pittsburgh Center for Chemical Methodologies and Library Development.

‡ Department of Chemistry, University of Pittsburgh.

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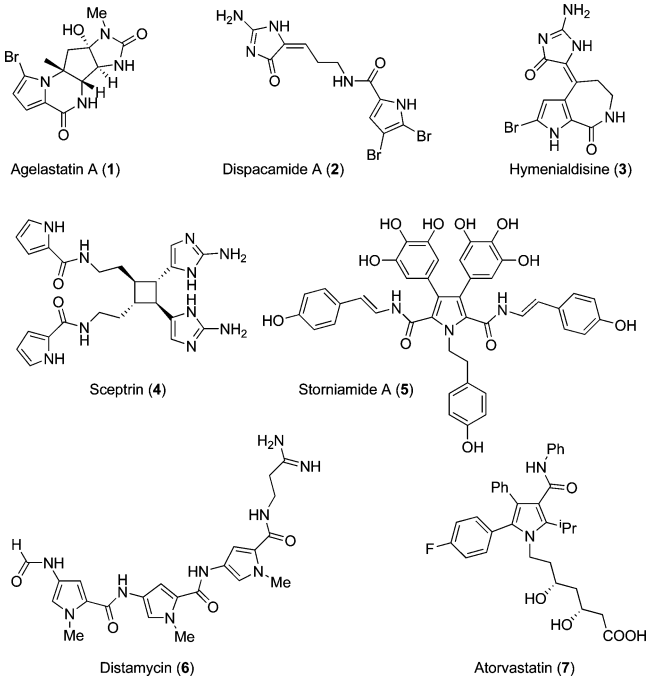


Figure 1. Examples of bioactive pyrrolecarboxamides.

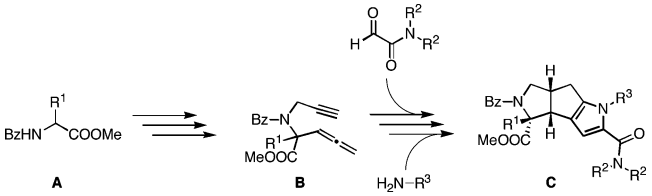


Figure 2. Forward synthetic analysis of the title compounds **C**.

is needed. We recently developed such a sequence consisting of a Pauson−Khand/Stetter/Paal−Knorr reaction that allows us to approach the tricyclic pyrrolecarboxamides **C** in only four steps from the allenynes **B**, which are derived from the protected amino acid esters **A** (Figure 2).[7a,22] Installing appendages onto the core unit by using appropriate building blocks leads to a set of compounds with diverse physicochemical properties: the discovery library.

This library has three points of diversity: the amino acid (R^1), the glyoxaldehyde (R^2), and the primary amine (R^3). The first two building blocks were introduced in early stages; therefore, it was decided to work with only three amino acids and two glyoxaldehydes. In our earlier work, we reported that R^1 has to be an aromatic substituent; otherwise, a diastereomer is formed in the Pauson−Khand reaction that does not undergo the Stetter reaction.[7a,22] Therefore, the benzoyl-protected phenylalanine methyl ester derivatives **8**{*1*−*3*} were chosen (Figure 3). The carboxamide functionality was introduced by the two glyoxaldehydes **9**{*1*−*2*}.

To identify subsets for a library with three points of diversity, a reagent-based selection is normally preferred over a product-based selection, because it deals with fewer compounds that have to be compared.[23] In the library reported here, a design was chosen in which the amines **10**{*1*−*41*} that were incorporated in the last step were the major point of diversity. This approach allowed a product-based design of the library without a large number of calculations because the properties of the products were mainly influenced by the amine that was used in the Paal−Knorr reaction.

Hence, a virtual library with 300 α-unsubstituted primary amines that are commercially available from four major suppliers was created.[24] This set was analyzed according to the following properties: (1) chemoselective reaction, (2) regioselective reaction, (3) avoidance of a diastereoselective mixture, (4) molecular weight, (5) clogP, (6) functional group diversity, and (7) cost.

A few exceptions were made when the amines showed interesting properties, for example, **10**{*7*}. After examination of these properties, a very diverse set of 41 primary amines **10**{*1*−*41*} was obtained. This set contained aliphatic, benzylic, heteroaromatic, and phenethylamines bearing hydroxyl groups, secondary amines, ureas, esters, nitro groups, ethers, halides, thioethers, and sulfonyl groups.

Library Synthesis. As described previously,[7a,22] the benzoyl-protected amino acid methyl esters **8**{*1*−*3*} were hydrolyzed and esterified with propargyl alcohol to give the propargyl esters **11**{*1*−*3*} in yields of 42−95% (Scheme 1). Applying the protocol developed by Castelhano and Krantz,[25] esters **11**{*1*−*3*} were then converted by a Claisen rearrangement to allenes **12**{*1*−*3*} that were obtained in yields of 55−70%. Propargylation gave eneynes **13**{*1*−*3*} in yields of 80−85%. In the next step, the three key intermediates **14**{*1*−*3*} were prepared by a Pauson−Khand reaction in the presence of $Mo(CO)_6$ (40−50% isolated yield of the major diastereomer). Intermediates **14**{*1*−*3*} were obtained in a diastereomeric ratio of 3:1, and the minor diastereomer was removed by chromatography. The relative stereochemistry of **14**{*1*}, the major diastereomer in the reaction of **13**{*1*}, was determined by single-crystal X-ray crystallography. The stereochemistry of **14**{*2*} and **14**{*3*} is based on similarity of the ^{1}H and ^{13}C NMR spectra with those of **14**{*1*}.[22]

In the following Stetter reaction, the three cyclopentenones **14**{*1*−*3*} were converted to the six α,*β*-unsaturated 1,4-diketones **15**{*1*−*3*} using 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride as catalyst. In this step, the second building block **9**{*1*−*2*} was incorporated, and the six reactions were performed in parallel in a Radley's carousel reaction station. Heating the reaction mixtures to 70 °C for 20 min gave **15**{*1*−*3,1*−*2*} in yields ranging from 75 to 93%. Unfortunately, the bicyclic systems **15**{*1*−*3,1*−*2*} had to be purified by chromatography twice, since traces of impurities poisoned the palladium catalyst in the next step. Compounds **15**{*1*−*3,1*−*2*} were obtained as single diastereomers, as observed by ^{1}H NMR and LC analysis. The relative stereochemistry was assigned by comparison with a compound previously prepared and characterized by single-crystal X-ray crystallography.[22] Next, reduction of the double bond gave the 1,4-diketones **16**{*1*−*3,1*−*2*} in yields of 88−99% as single diastereomers in quantities of 1.0 g (**16**{*1,1*−*2*}) or 2.0 g (***16***{*2,1*−*2*} and **16**{*3,1*−*2*}). Compounds **16**{*1*−*3,1*−*2*} were used in the following Paal−Knorr reaction without further purification.

While optimizing the protocol for the Paal−Knorr reaction, it was noticed that this reaction is not only 3−5 times faster in the microwave, as anticipated, but that it also gave higher yields when performed under microwave irradiation. The

