# Design and Synthesis of a 3,4-Dehydroproline Amide Discovery Library

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The synthesis of a discovery library of 80 3,4-dehydroproline amides was achieved in a four-step reaction sequence from easily accessible 3-aminoallene-3-carboxylate methyl esters. Diversification of these proline mimics was introduced at five different sites: the substituents at the 3-pyrroline unit ($R^1$, $R^2$, $R^3$), at the nitrogen ($R^4$), and the *C*-terminus ($R^5$). The 3-pyrroline scaffold was synthesized in excellent yields by a silver-catalyzed intramolecular cyclization of aminoallenes, followed by *N*-functionalization reactions. Maximum diversity was introduced in the final step of the reaction sequence by taking advantage of the carboxylic acid handle of the 3-pyrroline subunit. Amide coupling reactions using polystyrene-carbodiimide (PS-carbodiimide) and 1-hydroxybenzotriazole (HOBt) under microwave irradiation led to 3,4-dehydroproline amides that were obtained in purities greater than 85% by LC/MS/ESLD after scavenging the excess HOBt on a silica-bound carbonate SPE cartridge.

## Introduction

L-Proline holds a unique position among the 20 proteinogenic amino acids because of its distinctive cyclic structure and secondary amine functionality. It induces $\beta$-turns and initiates peptide folding of the α-helix; therefore, it plays a key role in the activity of several proteins. It has been shown that the replacement of proline by proline analogues[1] such as 3,4-dehydroproline **1** (Figure 1) can even increase biological activity which has been attributed to a stronger receptor binding based on additional $\pi-\pi$-interactions with the carbon−carbon double bond.[2,3] In addition, the conformational flexibility of the ring system in 3,4-dehydroproline **1** is further restricted compared to that of proline.[4]

3,4-Dehydroproline itself is an important inhibitor of peptidyl proline hydroxylation. It acts as an enzyme-activated suicide inhibitor of prolyl hydroxylase[5] and was found to inhibit the formation of collagen.[6] Meienhofer and Walter showed that the uterotonic potency of the oxytocin hormone **2** can be increased by a factor of 2 if the proline unit is replaced by 3,4-dehydroproline.[2] Similarly, Walter could increase the antidiuretic potency of the related arginine-vasopressin hormone **3** (AVP) by replacing the proline unit in AVP by 3,4-dehydroproline.[3] In another study, the 3,4-dehydroproline analogue of the immunopotentiating tetrapeptide tuftsin **4** showed enhanced phagocytic activity of human PMN compared to tuftsin itself.[7] To synthesize tritium-labeled versions of the angiotensin-converting enzyme inhibitor $BPP_{9a}$ **5** by catalytic reduction in tritium gas, Fisher and Ryan prepared analogs of the nonapeptide $BPP_{9a}$, containing a single 3,4-dehydroproline in place of a proline at the 3, 5, 8, or 9 position and an analog containing two

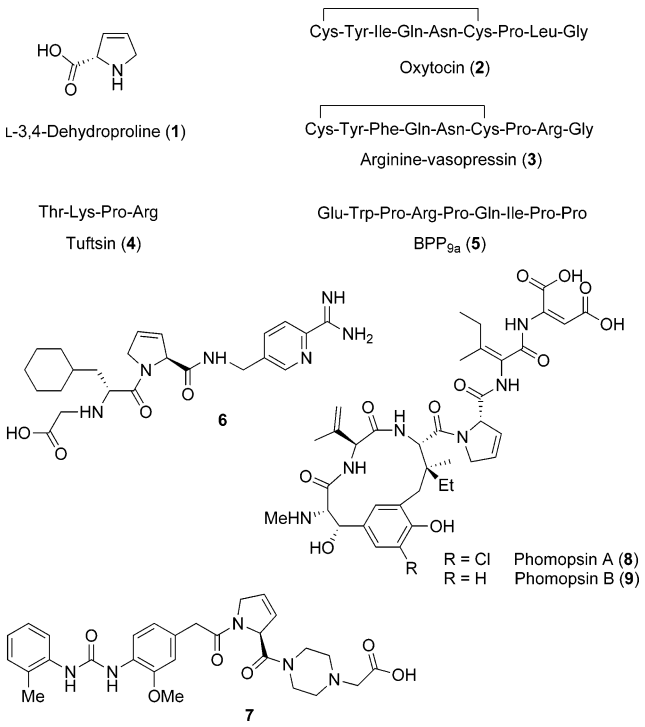


**Figure 1.** 3,4-Dehydroproline containing bioactive compounds and peptides where replacement of the proline unit by 3,4-dehydroproline led to increased potency.

3,4-dehydroprolines at the 3 and 9 positions. All analogues were found to be more potent than $BPP_{9a}$ **5**.[4] Recently, Lange developed a very potent thrombin inhibitor **6** that contains a 3,4-dehydroproline unit.[8] Again, the 3,4-dehydroproline analogue showed a higher potency and a higher oral bioavailability than the corresponding proline version. Chiba developed a potent, non-peptidic, and orally active VLA-4 antagonist **7** that incorporates a 3,4-dehydroproline.[9]

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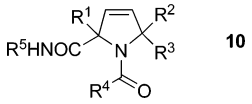



**10**

**Figure 2.** 3,4-Dehydroproline amide scaffold **10**.

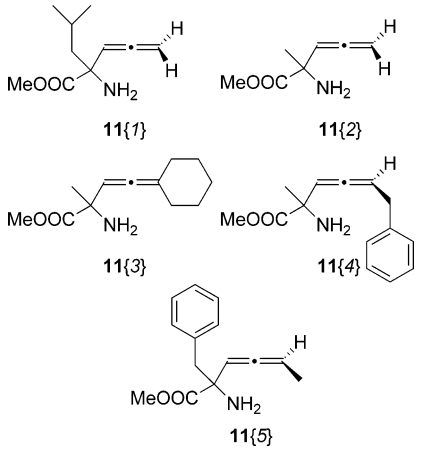



**Figure 3.** Building blocks **11**{*1*−*5*} used in the synthesis of the 3,4-dehydroproline amide library

Interestingly, only two natural products have been identified that contain a 3,4-dehydroproline unit, Phomopsin A and B (**7** and **8**).[10] Phomopsin A is a potent antimitotic drug that protects the tubulin molecule from decay.

These examples show the importance of 3,4-dehydroproline as a proline mimic. It is therefore surprising that in all SAR studies the unsubstituted 3,4-dehydroproline unit has been applied; further substituted 3,4-dehydroprolines are very rare,[11,12,13,14] and the α,α-disubstituted versions are virtually unknown.[15,16] This might be because there are a limited number of synthetic approaches to these amino acids. In the past, 3,4-dehydroprolines have been prepared through dehydration of 4-hydroxyprolines,[11] base-promoted ring formation of *Z*-amino allylic mesylates,[12] anionic condensation and fragmentation of 7-azabicyclo[2.2.1]heptenones,[13] and the reaction of lithium trimethylsilyldiazomethane with *N*,*N*-disubstituted α-amino ketones.[14] More substituted 3,4-dehydroprolines have been obtained by enyne metathesis[15] and through the Birch reduction of pyrroles.[16] The silver-(I)-catalyzed cyclization[17] of amino acid-derived allenes to prepare more substituted 3,4-dehydroprolines has been described recently by Brummond and Mitasev.[18] This approach leads to α,α-disubstituted 3,4-dehydroprolines and tolerates multiple substituents on the 3-pyrroline scaffold. α,α-Disubstituted amino acids are known to be more stable toward enzymatic hydrolysis than proteinogenic amino acids.[15,19] In the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD), we have applied this methodology to the diversity-oriented synthesis of a small molecule discovery library, and we are now reporting the design and synthesis of the first library of 3,4-dehydroproline amides.

## Results and Discussion

**Library Design.** The present library was designed as a structurally truncated version of a previously synthesized library of tricyclic pyrrole-2-carboxamides[20] by the UPCMLD. Diversity was introduced at five sites of the 3,4-dehydroproline amide scaffold **10**, the substituents at C-2 and C-5 of the 3-pyrroline unit ($R^1$, $R^2$, $R^3$), the amine nitrogen ($R^4$), and the carboxamide ($R^5$) (Figure 2).