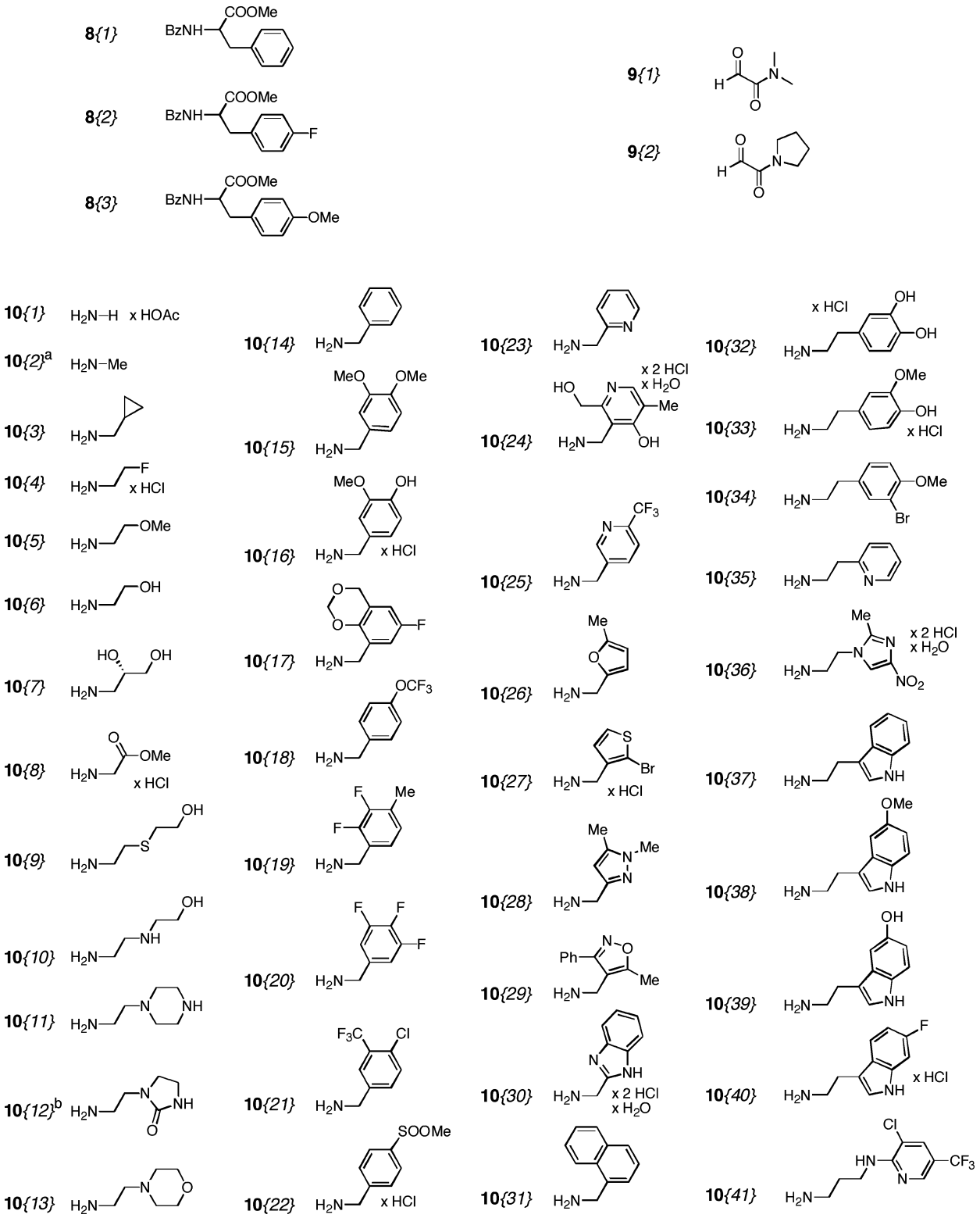
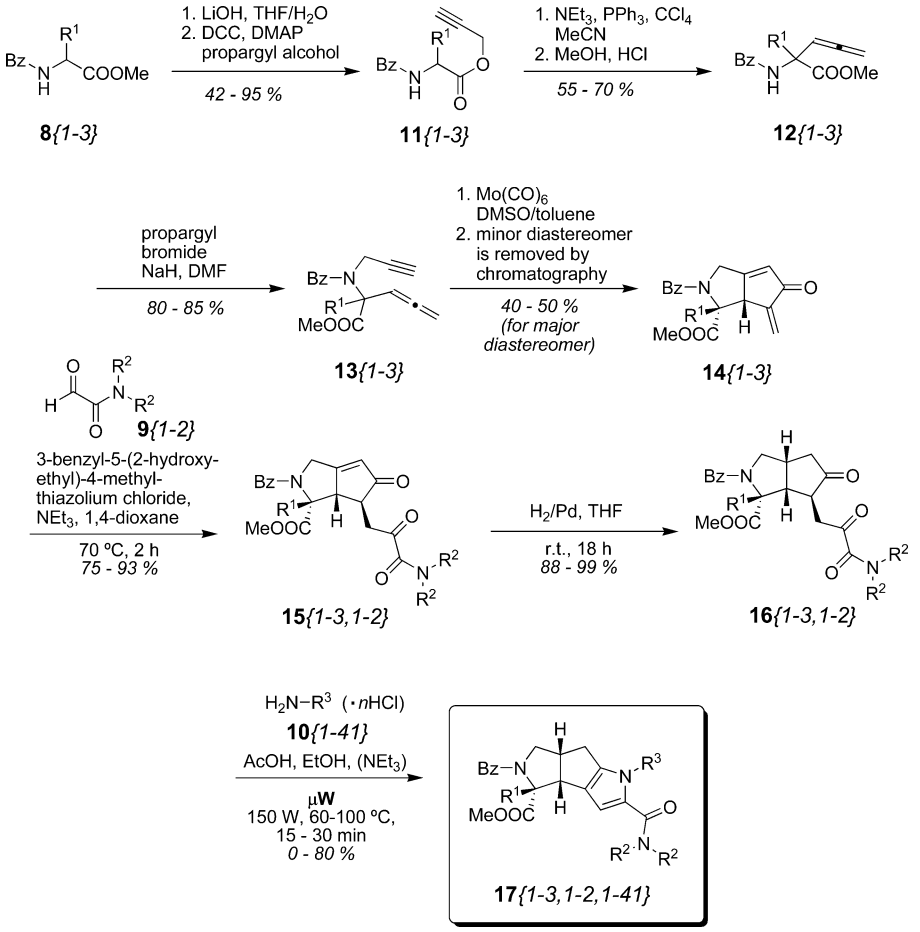


Figure 3. Diversity elements **8**{*1*−*3*} for R^1, **9**{*1*−*2*} for R^2, and **10**{*1*−*41*} for R^3: (a) 33% in ethanol, (b) 50% in 2-propanol.

higher yields are presumably due to the shorter reaction times and less thermal decomposition.[26] In preliminary studies, the reactivity of several amines was compared, and it was found that most reactions were complete by TLC analysis within 10 min when irradiated in an automated Emrys Optimizer single mode microwave reactor at 80 °C. To ensure complete reaction, every reaction mixture was irradiated for 15 min at 80 °C. In a typical example, the 1,4-diketone **16** (0.06 mmol) was dissolved in ethanol (600 μL) and acetic acid (60 μL) in an Emrys Process Vial. The corresponding amine (3 equiv) was added, and the microwave tube was sealed and irradiated with an initial power of 150 W at 80 °C for 15 min. When the hydrochloride ammonium salts of the amine were used (Figure 3), triethylamine was added prior to irradiation, and the reaction times were found to be longer; therefore, the irradiation time was doubled. In the case of

Scheme 1. Synthesis Route to the Tricyclic Pyrrolecarboxamides **17**



very volatile amines, such as **10**{*1*}, **10**{*2*}, and **10**{*3*}, the temperature was reduced to 60 °C, and the reaction time was extended to 30 min. Five equivalents of amine had to be used in the cases of **10**{*1*} and **10**{*3*}, and 10 equiv in the case of **10**{*2*}. The least reactive amine was **10**{*36*}, which required a temperature of 100 °C and irradiation for 30 min.

Pyrroles **17**{*1−3,1−2,1−41*} were synthesized in batches of 10 or 20. After the reaction was complete, the microwave tubes were opened, and all volatile components were removed within 10 min using a stream of argon in a Radley's GreenHouse blowdown evaporator, which fits up to 24 microwave tubes. The crude mixtures were loaded with methylene chloride (500 μL) onto 4-g RediSep disposable flash columns, and 10 reactions were purified by automated parallel chromatography using an ISCO Optix 10 system with a gradient of hexanes and ethyl acetate. It proved to be advantageous to group 10 reactions with amines of a similar polarity together because the amine had the strongest effect on the polarity of the final product. For the reaction mixtures **17**{*1−3,1−2,10*} and **17**{*1−3,1−2,11*}, which bear a secondary amine, reversed-phase (C-18) RediSep columns were used, and they were eluted with acetonitrile and water.

Applying this procedure, 210 reactions were carried out, of a 246 possible reactions (array 3 × 2 × 41 = 246). Because of limited amounts of **16**{*1−3,1−2*} that were available, not all 246 compounds could be prepared, but to obtain a sufficient amount of every library member for a broad biological evaluation, all reactions were carried out on the same scale. The tricyclic pyrrole-2-carboxamides **17**{*1−3,1−2,1−41*} were isolated with an average yield of 53% (Table 1) and an average amount of 14.7 mg.

Purity Analysis. To pass the purity criteria for our compound collection, library members must be at least 85% pure at 210, 220, and 240 nm, and the structure is confirmed by MS or ^{1}H NMR spectroscopy. All 210 tricyclic pyrroles were analyzed by reversed-phase HPLC with UV and MS detection using a Thermo Finnigan Surveyor LC and LCQ Advantage MS system before purification by HPLC (Table 1 and Supporting Information).[27] One hundred and twelve library members met these requirements. Twenty-four compounds were analyzed by ^{1}H NMR, since the molecular mass was not observed. Seventy-four library members showed the correct molecular mass, but the purity was lower than 85% for at least one of the three wavelengths, so these were purified on an automated HPLC system (Gilson). After purification, they were reanalyzed by LC/MS, and 66 compounds passed the purity criteria (Figure 4). Altogether, 178 library members were added to our compound collection, with an average purity of 94% at 210, 220, and 240 nm. Thirty-two reactions did not lead to the desired pyrroles or gave purities below 85%, even after purification by HPLC (Table 1). It has to be assumed that the differences in yields and purities are due to the fact that the applied protocol could only be optimized for a few representative amines but not for every single reaction. 2-(2-Aminoethylamino)ethanol (**10**{*10*}) and 1-(2-aminoethyl)piperazine (**10**{*11*}) were the