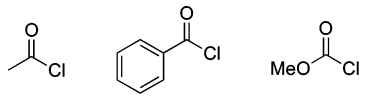



**Figure 4.** Building blocks **12**{*1*−*3*} used in the synthesis of the 3,4-dehydroproline amide library.

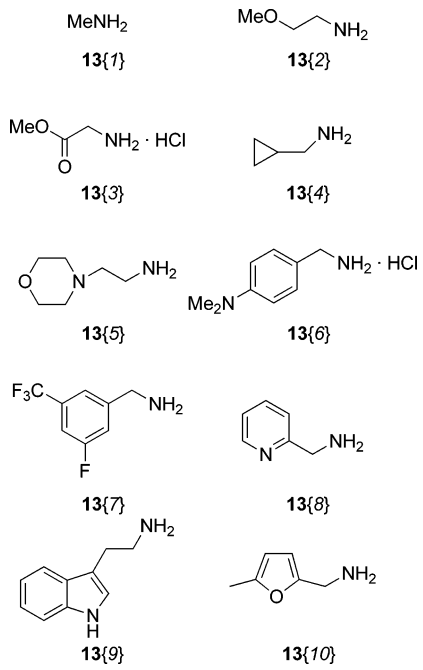
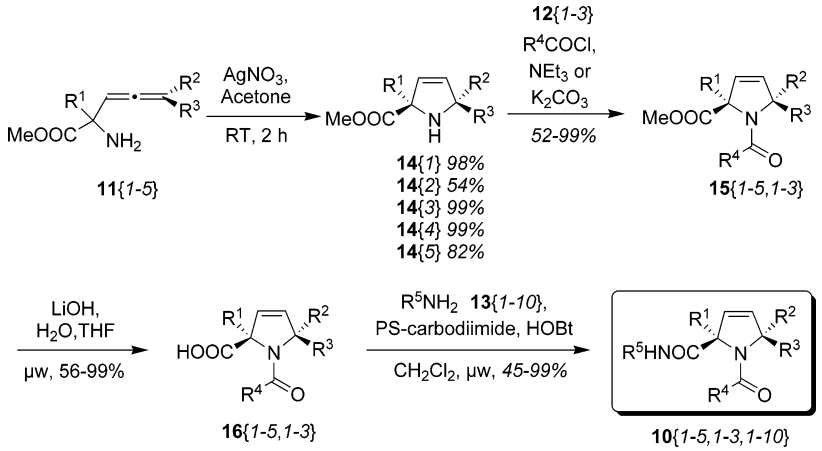



**Figure 5.** Building blocks **13**{*1*−*10*} used in the synthesis of the 3,4-dehydroproline amide library.

The substituents $R^1$, $R^2$, and $R^3$ are derived from the racemic aminoallene precursors **11**{*1*−*5*} and were chosen to maximize the steric diversity surrounding the 3-pyrroline scaffold (Figure 3). Cyclization of each of these aminoallenes afforded the corresponding 3-pyrroline-2-carboxamide scaffolds **14**{*1*−*5*} (Scheme 1).[18] Next, functionalization of the 3-pyrroline nitrogen to provide steric and electronic diversity was accomplished by forming an acylamide, benzoylamide, and methyl carbamate from the building blocks **12**{*1*−*3*} (Figure 4). The final diversification of the 3-pyrroline scaffold involved formation of a carboxamide from the corresponding carboxylic acid and ten commercially available amines (Figure 5). To probe the importance of the carboxamide handle on the biological activity, small to medium size aliphatic amines (**13**{*1*−*5*}), electron-rich (**13**{*6*}) and electron-poor benzylamines (**13**{*7*}), and heteroaromatic amines (**13**{*8*−*10*}) were applied. In addition to these carboxamide-containing compounds, the ester and carboxylic acid precursors were included into the final library.

Prior to synthesis of these compounds, the structures of a virtual library of all 150 possible combinations (5 × 3 × 10) were minimized using an MM2 force field in MacroModel 8.6 and important physicochemical properties like molecular weight, number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), clogP, and

**Scheme 1.** Synthesis of 3,4-dehydroproline Amides **10**{*1−5,1−3,1−10*}




logS (aqueous solubility) were calculated computationally with QikProp 2.1.[21] To synthesize only library members with tool-like properties[22] that show a sufficient solubility in biological assays a filter was applied, requiring clogP to be smaller than 5 and logS to be greater than −6. The physicochemical properties of most virtual library members fit well within this range. Only eleven of these virtual compounds were found to show clogP > 5, logS < −6, or both. Because we were interested in preparing large quantities of each compound, the number of compounds to be prepared was reduced to approximately half the original number by removing compounds where there were significant overlaps in the physicochemical properties and structures to maximize the physicochemical property diversity.

**Library Synthesis.** Our synthetic approach toward the synthesis of the discovery library of 3,4-dehydroproline amides involved (1) scaffold generation by a silver-catalyzed intramolecular cyclization of aminoallenes, (2) *N*-functionalization, and (3) a microwave-assisted saponification of the methyl ester, followed by formation of an amide by application of a polymer-bound carbodiimide. All reaction conditions were optimized using the reaction sequence starting with methyl 2-amino-2-isobutylpenta-3,4-dienoate **11**{*1*} and applied to the other derivatives with minimal changes.

Reaction of aminoallenes **11**{*1−5*} with a catalytic amount of silver nitrate in acetone[17,18] afforded 3-pyrrolines **14**{*1−5*} in 54−99% yield (Scheme 1). The cyclization proceeded with complete transfer of chiral information from **11**{*4−5*} and provided **14**{*4−5*} in a diastereomeric ratio of 95:5.[18] Each of the cyclization reactions was performed at room temperature on a 2 g scale and was complete in less than 2 h. A lower yield was observed in the case of **14**{*2*} because of its volatility. All 3-pyrroline derivatives were analyzed by $^1$H NMR and carried directly on to the next step.

*N*-Functionalization of 3-pyrrolines **14**{*1−5*} was achieved by treating each 3-pyrroline with acetyl chloride **12**{*1*}, benzoyl chloride **12**{*2*}, or methyl chloroformate **12**{*3*}, respectively (Table 1). For example, **14**{*1−5*} was *N*-acetylated to give *N*-acetyl derivatives **15**{*1−5,1*} in 52−96% yield using 2 equiv of acetyl chloride **12**{*1*} and 3 equiv of triethylamine in dichloromethane at room temperature in 30 min. The crude product was purified on an ISCO Companion chromatography system. Acetylation of the sterically hindered 3-pyrroline **14**{*3*} was very sluggish under these reaction conditions. Stirring the reaction mixture at room temperature for 24 h gave **15**{*3,1*} in only 52% yield; 41% of the starting material was recovered.

**Table 1.** Isolated Yield (%) for *N*-Functionalization of **14**{*1−5*} (Crude Yield (%) for Saponification of **15**(*1−5,1−3*})

| | **12**{*1*} | **12**{*2*} | **12**{*3*} |
|---|---|---|---|
| **14**{*1*} | 96 (93) | 98 (92) | 75 (85) |
| **14**{*2*} | 75 (56) | 66 (99) | 62 (85) |
| **14**{*3*} | 52 (81) | 77 (93) | 85[a] (69) |
| **14**{*4*} | 87 (97) | 99 (99) | 93[a] (98) |
| **14**{*5*} | 90 (99) | 99 (95) | 92[a] (94) |

[a] With $K_2CO_3$ as base instead of triethylamine.

Treatment of **14**{*1*} with 2 equiv of benzoyl chloride **12**{*2*} and 3 equiv of triethylamine in dichloromethane at room temperature for 24 h led to the formation of the *N*-benzoylated-3-pyrroline **15**{*1,2*} in 43% yield. The reaction time was reduced from 24 h to 15 min by irradiating the mixture under microwave conditions at 100 °C in dichloromethane. Under those conditions, all 3-pyrroline derivatives reacted smoothly to yield the *N*-benzoyl derivatives **15**{*1−5,2*} in 66−99% after purification on an ISCO Companion chromatography system (Table 1).

The initial reactions for the carbamate formation were carried out by treating the 3-pyrrolines with 2 equiv of methyl chloroformate and 2 equiv of triethylamine in dichloromethane at room temperature. 3-Pyrrolines **14**{*1*} and **14**{*2*} reacted under these conditions to give the *N*-carbamate derivatives **15**{*1,3*} and **15**{*2,3*} in 75 and 62% yield, respectively, while **14**{*3*}, **14**{*4*}, and **14**{*5*} required modified reaction conditions. Simply changing the base from triethylamine to potassium carbonate gave **15**{*3,3*}, **15**{*4,3*}, and **15**{*5,3*} in excellent yields of 85−93% (Table 1). The $^1$H NMR spectra of carbamates **15**{*1−5,3*} showed two sets of resonances and peak broadening resulting from the formation of rotamers; however, heating the sample to 90 °C gave interpretable spectra.

Next, the fifteen *N*-protected methyl esters **15**{*1−5,1−3*} were subjected to hydrolysis with lithium hydroxide in THF/water (Table 1). The reactions were again carried out in an Emrys Optimizer microwave reactor. Hydrolysis was very effective under microwave irradiations at 100 °C for

**Table 2.** Library of 3,4-dehydroproline Amides **10**{*1*−*5*,*1*−*3*,*1*−*10*} (Compound, Isolated Yield (%) (Purity by ELSD (%)))