Table 1. Library Matrix for the Tricyclic Pyrrolecarboxamides **17**

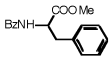
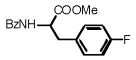
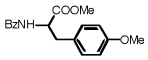
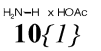
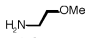
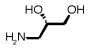
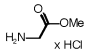
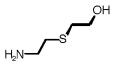
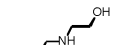
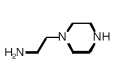
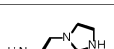
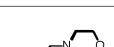
compound isolated yield[a] (average purity)[b]	 **8**{*1*}		 **8**{*2*}		 **8**{*3*}	
	 **9**{*1*}	 **9**{*2*}	 **9**{*1*}	 **9**{*2*}	 **9**{*1*}	 **9**{*2*}
 **10**{*1*}	**17**{*1,1,1*} 63 (100)	**17**{*1,2,1*} 66 (100)	**17**{*2,1,1*} 58 (87)	d	**17**{*3,1,1*} 78 (100)	**17**{*3,2,1*} 43 (100)
 **10**{*2*}	**17**{*1,1,2*} 29 (87)	**17**{*1,2,2*} 40 (94)	**17**{*2,1,2*} 30 (87)	**17**{*2,2,2*} 36 (88)	**17**{*3,1,2*} 29 (97)[c]	d
 **10**{*3*}	-	**17**{*1,2,3*} 47 (98)	**17**{*2,1,3*} 57 (100)[c]	**17**{*2,2,3*} 80 (92)[c]	-	-
 **10**{*4*}	d	-	**17**{*2,1,4*} 70 (92)[c]	**17**{*2,2,4*} 48 (89)	**17**{*3,1,4*} 86 (100)[c]	**17**{*3,2,4*} 39 (96)
 **10**{*5*}	-	**17**{*1,2,5*} 70 (100)	**17**{*2,1,5*} 61 (100)[c]	**17**{*2,2,5*} 76 (92)	**17**{*3,1,5*} 69 (87)	**17**{*3,2,5*} 61 (99)
 **10**{*6*}	**17**{*1,1,6*} 58 (100)	**17**{*1,2,6*} 56 (100)	**17**{*2,1,6*} 72 (100)	**17**{*2,2,6*} 67 (95)	**17**{*3,1,6*} 50 (100)	**17**{*3,2,6*} 62 (94)
 **10**{*7*}	**17**{*1,1,7*} 46 (93)	**17**{*1,2,7*} 46 (100)	**17**{*2,1,7*} 46 (100)	**17**{*2,2,7*} 64 (100)	**17**{*3,1,7*} 62 (100)	**17**{*3,2,7*} 48 (100)
 **10**{*8*}	**17**{*1,1,8*} 31 (94)[c]	**17**{*1,2,8*} 56 (100)	**17**{*2,1,8*} 72 (98)[c]	**17**{*2,2,8*} 73 (89)	**17**{*3,1,8*} 76 (99)[c]	**17**{*3,2,8*} 34 (95)[c]
 **10**{*9*}	**17**{*1,1,9*} 38 (100)[c]	**17**{*1,2,9*} 55 (91)	**17**{*2,1,9*} 49 (89)	**17**{*2,2,9*} 62 (92)	**17**{*3,1,9*} 57 (88)	**17**{*3,2,9*} 47 (100)
 **10**{*10*}	d	d	–	d	–	d
 **10**{*11*}	d	d	–	d	–	d
 **10**{*12*}	**17**{*1,1,12*} 54 (87)[c]		-	**17**{*2,2,12*} 40 (86)	**17**{*3,1,12*} 58 (93)[c]	**17**{*3,2,12*} 63 (86)
 **10**{*13*}	-	d	**17**{*2,1,13*} 50 (96)	-	d	**17**{*3,2,13*} 35 (100)
 **10**{*14*}	**17**{*1,1,14*} 53 (98)[c]	**17**{*1,2,14*} 77 (94)	**17**{*2,1,14*} 56 (87)	**17**{*2,2,14*} 74 (96)[c]	**17**{*3,1,14*} 57 (98)[c]	**17**{*3,2,14*} 57 (93)

Table 1. (Continued)

compound isolated yield[a] (average purity)[b]	**8**{*1*}		**8**{*2*}		**8**{*3*}	
	9{*1*}	**9**{*2*}	**9**{*1*}	**9**{*2*}	**9**{*1*}	**9**{*2*}
10{*15*}	**17**{*1,1,15*} 39 (97)[c]	**17**{*1,2,15*} 50 (96)	**17**{*2,1,15*} 67 (95)[c]	-	**17**{*3,1,15*} 51 (98)[c]	**17**{*3,2,15*} 55 (100)
10{*16*}	**17**{*1,1,16*} 31 (89)	**17**{*1,2,16*} 22 (98)	**17**{*2,1,16*} 64 (87)	-	**17**{*3,1,16*} 64 (91)[c]	**17**{*3,2,16*} 48 (100)
10{*17*}		**17**{*1,2,17*} 66 (100)[c]	**17**{*2,1,17*} 80 (98)[c]	**17**{*2,2,17*} 33 (98)[c]	d	**17**{*3,2,17*} 56 (92)[c]
10{*18*}		**17**{*1,2,18*} 57 (96)[c]	**17**{*2,1,18*} 70 (86)	**17**{*2,2,18*} 64 (95)[c]	**17**{*3,1,18*} 67 (98)[c]	**17**{*3,2,18*} 31 (89)[c]
10{*19*}	**17**{*1,1,19*} 68 (100)	-	**17**{*2,1,19*} 72 (98)[c]	**17**{*2,2,19*} 66 (97)[c]	**17**{*3,1,19*} 54 (98)[c]	**17**{*3,2,19*} 73 (91)
10{*20*}	**17**{*1,1,20*} 47 (95)[c]	-	**17**{*2,1,20*} 94 (96)[c]	-	**17**{*3,1,20*} 63 (93)[c]	**17**{*3,2,20*} 66 (93)[c]
10{*21*}	**17**{*1,1,21*} 45 (99)	d	**17**{*2,1,21*} 67 (96)[c]	**17**{*2,2,21*} 73 (88)[c]	**17**{*3,1,21*} 81 (96)[c]	**17**{*3,2,21*} 64 (95)
10{*22*}	**17**{*1,1,22*} 53 (100)[c]	**17**{*1,2,22*} 63 (98)	**17**{*2,1,22*} 64 (87)	**17**{*2,2,22*} 61 (100)[c]	**17**{*3,1,22*} 60 (94)[c]	**17**{*3,2,22*} 66 (88)
10{*23*}	**17**{*1,1,23*} 54 (100)	**17**{*1,2,23*} 71 (99)	**17**{*2,1,23*} 59 (97)	**17**{*2,2,23*} 68 (95)	**17**{*3,1,23*} 30 (88)	**17**{*3,2,23*} 46 (99)
10{*24*}	**17**{*1,1,24*} 51 (100)	**17**{*1,2,24*} 54 (100)	**17**{*2,1,24*} 66 (100)	**17**{*2,2,24*} 67 (100)	**17**{*3,1,24*} 55 (100)	**17**{*3,2,24*} 48 (100)
10{*25*}	**17**{*1,1,25*} 28 (97)	**17**{*1,2,25*} 64 (97)	**17**{*2,1,25*} 69 (91)	**17**{*2,2,25*} 62 (87)	**17**{*3,1,25*} 30 (92)[c]	**17**{*3,2,25*} 26 (97)[c]
10{*26*}	**17**{*1,1,26*} 22 (95)[c]	**17**{*1,2,26*} 62 (96)	**17**{*2,1,26*} 71 (88)	**17**{*2,2,26*} 75 (89)	**17**{*3,1,26*} 71 (92)	**17**{*3,2,26*} 28 (100)[c]
10{*27*}	**17**{*1,1,27*} 73 (91)[c]	**17**{*1,2,27*} 54 (89)	**17**{*2,1,27*} 65 (98)[c]	d	**17**{*3,1,27*} 43 (97)[c]	**17**{*3,2,27*} 75 (91)[c]
10{*28*}	**17**{*1,1,28*} 51 (94)	-	**17**{*2,1,28*} 63 (98)	**17**{*2,2,28*} 62 (98)	**17**{*3,1,28*} 41 (100)	**17**{*3,2,28*} 59 (100)