| | **11**{*1*}[a] | | **11**{*2*} | | | **11**{*3*} | | | **11**{*4*} | | | **11**{*10*} | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **12**{*1*} | **12**{*2*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} |
| **13**{*1*} | **10**{*1,1,1*} 90 (>99) | **10**{*1,2,1*} >99 (>99) | - | **10**{*2,2,1*} >99 (>99) | **10**{*2,3,1*} 45 (>99) | **10**{*3,1,1*} 73 (>99) | - | **10**{*3,3,1*} 78 (>99) | **10**{*4,1,1*} 99 (>99) | - | **10**{*4,3,1*} 95 (>99) | **10**{*5,1,1*} 99 (>99) | - | **10**{*5,3,1*} >99 (96) |
| **13**{*2*} | **10**{*1,1,2*} 84 (99) | **10**{*1,2,2*} >99 (98) | **10**{*2,1,2*} >99 (95) | - | **10**{*2,3,2*} 59 (>99) | - | **10**{*3,2,2*} >99(>99) | - | - | **10**{*4,2,2*} >99 (>99) | - | **10**{*5,1,2*} >99 (>99) | - | **10**{*5,3,2*} >99 (98) |
| **13**{*3*} | **10**{*1,1,3*} >99 (95) | **10**{*1,2,3*} >99 (92) | - | **10**{*2,2,3*} >99 (99) | - | **10**{*3,1,3*} >99 (90)[b,c] | - | **10**{*3,3,3*} 84 (>99)[c] | **10**{*4,1,3*} 94 (92) | - | **10**{*4,3,3*} 95 (96) | - | **10**{*5,2,3*} 94 (90) | **10**{*5,3,3*} >99 (90) |
| **13**{*4*} | **10**{*1,1,4*} 100 (99) | **10**{*1,2,4*} >99 (98) | **10**{*2,1,4*} >99 (92) | - | **10**{*2,3,4*} 79 (94) | - | **10**{*3,2,4*} >99(>99) | - | - | **10**{*4,2,4*} >99 (92)[c] | - | - | **10**{*5,2,4*} 100 (97) | - |
| **13**{*5*} | **10**{*1,1,7*} >99 (95) | **10**{*1,2,7*} 97 (91) | - | **10**{*2,2,7*} 88 (99) | **10**{*2,3,7*} 98 (98) | **10**{*3,1,7*} >99 (>99) | **10**{*3,2,7*} >99 (89) | - | **10**{*4,1,7*} >99 (99) | **10**{*4,2,7*} 96 (91)[d] | - | **10**{*5,1,7*} 91 (>99) | **10**{*5,2,7*} 99 (93)[d] | - |
| **13**{*6*} | - | - | | **10**{*2,2,5*} >99 (96) | - | - | - | **10**{*3,3,5*} >99 (96) | - | - | **10**{*4,3,5*} >99 (96)[c] | - | - | - |
| **13**{*7*} | **10**{*1,1,6*} >99 (>99) | **10**{*1,2,6*} 96 (88) | **10**{*2,1,6*} >99 (97) | - | **10**{*2,3,6*} 96 (97) | **10**{*3,1,6*} 63 (90)[c] | **10**{*3,2,6*} >99 (90)[c] | - | **10**{*4,1,6*} 97 (98) | - | - | **10**{*5,1,6*} 92 (98) | - | - |
| **13**{*8*} | **10**{*1,1,8*} >99 (93) | **10**{*1,2,8*} >99 (92) | - | **10**{*2,2,8*} >99 (99) | - | **10**{*3,1,8*} 79 (98) | - | **10**{*3,3,8*} 91 (>99) | **10**{*4,1,8*} 92 (97) | - | **10**{*4,3,8*} 95 (>99) | **10**{*5,1,8*} >99 (>99) | - | **10**{*5,3,8*} >99 (99) |
| **13**{*9*} | **10**{*1,1,9*} 73 (92) | **10**{*1,2,9*} 94 (96) | - | **10**{*2,2,9*} 83 (>99) | - | - | **10**{*3,2,9*} >99 (99) | - | **10**{*4,1,9*} 95 (>99) | - | - | **10**{*5,1,9*} 75 (>99) | - | - |
| **13**{*10*} | **10**{*1,1,10*} 97(87) | **10**{*1,2,10*} >99 (90)[b,c] | **10**{*2,1,10*} 98 (88) | - | **10**{*2,3,10*} 94 (>99) | **10**{*3,1,10*} 70 (91) | - | **10**{*3,3,10*} 93 (90)[c] | **10**{*4,1,10*} >99 (99) | - | **10**{*4,3,10*} 91 (96) | **10**{*5,1,10*} 98 (>99) | - | **10**{*5,3,10*} 88 (99) |

[a] Compound **11**{*1*} was used to optimize acylation conditions with **12**{*1*} and **12**{*2*}; reactions with **12**{*3*} were not attempted. [b] Repurified on an ISCO Companion chromatography system. [c] Estimated purity by $^1$H NMR. [d] Purity by UV detection at 210, 220, and 254 nm.

*N*-acetyl and *N*-benzoyl derivatives **15**{*1*−*5*,*1*−*2*} and at 60 °C for *N*-carbamate derivatives **15**{*1*−*5*,*3*}. The reaction time varied depending upon the substituents at the 2 and 5 positions of the 3-pyrroline. For example, sterically hindered substrates **15**{*3*,*3*}, **15**{*4*,*2*}, **15**{*4*,*3*}, **15**{*5*,*2*}, and **15**{*5*,*3*} required irradiation times of 60 min, while all other substrates were hydrolyzed within 10−30 min. Carboxylic acids **16**{*1*−*5*,*1*−*3*} were obtained in moderate to excellent yields ranging from 56−99%.