Table 1. (Continued)

compound isolated yield[a] (average purity)[b]	**8**{*1*}		**8**{*2*}		**8**{*3*}	
	9{*1*}	**9**{*2*}	**9**{*1*}	**9**{*2*}	**9**{*1*}	**9**{*2*}
10{*29*}	**17**{*1,1,29*} 56 (89)[c]	-	d	-	d	**17**{*3,2,29*} 31 (89)[c]
10{*30*}	**17**{*1,1,30*} 39 (87)	**17**{*1,2,30*} 42 (98)	**17**{*2,1,30*} 57 (93)	-	**17**{*3,1,30*} 38 (89)	**17**{*3,2,30*} 62 (100)
10{*31*}	-	**17**{*1,2,31*} 61 (94)[c]	**17**{*2,1,31*} 47 (97)[c]	**17**{*2,2,31*} 63 (90)[c]	**17**{*3,1,31*} 68 (90)[c]	**17**{*3,2,31*} 26 (96)[c]
10{*32*}	d	-	**17**{*2,1,32*} 23 (89)	**17**{*2,2,32*} 47 (96)	d	**17**{*3,2,32*} 48 (89)
10{*33*}	**17**{*1,1,33*} 54 (94)[c]	-	**17**{*2,1,33*} 17 (91)[c]	-	**17**{*3,1,33*} 35 (86)	**17**{*3,2,33*} 46 (93)[c]
10{*34*}	-	-	**17**{*2,1,34*} 54 (91)	**17**{*2,2,34*} 61 (95)	**17**{*3,1,34*} 53 (88)	**17**{*3,2,34*} 64 (97)[c]
10{*35*}	-	**17**{*1,2,35*} 49 (95)	**17**{*2,1,35*} 49 (93)	**17**{*2,2,35*} 52 (90)	**17**{*3,1,35*} 35 (94)	**17**{*3,2,35*} 68 (98)
10{*36*}	**17**{*1,1,36*} 20 (95)[c]	**17**{*1,2,36*} 37 (92)	**17**{*2,1,36*} 21 (93)[c]	**17**{*2,2,36*} 56 (96)	-	**17**{*3,2,36*} 41 (98)
10{*37*}	d	-	d	**17**{*2,2,37*} 38 (95)[c]	d	**17**{*3,2,37*} 62 (92)
10{*38*}	d	-	**17**{*2,1,38*} 19 (88)[c]	**17**{*2,2,38*} 54 (96)	d	**17**{*3,2,38*} 57 (91)
10{*39*}	**17**{*1,1,39*} 34 (87)	-	-	-	**17**{*3,1,39*} 27 (89)[c]	**17**{*3,2,39*} 45 (92)
10{*40*}	d	-	d	**17**{*2,2,40*} 22 (92)	d	**17**{*3,2,40*} 29 (97)
10{*41*}	d	-	**17**{*2,1,41*} 60 (94)	**17**{*2,2,41*} 56 (86)	d	**17**{*3,2,41*} 59 (86)

[a] Isolated yield for the last step after parallel chromatography (ISCO Optix 10 system). [b] Purity was determined by HPLC/MS on an Alltech Varian column, 1 mL/min, 35% H_2O/MeOH (95/5), 15% MeOH, 50% MeCN. [c] Compound was repurified on a serial HPLC system (Gilson) with a Varian C-18 column (250 × 21.4 mm), 15 mL/min, 15-min run time, 70−95% MeOH/MeCN (1/3), 30−5% H_2O. [d] Reaction failed because no molecular mass was found or the purity after repurification was lower than 85% at 210, 220, or 240 nm.

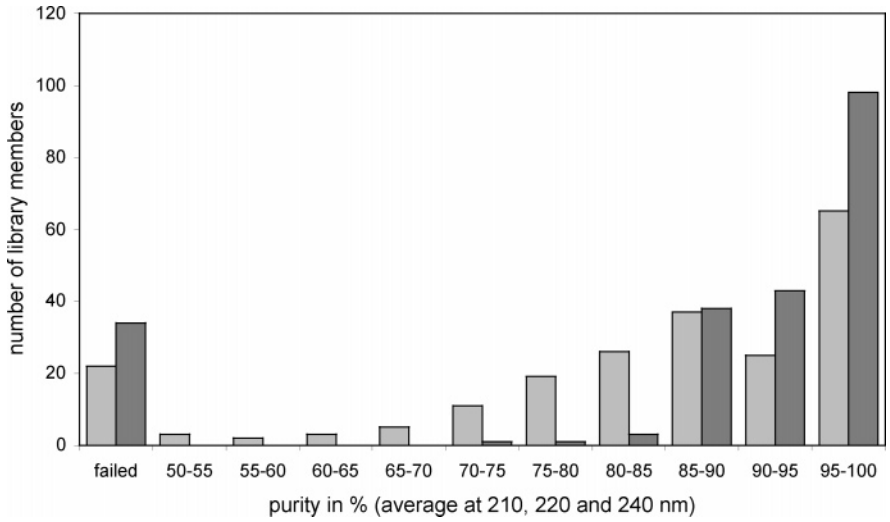


Figure 4. Purity of the 178 library members before purification by HPLC (light gray) and after purification by HPLC (dark gray); if the purity was lower than 50% or no molecular mass was detected by LC/MS analysis, the reaction was classified as "failed".

Table 2. Computational Analysis of Molecular Descriptors for the Pyrroles **17**{*1−3,1−2,1−41*} Using QikProp 2.1[30]

parameter	range for 95% of all drugs	av ± SD for 179 pyrroles	no. compds out of range
mol mass (g/mol)	130−725	620 ± 57	5
mol vol (Å^3)[a]	500−2000	1800 ± 100	3
FISA (Å^2)[b]	7−330	64 ± 33	0
no. rotatable bonds[c]	0−15	8.3 ± 1.5	0
no. hydrogen bond donors[d]	0−6	0.5 ± 0.7	0
no. hydrogen bond acceptors[e]	2−20	9.6 ± 1.3	0
logP (octanol/water)	−2 to 6	6.6 ± 1.3	119
logS (aqueous solubility)	−6 to 0.5	−7.4 ± 1.5	149
log Khsa (serum protein binding)	−1.5 to 1.2	1.2 ± 0.5	94
Caco permeability (nm/s)	<25 poor, >500 great	3200 ± 2100	0
MDCK permeability (nm/s)	<25 poor, >500 great	3400 ± 3300	0
no. primary metabolites	1−8	5.0 ± 1.3	6

[a] Total solvent accessible volume using a probe with a 1.4-Å radius. [b] Hydrophilic component of the solvent accessible surface area (SASA), using a probe with a 1.4-Å radius (SASA on N, O, and attached H). [c] Nontrivial (not CX_3), nonhindered (not alkene, amide, small ring). [d] Estimated number of hydrogen bonds that would be donated by the solute from water molecules in an aqueous solution. [e] Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution.

only amines that gave completely failed reactions. Both bear an additional secondary amine functionality, and it was assumed that this led to unselective reactions.

All library members **17**{*1−3,1−2,1−41*} were analyzed by LC/MS, 34 library members (20%) were analyzed by ^{1}H NMR, and 10 library members (5%) were fully characterized by ^{1}H, ^{13}C, ^{19}F NMR, IR, MS, HRMS, and mp. These compounds are all currently stored as DMSO solution (20 mg/mL) at −78 °C.

Stability studies[28] are part of the physicochemical profiling of a compound library and were performed on selected library members before synthesizing the final library. To test the stability of the tricyclic pyrrole-2-carboxamides in DMSO, **17**{*1,2,14*} was dissolved in DMSO-d_6 and stored at room temperature in a sealed NMR tube. 4-Phthalic acid ethyl ester was used as internal standard, and ^{1}H NMR monitoring indicated no decomposition over a period of 60 days. During this time, the NMR tube was sealed with a rubber septum and kept on the laboratory benchtop without specific care being taken to exclude air or light. In a second experiment, **17**{*3,2,16*}, dissolved in dry DMSO (20 mg/mL) and sealed with a silicon septum, was submitted to 30 freezing (−78 °C) and thawing (room temperature) cycles (one cycle/day), and the purity was checked by HPLC/MS with biphenyl as internal standard. Again, no decomposition was observed.

Computational Analysis. 3-D structures of all library members **17**{*1−3,1−2,1−41*} were built and minimized using the MM2 force field in MacroModel 8.6. The physicochemical profiling of the 178 library members was analyzed computationally using QikProp 2.1.[29] (Table 2). Most of the molecular descriptors, such as molecular weight, molecular volume, the hydrophilic component of the solvent accessible surface area (FISA), number of rotatable bonds, number of hydrogen bond donors and acceptors, number of primary metabolites, and Caco and MDCK permeability were within the range of 95% of current drugs. In contrast, several pyrroles **17**{*1−3,1−2,1−41*} had logP and logS values outside this range; they are more lipophilic than most drugs. Another concern was the serum protein binding (log K_{hsa}). The pyrroles were predicted to bind very well to human serum albumin, and this could reduce the biological activity.