The use of polymer-bound reagents has emerged as a powerful tool for combinatorial chemistry. Amides **10**{*1*−*5*,*1*−*3*,*1*−*10*} were synthesized using polystyrene-carbodiimide (PS-carbodiimide) and 1-hydroxybenzotriazole (HOBt), followed by filtration through a silica-bound carbonate SPE cartridge to scavenge any unreacted acid and HOBt.[23] The reaction mixture was irradiated under microwave conditions at 100 °C for 10 min. For volatile amines, the reaction was carried out at 60 °C for 30 min. The yield dropped from 100 to 37% in the absence of HOBt as evidenced by treatment of **16**{*1*,*2*} with **13**{*2*} under otherwise identical conditions. This protocol was very efficient and gave nearly quantitative yields of **10**{*1*−*5*,*1*−*3*,*1*−*10*} with excellent purities. Seventy library members were synthesized in 90−99% yield, four library members in 80−89% yield, and six library members in 44−80% using this method (Table 2). Success with a wide range of amines and carboxylic acids demonstrated the general applicability of this protocol.

**Analysis.** All library members were submitted directly after SPE purification to LC/MS/ELSD analysis for evaluation of their purities. Seventy-four compounds showed purities above 85%, which is the purity criteria for the UPCMLD compound collection (Table 2). Only six compounds had purities below 85% and had to be repurified on an ISCO Companion chromatography system.

All compounds met the filter criteria (vide supra) for physicochemical properties (Table 3). The 3,4-dehydroproline amides have an average molecular weight of 350 ± 75, with an average number of HBD of 1.1 ± 0.4 and of HBA of 6.4 ± 1.2. Those library members also show interesting values for *c* log *P* (average of 2.7 ± 1.6) and log *S* (average of −2.9 ± 1.9).

## Conclusion

In the present study, we reported a convenient and efficient protocol for the synthesis of an 80-member 3,4-dehydroproline amide library. All reactions requiring elevated temperatures, such as the ester hydrolyses and *N*- and *C*-functionalizations, were conducted in a microwave reactor. The combination of polymer-bound reagents and scavenging techniques saved a significant amount of time and provided the library members in good to excellent yields and purities without the need for expensive and time-consuming chromatography. Biological evaluation of this 3,4-dehydroproline amide discovery library is ongoing and will be reported in due course.

## Experimental Section

**General.** All solvents or reagents were used without further purification. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 $F_{254}$ plates, 250 $\mu$m layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with Vaughn's

**Table 3.** Physicochemical Properties[a] for All Synthesized 3,4-Dehydroproline Amides **10**{*1*−*5*,*1*−3,1−10} (Compound, MW, clogP, logS)