An important factor for diversity in a discovery library and especially for a library of tool-like compounds is the distribution of those physicochemical parameters. In Figure 5, the distribution for the classical "rule of five" parameters, the number of rotatable bonds, and FISA is shown. Molecular weight and logP show a very broad distribution what is

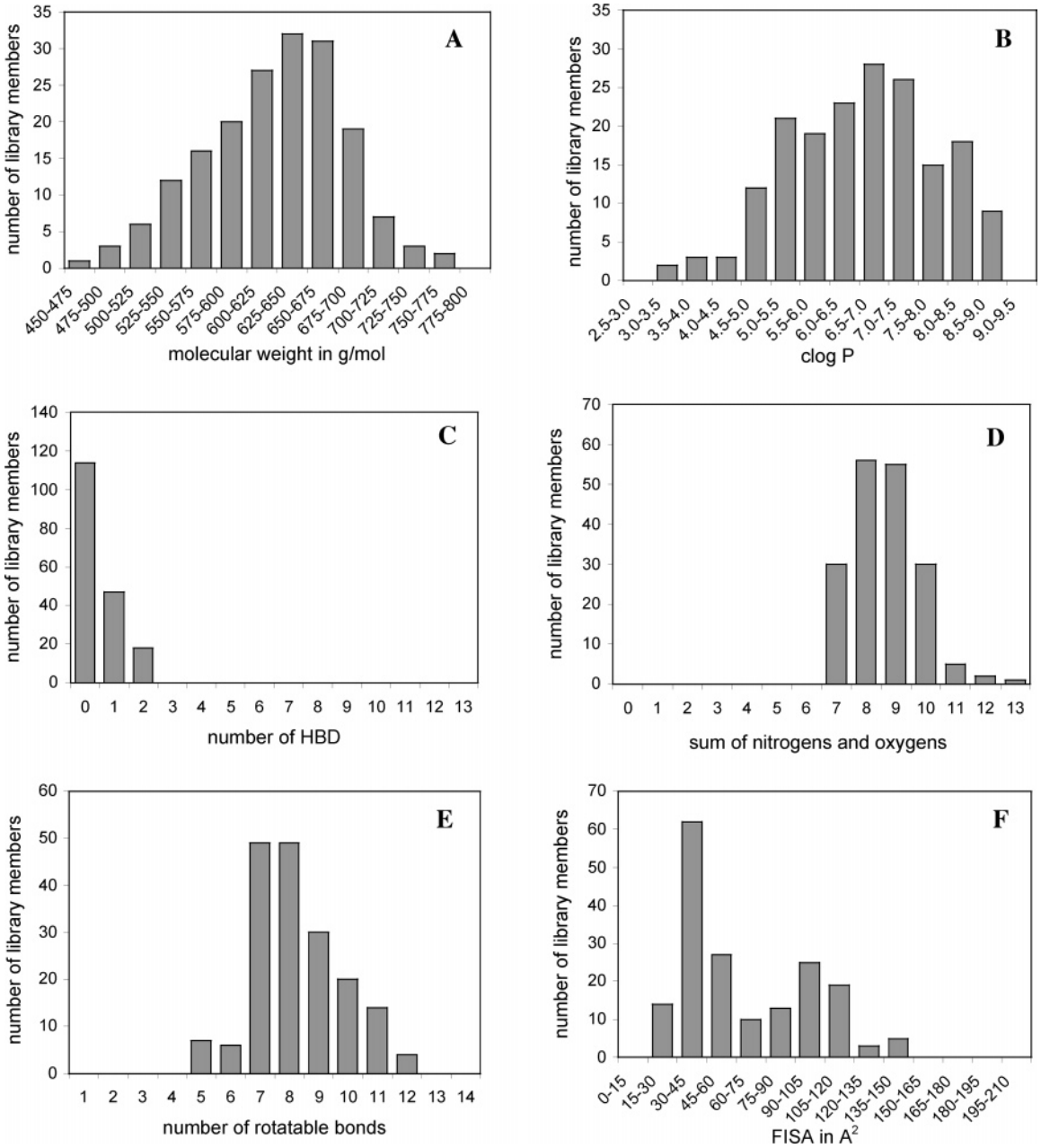


Figure 5. Distribution for the rule of five parameters molecular weight (A), log of the octanol/water partition coefficient (logP) (B), number of hydrogen donor bonds (HBD) (C), sum of nitrogen and oxygen atoms (D), the number of rotatable bonds (E), and the hydrophilic component of the solvent accessible surface area (FISA) (F); calculated for the 178 pyrroles **17**{*1−3,1−2,1−41*} using QikProp 2.1.[30]

essential for a diverse library. The average molecular weight is 620 g/mol, with a range from 472 to 763 g/mol. The logP distribution is even broader with a minimum of 3.3 and a maximum of 8.9, the average being 6.6. The average number of hydrogen bond acceptors is 9.6 (range from 8 to 13.25), and the average number of hydrogen bond donors was 0.5 (range from 0 to 2). The number of rotatable bonds ranges from 5 to 12, the average being 8.3. The mean of the FISA is 64.3 Å^2, ranging from 15.4 to 153.1 Å^2.

Conclusions

We have developed a method for a midsize, solution-phase library of tricyclic pyrrole-2-carboxamides. The application of parallel synthesis methods and automated purification techniques allowed us to prepare this library in only 2 months. One hundred and seventy-eight library members were obtained with an average purity of 94% and an average amount of 14 mg. They were added to our compound collection and are tested currently against a variety of different targets. Preliminary biological data show promising potential, and detailed studies are ongoing.

Experimental Section

General. All air- and moisture-sensitive reactions were performed under an argon atmosphere. THF was dried by distillation from Na/benzophenone, and 1,4-dioxane was used as obtained (quality "extra dry" from Acros). Other solvents or reagents were used without further purification. NMR spectra were recorded in $CDCl_3$ (298 K) at either 300.1 (^{1}H), 75.5 (^{13}C) or 282.3 MHz (^{19}F) using a Bruker Avance 300 with XWIN NMR software. Chemical shifts (δ) are reported in parts per million (ppm). Tetramethylsilane (^{1}H), chloro-

trifluoromethane (^{19}F), or chloroform-*d* (^{13}C) was used as internal standards. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = dublet, t = triplet, q = quartet, quin = quintet, m = multiplet, bs = broad singlet, app = apparent), integration, and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FTIR E.S.P. spectrometer. Mass spectra were obtained on a Waters QToF API US. Melting points were obtained using a heating rate of 2 °C/min on a MelTemp melting point apparatus with digital temperature reading and are reported uncorrected. All microwave-assisted reactions were performed in an Emrys Optimizer microwave reactor (Biotage) using 0.5−2-mL Emrys process vials. The synthesis of the Pauson−Khand products **14**{*1−3,1−2*} was described previously.[22]

General Procedure for the Stetter Reaction. The conversions of the cyclopentenones **14** to the 1,4-diketones **15** were performed in parallel in a Radley's carousel reaction station on a 1-g scale under an argon atmosphere. To a solution of cyclopentenone **14**{*1*}, **14**{*2*}, or **14**{*3*} (1.00 g, 1 equiv) in dry 1,4-dioxane (15 mL) at room temperature was added glyoxaldehyde **9**{*1*} or **9**{*2*} (5 equiv) and triethylamine (3 equiv), followed by 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.3 equiv). The reaction mixtures were heated to 70 °C for 20 min, then cooled to room temperature, poured into water (50 mL), and extracted with diethyl ether (3 × 50 mL). The organic layers were combined, washed with brine (2 × 50 mL), dried over magnesium sulfate, and concentrated in vacuo. The residues were purified by parallel chromatography using an ISCO Optix 10 chromatography system (40-g RediSep cartridges, 40 mL/min, gradient hexanes/ethyl acetate 60/40 to 20/80). Two chromatographies were necessary to remove impurities that otherwise poisoned the palladium catalyst in the following step. The products **15**{*1−3,1−2*} were obtained as colorless crystals in 75−93% yield.

***rac*-(1*R*,6*S*,6a*S*)-2-Benzoyl-6-(2,3-dioxo-3-pyrrolidin-1-ylpropyl)-1-(4-fluorobenzyl)-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Methyl Ester (15{*2,2*}).** mp 92−94 °C; IR 2953, 2883, 1716, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53−7.43 (m, 5H), 7.19 (dd, 2H, J = 8.5, 5.5 Hz), 7.01 (app t, 2H, J = 8.6 Hz), 5.93 (s, 1H), 4.28 (d, 1H, J = 15.9 Hz), 4.14 (d, 1H, J = 14.1 Hz), 4.09 (d, 1H, J = 15.3 Hz), 3.81 (s, 3H), 3.63 (app t, 2H, J = 6.4 Hz), 3.57 (app t, 2H, J = 6.4 Hz), 3.50 (dd, 1H, J = 18.9, 5.0 Hz), 3.40 (m, 1H), 3.31 (dd, 1H, J = 18.8, 5.3 Hz), 3.21 (d, 1H, J = 14.5 Hz), 2.45 (app q, 1H, J = 4.7 Hz), 2.02−1.88 (m, 4H); ^{13}C ($CDCl_3$) δ 207.1, 198.2, 173.8, 171.4, 171.1, 162.2, 162.1 (d, J_{CF} = 244.7 Hz), 135.6, 132.6 (d, J_{CF} = 7.8 Hz), 131.3 (d, J_{CF} = 3.3 Hz), 131.1, 128.7, 127.1, 123.5, 115.3 (d, J_{CF} = 21.0 Hz), 71.6, 53.3, 52.5, 51.7, 47.2, 46.3, 46.0, 37.7, 36.4, 26.2, 23.6; ^{19}F NMR ($CDCl_3$) δ −115.7 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 555 (M^+ + Na, 100), 533 (M^+ + H, 17), 473 (17); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{29}N_2O_6FNa$ 555.1907, found 555.1918.