| | **11**{*1*} | | **11**{*2*} | | | **11**{*3*} | | | **11**{*4*} | | | **11**{*5*} | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **12**{*1*} | **12**{*2*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} | **12**{*1*} | **12**{*2*} | **12**{*3*} |
| **13**{*1*} | **10**{*1,1,1*} 224.3 0.6, -0.24 | **10**{*1,2,1*} 286.4 2.2, -2.4 | - | **10**{*2,2,1*} 244.3 1.2, -1.6 | **10**{*2,3,1*} 198.2 0.4, -0.9 | **10**{*3,1,1*} 250.3 0.9, 0.7 | - | **10**{*3,3,1*} 266.3 1.7, -2.0 | **10**{*4,1,1*} 272.3 1.5, -1.3 | - | **10**{*4,3,1*} 288.3 2.7, -3.2 | **10**{*5,1,1*} 272.3 1.4, -1.0 | - | **10**{*5,3,1*} 288.3 2.7, -2.9 |
| **13**{*2*} | **10**{*1,1,2*} 268.4 0.8, -1.0 | **10**{*1,2,2*} 330.4 2.4, -2.8 | **10**{*2,1,2*} 226.3 -0.6, 0. | - | **10**{*2,3,2*} 242.3 0.6, -1.1 | - | **10**{*3,2,2*} 356.5 2.9, -3.0 | - | - | **10**{*4,2,2*} 378.5 3.5, -3.6 | - | **10**{*5,1,2*} 316.4 1.5, -1.0 | - | **10**{*5,3,2*} 332.4 2.7, -2.7 |
| **13**{*3*} | **10**{*1,1,3*} 282.3 0.7, -0.67 | **10**{*1,2,3*} 344.4 2.4, -3.1 | - | **10**{*2,2,3*} 302.3 1.4, -2.2 | - | **10**{*3,1,3*} 308.4 0.94, -0.77 | - | **10**{*3,3,3*} 324.4 1.9, -2.8 | **10**{*4,1,3*} 330.4 1.7, -1.8 | - | **10**{*4,3,3*} 346.4 3.0, -26.6 | - | **10**{*5,2,3*} 392.5 3.4, -3.6 | **10**{*5,3,3*} 407.5 4.5, -4.7 |
| **13**{*4*} | **10**{*1,1,4*} 264.4 1.5, -1.0 | **10**{*1,2,4*} 326.4 3.2, -3.5 | **10**{*2,1,4*} 222.3 0.3, -0.3 | - | **10**{*2,3,4*} 238.3 1.5, -2.1 | - | **10**{*3,2,4*} 352.5 3.4, -3.6 | - | - | **10**{*4,2,4*} 374.5 4.4, -4.6 | - | - | **10**{*5,2,4*} 374.5 4.5, -4.7 | - |
| **13**{*5*} | **10**{*1,1,7*} 323.4 -0.01, 1.5 | **10**{*1,2,7*} 385.5 1.9, 1.0 | - | **10**{*2,2,7*} 343.4 0.8, -0.5 | **10**{*2,3,7*} 297.4 0.2, -0.16 | **10**{*3,1,7*} 349.5 0.5, 0.2 | **10**{*3,2,7*} 411.5 2.4, -2.1 | - | **10**{*4,1,7*} 371.5 0.9,-0.01 | **10**{*4,2,7*} 433.5 3.0, -2.8 | - | **10**{*5,1,7*} 371.5 1.0, -0.16 | **10**{*5,2,7*} 433.5 3.0, -2.6 | - |
| **13**{*6*} | - | - | | **10**{*2,2,5*} 363.5 3.5, -4.3 | - | - | [b] | **10**{*3,3,5*} 385.5 4.0, -4.8 | - | [b] | **10**{*4,3,5*} 407.5, 4.9, -5.5 | - | [b] | - |
| **13**{*7*} | **10**{*1,1,6*} 386.4 3.4, -3.4 | **10**{*1,2,6*} 448.5 5.2, -6.0 | **10**{*2,1,6*} 344.3 2.0, -2.5 | - | **10**{*2,3,6*} 360.3 3.4, -4.8 | **10**{*3,1,6*} 412.4 3.6, -3.7 | **10**{*3,2,6*} 474.5 5.5, -5.8 | - | **10**{*4,1,6*} 434.4 4.2, -4.9 | [b] | [b] | **10**{*5,1,6*} 434.4 3.8, -3.4 | [b] | [b] |
| **13**{*8*} | **10**{*1,1,8*} 301.4 1.7, -1.5 | **10**{*1,2,8*} 363.5 3.4, -3.8 | - | **10**{*2,2,8*} 321 2.4, -3.1 | - | **10**{*3,1,8*} 327.4 1.9, -1.7 | - | **10**{*3,3,8*} 343.4 2.9, -3.8 | **10**{*4,1,8*} 349.4 2.7, -2.6 | - | **10**{*4,3,8*} 365.4 3.8, -4.1 | **10**{*5,1,8*} 349.4 2.5, -2.1 | - | **10**{*5,3,8*} 365.4 3.7, -4.3 |
| **13**{*9*} | **10**{*1,1,9*} 353.5 2.7, -2.5 | **10**{*1,2,9*} 415.5 4.6, -4.7 | - | **10**{*2,2,9*} 373.5 3.7, -4.8 | - | - | **10**{*3,2,9*} 441.6 4.8, -5.0 | - | **10**{*4,1,9*} 401.5 3.9, -4.2 | [b] | [b] | **10**{*5,1,9*} 401.5 3.8, -3.8 | [b] | [b] |
| **13**{*10*} | **10**{*1,1,10*} 304.4 1.8, -1.8 | **10**{*1,2,10*} 366.5 3.7, -4.2 | **10**{*2,1,10*} 262.3 0..9, -0.8 | - | **10**{*2,3,10*} 278.3 2.1, -2.5 | **10**{*3,1,10*} 330.4 2.2, -1.9 | - | **10**{*3,3,10*} 346.4 3.3, -3.5 | **10**{*4,1,10*} 352.4 2.7, -2.3 | - | **10**{*4,3,10*} 368.4, 4.0, -4.1 | **10**{*5,1,10*} 352.4 2.6, -2.1 | - | **10**{*5,3,10*} 368.4 3.9, -3.9 |

[a] Calculated with QikProp 2.1 after minimization with MacroModel 8.6. [b] Compounds that were screened out by the applied filter.

reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.2 g of $Ce(SO_4)_2\cdot 4H_2O$ in 10 mL of concentrated $H_2SO_4$ and 90 mL of $H_2O$) and $KMnO_4$. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ at either 300.1 or 500.1 MHz ($^1$H) and 75.4 or 125 MHz ($^{13}$C) using a Bruker Avance 300.1 or Bruker Avance 500.1 with XWIN-NMR software. Chemical shifts ($\delta$) are reported in parts per million (ppm). Chloroform-*d* or DMSO-$d_6$ were used as internal standards. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = dublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, app. = apparent), integration, and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR ESP spectrometer. Mass spectra were obtained on a Micromass Autospec double-focusing instrument (EI) or a Waters Q-Tof mass spectrometer (ESI). Melting points were obtained using a heating rate of 2 °C min$^{-1}$ on a MelTemp melting-point apparatus with digital temperature reading and are reported uncorrected.