15{*1,1*} and **15**{*1,2*} were previously described;[22] **15**{*2,1*}, **15**{*3,1*}, and **15**{*3,2*} are described in the Supporting Information.

General Procedure for the Hydrogenation. Each of the diketones **15**{*1−3,1−2*} (1 equiv) was dissolved in THF (10 mL), and Pd/C (10 wt %, 0.15 equiv) was added at room temperature. The flask was immersed into a warm water bath (40 °C), and the atmosphere was replaced three times with hydrogen. After vigorous stirring for 16 h at room temperature, the suspension was filtered over 4-cm Celite 545 and washed with ethyl acetate (100 mL) and dichloromethane (100 mL). Evaporation of the solvents gave the products **16**{*1−3,1−2*} as colorless crystals in 88−99% yield. The 1,4-diketones **16**{*1−3,1−2*} were used in the Paal−Knorr reaction without further purification.

***rac*-(1*R*,3a*S*,6*S*,6a*R*)-2-Benzoyl-6-(2,3-dioxo-3-pyrrolidin-1-ylpropyl)-1-(4-fluorobenzyl)-5-oxooctahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Methyl Ester (16{*2,2*}).** mp 196−198 °C; IR 2979, 2959, 1738, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48−7.43 (m, 5H), 7.23 (dd, 2H, J = 8.7, 5.5 Hz), 7.04 (app t, 2H, J = 8.7 Hz), 4.15 (d, 1H, J = 14.0 Hz), 3.86 (s, 3H), 3.65 (app t, 2H, J = 6.6 Hz), 3.53 (app t, 2H, J = 6.7 Hz), 3.33 (dd, 1H, J = 10.9, 8.3 Hz), 3.27 (d, 1H, J = 14.4 Hz), 3.24 (dd, 1H, J = 10.8, 9.2 Hz), 3.12−3.08 (m, 2H), 2.90−2.85 (m, 2H), 2.26 (dd, 1H, J = 19.3, 8.5 Hz), 2.08 (dd, 1H, J = 19.2, 3.3 Hz), 2.01−1.85 (m, 5H); ^{13}C ($CDCl_3$) δ 216.2, 198.0, 171.2, 169.5, 161.9 (d, J_{CF} = 244.4 Hz), 161.8, 136.6, 132.3 (d, J_{CF} = 3.5 Hz), 131.9 (d, J_{CF} = 7.5 Hz), 129.9, 128.4, 126.1, 115.3 (d, J_{CF} = 21.0 Hz), 72.6, 55.3, 52.6, 52.0, 47.1, 46.3, 45.4, 39.1, 38.6, 38.4, 36.1, 26.2, 23.4; ^{19}F NMR ($CDCl_3$) δ −115.8 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 557 (M^+ + Na, 100), 535 (M^+ + H, 10), 503 (13), 475 (18); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{31}N_2O_6FNa$ 557.2064, found 557.2089.

16{*1,1*} and **16**{*1,2*} were previously described;[22] **16**{*2,1*}, **16**{*3,1*} and **16**{*3,2*} are described in the Supporting Information.

General Procedure for the Paal−Knorr Reaction. The Paal−Knorr reaction was performed in batches of 10 reactions. All reaction mixtures were prepared at the same time, and then the microwave tubes were queued up for irradiation in an automated, single-mode microwave reactor.

To a solution of **16**{*1−3,1−2*} (30 mg, 1 equiv) in ethanol (600 μL) in an Emrys process vial (0.5−2 mL) was added glacial acetic acid (60 μL) and amine **10**{*1−41*} (3 equiv). In the case of hydrochloride ammonium salts, triethylamine (1.5 equiv for monohydrochloride salts, 3.0 equiv for dihydrochloride salts) was added. The microwave tube was sealed without using an inert gas atmosphere and irradiated in the microwave at 80 °C for 15 min (in the case of hydrochloride ammonium salts, for 30 min). An initial power of 150 W was applied. The reactions with **10**{*1*}, **10**{*2*}, and **10**{*3*} were performed at 60 °C for 30 min. Five equivalents of amine had to be used in the case of **10**{*1*} and **10**{*3*}, and 10 equiv in the case of **10**{*2*}. **10**{*36*} required a temperature of 100 °C and irradiation for 30 min. The tube was opened, and completion of the reaction was confirmed by TLC analysis, then all volatile components were removed using a Radley's GreenHouse Blowdown Evaporator.[30] Up to two batches of 10 reactions each were dried within 10 min using a stream of argon. The crude reaction mixtures were loaded in dichloromethane (500 μL)

onto SiO_2 cartridges and purified using an ISCO Optix 10 chromatography system (4-g RediSep cartridge, 18 mL/min). Ten compounds were purified in parallel using customized hexanes/ethyl acetate gradients based on their R_f by TLC. All volatile components were removed in vacuo, and the compounds were dried in a Christ alpha RVC evaporator for 12 h at 40 °C (<0.1 mbar) prior to analysis.

All compounds were analyzed by LC/MS (APCI positive and negative mode, Alltech Prevail C-18, 100 × 4.6 mm, 1 mL/min, 50% MeCN, 35% H_2O/MeOH 95/5, 15% MeOH), 20% of the library members were analyzed by ^{1}H NMR, and 5% were completely characterized (mp, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, MS, HRMS). All compounds that were not more than 85% pure at 210, 220, and 240 nm were further purified by serial automated HPLC (Varian Dynamix C-18, 250 × 21.4 mm, 15 mL/min, 70−95% MeCN/MeOH 3/1, 30−5% H_2O).

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-1-cyclopropylmethyl-4-(4-fluorobenzyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,3*}).** mp 102−104 °C; IR 2949, 2874, 1737, 1640, 1605, 1509, 1446, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48−7.38 (m, 5H), 7.31 (dd, 2H, J = 8.5, 5.6 Hz), 7.04 (app t, 2H, J = 8.6 Hz), 6.18 (s, 1H), 4.20 (d, 1H, J = 13.8 Hz), 4.06 (dd, 1H, J = 14.0, 7.0 Hz), 3.86−3.77 (m, 2H), 3.72−3.55 (m, 4H), 3.62 (s, 3H), 3.38 (d, 1H, J = 13.4 Hz), 3.37 (dd, 1H, J = 10.3, 8.1 Hz), 3.21 (dd, 1H, J = 10.4, 8.6 Hz), 2.59 (dd, 1H, J = 15.1, 7.0 Hz), 2.34 (app quin, 1H, J = 7.5 Hz), 2.26 (d, 1H, J = 15.3 Hz), 2.00−1.88 (m, 4H), 1.13−1.00 (m, 1H), 0.48−0.37 (m, 2H), 0.24−0.16 (m, 2H); ^{13}C ($CDCl_3$) δ 172.2, 169.9, 162.2, 162.0 (d, J_{CF} = 243.8 Hz), 140.2, 137.4, 132.7 (d, J_{CF} = 3.2 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 129.7, 129.5, 128.4, 126.2, 122.1, 115.0 (d, J_{CF} = 20.9 Hz), 108.4, 72.9, 56.3, 52.1 (two resonances overlap), 50.9, 50 (br), 46 (br), 45.5, 38.5, 28.9, 27 (br), 24 (br), 12.6, 3.8, 3.5; ^{19}F NMR ($CDCl_3$) δ −116.5 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 592 (M^+ + Na, 100), 570 (M^+ + H, 25), 510 (32); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{36}N_3O_4FNa$ 592.2588, found 592.2589.

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-4-(4-fluorobenzyl)-1-(2-methoxyethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,5*}).** mp 95−97 °C; IR 2949, 2873, 1734, 1640, 1604, 1509, 1446, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43−7.38 (m, 5H), 7.31 (dd, 2H, J = 8.4, 5.5 Hz), 7.04 (app t, 2H, J = 8.6 Hz), 6.22 (s, 1H), 4.33 (ddd, 1H, J = 13.9, 5.6, 4.2 Hz), 4.20 (d, 1H, J = 13.8 Hz), 4.08 (ddd, 1H, J = 14.0, 6.0, 4.4 Hz), 3.83 (d, 1H, J = 7.4 Hz), 3.68−3.55 (m, 9H), 3.40−3.34 (m, 2H), 3.24−3.20 (m, 4H), 2.60 (dd, 1H, J = 15.3, 7.0 Hz), 2.38−2.29 (m, 1H), 2.27 (d, 1H, J = 15.9 Hz), 1.98−1.89 (m, 4H); ^{13}C ($CDCl_3$) δ 172.0, 169.8, 161.8, 161.8 (d, J_{CF} = 243.9 Hz), 141.6, 137.3, 132.6 (d, J_{CF} = 3.1 Hz), 132.2 (d, J_{CF} = 7.7 Hz), 129.5, 129.1, 128.3, 126.0, 121.8, 114.9 (d, J_{CF} = 20.9 Hz), 108.8, 72.9, 72.8, 58.6, 56.2, 52.1, 51.9, 49.0 (br), 46.9, 46 (br), 45.2, 38.4, 28.6, 27 (br), 24 (br); ^{19}F NMR ($CDCl_3$) δ −116.5 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 596 (M^+ + Na, 100), 574 (M^+ + H, 72), 514 (30); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{36}N_3O_5FNa$ 595.2537, found 596.2544.

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-4-(4-fluorobenzyl)-1-(2-hydroxyethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,6*}).** mp 111−113 °C; IR 2950, 2873, 1735, 1636, 1602, 1509, 1446, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45−7.40 (m, 5H), 7.31 (dd, 2H, J = 8.6, 5.5 Hz), 7.04 (app t, 2H, J = 8.7 Hz), 6.25 (s, 1H), 4.22−4.08 (m, 3H), 3.84−3.76 (m, 3H), 3.73−3.53 (m, 4H), 3.63 (s, 3H), 3.37 (d, 1H, J = 13.7 Hz), 3.36 (dd, 1H, J = 10.6, 8.3 Hz), 3.25 (dd, 1H, J = 10.6, 8.2 Hz), 2.58 (dd, 1H, J = 15.2, 7.1 Hz), 2.41 (app quind, 1H, J = 7.6, 2.2 Hz), 2.26 (dd, 1H, J = 15.3, 1.9 Hz), 2.00−1.90 (m, 4H); ^{13}C ($CDCl_3$) δ 172.1, 169.8, 162.0, 162.0 (d, J_{CF} = 243.9 Hz), 141.2, 137.3, 132.6 (d, J_{CF} = 3.2 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 129.7, 129.7, 128.4, 126.2, 123.0, 115.1 (d, J_{CF} = 20.9 Hz), 109.1, 72.9, 62.5, 56.2, 52.1, 52.0, 49.8 (br), 48.8, 46.7 (br), 45.6, 38.4, 28.5, 26.5 (br), 24.0 (br); ^{19}F NMR ($CDCl_3$) δ −116.3 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 582 (M^+ + Na, 70), 560 (M^+ + H, 100), 528 (20), 500 (42); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{35}N_3O_5F$ 560.2561, found 560.2545.

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-4-(4-fluorobenzyl)-1-methoxycarbonylmethyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,-6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,8*}).** mp 114−116 °C; IR 2952, 2874, 1739, 1640, 1604, 1509, 1447, 1402 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43−7.38 (m, 5H), 7.30 (dd, 2H, J = 8.7, 5.5 Hz), 7.04 (dd, 2H, J = 8.7 Hz), 6.30 (s, 1H), 4.98 (d, 1H, J = 17.3 Hz), 4.67 (d, 1H, J = 17.3 Hz), 4.20 (d, 1H, J = 13.8 Hz), 3.87 (d, 1H, J = 7.6 Hz), 3.74−3.54 (m, 4H), 3.72 (s, 3H), 3.64 (s, 3H), 3.39 (dd, 1H, J = 10.5, 8.3 Hz), 3.38 (d, 1H, J = 13.8 Hz), 3.23 (dd, 1H, J = 10.6, 8.5 Hz), 2.55 (ddd, 1H, J = 15.2, 6.6, 0.8 Hz), 2.39 (app quind, 1H, J = 7.4, 2.0 Hz), 2.20 (dd, 1H, J = 15.3, 1.1 Hz), 1.98−1.88 (m, 4H); ^{13}C ($CDCl_3$) δ 172.1, 170.0, 169.4, 162.0 (d, J_{CF} = 243.9 Hz), 161.1, 141.4, 137.5, 132.7 (d, J_{CF} = 3.1 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 129.7, 129.6, 128.4, 126.2, 122.7, 115.0 (d, J_{CF} = 20.8 Hz), 109.4, 72.9, 56.3, 52.2, 52.2, 52.1, 49 (br), 48.4, 47 (br), 45.4, 38.6, 28.3, 27 (br), 24 (br); ^{19}F NMR ($CDCl_3$) δ −116.4 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m*/*z* (rel intensity) 610 (M^+ + Na, 100), 588 (M^+ + H, 35), 528 (12); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{34}N_3O_6FNa$ 610.2329, found 610.2344.

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-1-benzyl-4-(4-fluorobenzyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17 {*2,2,14*}).** mp 101−103 °C; IR 2949, 2873, 1737, 1640, 1604, 1509, 1446, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43−7.38 (m, 5H), 7.30 (dd, 2H, J = 8.7, 5.5 Hz), 7.26−7.19 (m, 3H), 7.02 (app t, 2H, J = 8.7 Hz), 6.99−6.96 (m, 2H), 6.21 (s, 1H), 5.43 (d, 1H, J = 15.4 Hz), 5.14 (d, 1H, J = 15.4 Hz), 4.20 (d, 1H, J = 13.8 Hz), 3.83 (d, 1H, J = 7.2 Hz), 3.61 (s, 3H), 3.58−3.46 (m, 4H), 3.38 (d, 1H, J = 13.9 Hz), 3.35 (dd, 1H, J = 10.6, 8.1 Hz), 3.17 (dd, 1H, J = 10.4, 8.6 Hz), 2.46−2.28 (m, 2H), 2.13 (d, 1H, J = 14.9 Hz), 1.93−1.77 (m, 4H); ^{13}C ($CDCl_3$) δ 172.1, 170.0, 162.1, 162.0 (d, J_{CF} = 244.0 Hz), 140.8, 138.6, 137.5, 132.8 (d, J_{CF} = 2.9 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 130.1, 129.7, 128.4, 128.4, 127.2, 126.9, 126.2, 122.6, 115.0 (d, J_{CF} = 21.0 Hz), 108.5, 73.0, 56.4, 52.1, 52.0, 49.9, 49 (br), 46 (br), 45.6,

38.6, 28.7, 26 (br), 24 (br); ^{19}F NMR ($CDCl_3$) δ −116.5 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity) 628 (M^+ + Na, 100), 606 (M^+ + H, 84), 546 (30); HRMS (ESI) *m/z* calcd for $C_{37}H_{37}N_3O_4F$ 606.2768, found 606.2788.

***rac*-(3b*R*,4*R*,6a*S*)-5-Benzoyl-4-(4-fluorobenzyl)-1-(4-methanesulfonylbenzyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,22*}).** mp 133−135 °C; IR 2951, 2874, 1737, 1636, 1602, 1509, 1446, 1405, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 8.5 Hz), 7.43−7.36 (m, 5H), 7.30 (dd, 2H, J = 8.7, 5.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.03 (app t, 2H, J = 8.7 Hz), 6.32 (s, 1H), 5.53 (d, 1H, J = 16.2 Hz), 5.29 (d, 1H, J = 16.2 Hz), 4.20 (d, 1H, J = 13.8 Hz), 3.86 (d, 1H, J = 7.4 Hz), 3.69−3.50 (m, 4H), 3.66 (s, 3H), 3.39 (d, 1H, J = 17.4 Hz), 3.38 (dd, 1H, J = 10.6, 7.7 Hz), 3.15 (dd, 1H, J = 10.9, 8.0 Hz), 3.01 (s, 3H), 2.45−2.35 (m, 2H), 2.16−2.08 (m, 1H), 1.95−1.87 (m, 4H); ^{13}C ($CDCl_3$) δ 172.0, 170.0, 162.0 (d, J_{CF} = 243.8 Hz), 161.4, 145.1, 141.1, 139.2, 137.2, 132.5 (d, J_{CF} = 3.0 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 129.8, 129.8, 128.5, 127.6, 127.2, 126.2, 123.2, 115.1 (d, J_{CF} = 20.8 Hz), 109.3, 72.9, 56.3, 52.1, 52.0, 49.7, 49 (br), 46 (br), 45.6, 44.4, 38.5, 28.4, 27 (br), 24 (br); ^{19}F NMR ($CDCl_3$) δ −116.3 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity) 706 (M^+ + Na, 100), 684 (M^+ + H, 23), 413 (23); HRMS (ESI) *m/z* calcd for $C_{38}H_{38}N_3O_6FSNa$ 706.2363, found 706.2391.

***rac*-(4*R*,6a*R*,3b*R*)-5-Benzoyl-4-(4-fluorobenzyl)-1-pyridin-2-ylmethyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,23*}).** mp 105−107 °C; IR 2950, 2872, 1374, 1640, 1604, 1509, 1446, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.46 (ddd, 1H, J = 4.9, 1.7, 0.9 Hz), 7.57 (td, 1H, J = 7.7, 1.8 Hz), 7.43−7.38 (m, 5H), 7.29 (dd, 2H, J = 8.7, 5.4 Hz), 7.11 (ddd, 1H, J = 7.5, 4.9, 1.1 Hz), 7.01 (app t, 2H, J = 8.7 Hz), 6.96 (dt, 1H, J = 7.8, 1.2 Hz), 6.27 (s, 1H), 5.56 (d, 1H, J = 15.8 Hz), 5.25 (d, 1H, J = 15.8 Hz), 4.20 (d, 1H, J = 13.8 Hz), 3.85 (d, 1H, J = 7.3 Hz), 3.69−3.51 (m, 4H), 3.63 (s, 3H), 3.38 (d, 1H, J = 14.0 Hz), 3.35 (dd, 1H, J = 10.6, 8.2 Hz), 3.17 (d, 1H, J = 10.5, 8.6 Hz), 2.44 (dd, 1H, J = 15.4, 7.1 Hz), 2.31 (app quind, 1H, J = 8.2, 1.2 Hz), 2.16 (d, 1H, J = 15.6 Hz), 1.95−1.85 (m, 4H); ^{13}C ($CDCl_3$) δ 172.1, 169.9, 161.9 (d, J_{CF} = 243.9 Hz), 161.8, 158.1, 148.9, 141.3, 137.3, 136.7, 132.6 (d, J_{CF} = 3.1 Hz), 132.2 (d, J_{CF} = 7.7 Hz), 129.9, 129.7, 128.4, 126.2, 122.7, 122.1, 121.3, 115.0 (d, J_{CF} = 20.9 Hz), 108.8, 72.9, 56.3, 52.1, 52.1, 52.0, 49.7 (br), 46.2 (br), 45.5, 38.5, 28.5, 26.5 (br), 24.1 (br); ^{19}F NMR ($CDCl_3$) δ −116.4 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity) 629 (M^+ + Na, 100), 607 (M^+ + H, 52), 536 (10); HRMS (ESI) *m/z* calcd for $C_{36}H_{35}O_4N_4FNa$ 629.2540, found 629.2555.

***rac*-(4*R*,6a*R*,3b*R*)-5-Benzoyl-4-(4-fluorobenzyl)-1-(4-hydroxy-2-hydroxymethyl-5-methyl-pyridin-3-ylmethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,24*}).** mp 177−179 °C; IR 2952, 2875, 1737, 1634, 1602, 1576, 1552, 1508, 1475, 1447, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.27 (bs, 1H), 7.68 (s, 1H), 7.42−7.33 (m, 5H), 7.24 (dd, 2H, J = 8.6, 5.4 Hz), 7.00 (app t, 2H, J = 8.7 Hz), 6.30 (s, 1H), 5.39 (d, 1H, J = 15.8 Hz), 5.27 (d, 1H, J = 15.7 Hz), 4.59 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.82−3.70 (m, 3H), 3.70−3.60 (m, 2H), 3.56 (s, 3H), 3.30 (d, 1H, J = 14.1 Hz), 3.25 (dd, 1H, J = 10.7, 8.3 Hz), 3.08 (dd, 1H, J = 10.7, 7.4 Hz), 2.39 (app quind, 1H, J = 7.7, 3.2 Hz), 2.38 (s, 3H), 2.16 (dd, 1H, J = 15.6, 7.6 Hz), 2.05−1.95 (m, 4H), 1.93 (dd, 1H, J = 15.9, 1.8 Hz); ^{13}C ($CDCl_3$) δ 171.9, 170.0, 162.0 (d, J_{CF} = 244.1 Hz), 162.9, 151.5, 149.8, 143.0, 138.5, 137.0, 132.4, 132,4 (d, J_{CF} = 3.4 Hz), 132.2 (d, J_{CF} = 7.7 Hz), 129.9, 129.6, 128.4, 127.5, 126.3, 124.3, 115.1 (d, J_{CF} = 21.3 Hz), 109.5 (br), 72.8, 61.1, 56.1, 51.9, 51.2, 49.9, 46.6, 46.0, 42.6, 38.3, 29.3, 26.4, 24.1, 19.2; ^{19}F NMR ($CDCl_3$) δ −116.3 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity) 689 (M^+ + Na, 30), 667 (M^+ + H, 100); HRMS (ESI) *m/z* calcd for $C_{38}H_{40}N_4O_6F$ 667.2932, found 667.2940.

***rac*-(4*R*,6a*R*,3b*R*)-5-Benzoyl-4-(4-fluorobenzyl)-2-(pyrrolidine-1-carbonyl)-1-(6-trifluoromethylpyridin-3-ylmethyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,25*}).** mp 110−112 °C; IR 2951, 2875, 1737, 1636, 1604, 1509, 1447, 1402, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.59 (s, 2H), 7.43−7.38 (m, 5H), 7.30 (dd, 2H, J = 8.1, 5.6 Hz), 7.04 (app t, 2H, J = 8.5 Hz), 6.32 (s, 1H), 5.55 (d, 1H, J = 16.0 Hz), 5.29 (d, 1H, J = 15.9 Hz), 4.20 (d, 1H, J = 13.8 Hz), 3.85 (d, 1H, J = 7.1 Hz), 3.64 (s, 3H), 3.70−3.49 (m, 4H), 3.42−3.38 (m, 1H), 3.38 (d, 1H, J = 13.9 Hz), 3.17 (dd, 1H, J = 10.4, 8.3 Hz), 2.49−2.37 (m, 2H), 2.17 (d, 1H, J = 13.7 Hz), 1.95−1.85 (m, 4H); ^{13}C ($CDCl_3$) δ 172.0, 170.0, 162.1 (d, J_{CF} = 244.0 Hz), 161.4, 148.4, 147.2 (q, J_{CF} = 34.3 Hz), 141.0, 137.5, 137.3, 136.0, 132.6 (d, J_{CF} = 2.9 Hz), 132.3 (d, J_{CF} = 7.5 Hz), 129.8, 129.8, 128.5, 126.3, 123.6, 121.5 (q, J_{CF} = 272.3 Hz), 119.7 (q, J_{CF} = 2.2 Hz), 115.1 (d, J_{CF} = 20.6 Hz), 109.7, 72.9, 56.3, 52.1, 52.0, 49 (br), 47.6, 47 (br), 45.7, 38.6, 28.6, 26 (br), 24 (br); ^{19}F NMR ($CDCl_3$) δ −68.3 (s, 3F), −116.2 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity) 697 (M^+ + Na, 100), 675 (M^+ + H, 80); HRMS (ESI) *m/z* calcd for $C_{37}H_{34}N_4O_4F_4Na$ 697.2438, found 697.2428.

***rac*-(4*R*,6a*R*,3b*R*)-5-Benzoyl-4-(4-fluorobenzyl)-1-(5-methylfuran-2-ylmethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diazacyclopenta[*a*]pentalene-4-carboxylic Acid Methyl Ester (17{*2,2,26*}).** mp 96−98 °C; IR 2950, 2873, 1736, 1639, 1604, 1509, 1446, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44−7.39 (m, 5H), 7.30 (dd, 2H, J = 8.6, 5.5 Hz), 7.03 (app t, 2H, J = 8.7 Hz), 6.17 (s, 1H), 6.01 (d, 1H, J = 3.0 Hz), 5.81 (dd, 1H, J = 3.0, 1.0 Hz), 5.35 (d, 1H, J = 15.5 Hz), 5.44 (d, 1H, J = 15.5 Hz), 4.19 (d, 1H, J = 13.8 Hz), 3.80 (d, 1H, J = 7.4 Hz), 3.64−3.56 (m, 4H), 3.57 (s, 3H), 3.37 (d, 1H, J = 13.9 Hz), 3.35 (dd, 1H, J = 10.3, 8.4 Hz), 3.20 (dd, 1H, J = 10.3, 8.5 Hz), 2.55 (dd, 1H, J = 15.8, 7.2 Hz), 2.32 (app quind, 1H, J = 7.2, 1.7 Hz), 2.25 (d, 1H, J = 16.0 Hz), 2.17 (s, 3H), 1.97−1.85 (m, 4H); ^{13}C ($CDCl_3$) δ 172.1, 169.8, 162.1, 161.9 (d, J_{CF} = 243.8 Hz), 151.6, 149.5, 140.6, 137.5, 132.7 (d, J_{CF} = 3.1 Hz), 132.3 (d, J_{CF} = 7.7 Hz), 129.6, 129.5, 128.4, 126.1, 122.3, 115.0 (d, J_{CF} = 20.9 Hz), 108.7, 108.6, 106.2, 72.9, 56.3, 52.1, 52.0, 50 (br), 46 (br), 45.5, 42.9, 38.5, 28.5, 27 (br), 24 (br), 13.5; ^{19}F NMR ($CDCl_3$) δ −116.5 (tt, 1F, J = 8.5, 5.6 Hz); MS (ESI) *m/z* (rel intensity)

632 ($M^+ + Na$, 100), 610 ($M^+ + H$, 72), 530 (14), 516 (30); HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_3O_5F$ 610.2717, found 610.2714.

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Supporting Information Available. Spectroscopic data for compounds **15**, **16**, and selected **17**, HPLC/MS analyses, LC/MS chromatograms, and QikProp analyses for all library members **17** are given in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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