Compounds were analyzed by reverse-phase HPLC (Alltech Prevail C-18, 100 × 4.6 mm, 1 mL min$^{-1}$, 50% MeCN, 50% $H_2O$/AcOH 99/1) with UV (210, 220, and 254 nm), ELS (nebulizer 45 °C, evaporator 45 °C, $N_2$ flow 1.25 SLM), and MS detection using a Thermo Finnigan Surveyor LC and LCQ Advantage MS system (ESI positive mode). All microwave-assisted reactions were carried out in an Emrys Optimizer microwave reactor using 0.2−5 mL Emrys process vials. PS-carbodiimide was purchased from Biotage, and silica-bound carbonate was purchased from Silicycle.

**General Procedure for the Silver Nitrate-Catalyzed Cyclization of 11{*1*−*5*} (Protocol A).** This procedure was slightly modified from the original report.[18] Allenic amine **11**{*4*} (1.3 g, 5.5 mmol, 1 equiv) in acetone (100 mL) was treated with silver nitrate (0.19 g, 1.1 mmol, 0.2 equiv) under argon. The flask was wrapped with aluminum foil to protect the reaction mixture from light, and the reaction mixture was stirred at room temperature for 2 h. Acetone was removed in vacuo, and the crude residue was dissolved in dichloromethane (3 × 100 mL), washed with saturated sodium bicarbonate solution (2 × 100 mL), dried over sodium sulfate, and concentrated in vacuo to yield 1.27 g (99%) of 3-pyrroline **14**{*4*}.

***rac*-(2*R*/*S*,5*R*/*S*)-5-Benzyl-2-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (14{*4*}).** Colorless oil. $^1$H NMR (300.1 MHz, 290 K, $CDCl_3$): $\delta$ 7.34−7.22 (m, 5H), 5.79 (app. s, 2H), 4.26 (app. t, $J$ = 7.1 Hz, 1H), 3.76 (s, 3H), 2.80 (dd, $J$ = 13.0, 7.3 Hz, 1H), 2.74 (dd, $J$ = 13.0, 6.8 Hz, 1H), 2.05 (bs, 1H), 1.42 (s, 3H). $^{13}$C NMR (75.4 MHz, 290 K, $CDCl_3$): $\delta$ 176.4, 138.6, 132.9, 131.9, 129.2, 128.5, 126.3, 72.1, 67.0, 52.5, 43.2, 26.9; IR (film) $\nu$ 3367, 2951, 1731, 1248, 1107 cm$^{-1}$. HR-MS (EI) Calcd for $[M - COOCH_3]^+$ $C_{12}H_{14}N_1$: 172.1126. Found: 172.1125. MS (EI) *m*/*z* (relative intensity in %): 172 (10), 140 (83), 108 (100), 91 (48).

**General Procedure for the *N*-Acetylation of 14{*1*−*5*} (Protocol B).** This procedure was slightly modified from the original procedure.[18] 3-Pyrroline **14**{*5*} (0.23 g, 1.0 mmol, 1 equiv) was dissolved in dichloromethane (20 mL) and treated with triethylamine (0.31 mL, 3.0 mmol, 3 equiv) and acetyl chloride **12**{*1*} (0.16 mL, 2.0 mmol, 2 equiv). The reaction mixture was stirred under argon at room temperature for 30 min and extracted wth dichloromethane (3 × 50 mL), washed with saturated sodium bicarbonate solution (2 × 25 mL), saturated ammonium chloride solution (25 mL), and

dried over sodium sulfate, and all volatile components were removed in vacuo. The crude residue was purified by chromatography on an ISCO Companion system (12 g, Redisep cartridge) using a gradient of hexane/ethyl acetate (100/0 to 80/20) to yield 0.25 g (90%) of the *N*-acetyl-3-pyrroline **15**{*5,1*}.

***rac*-(2*R*/*S*,5*R*/*S*)-1-Acetyl-2-benzyl-5-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (15{*5,1*}).** Colorless solid. mp: 115−117 °C. $^1$H NMR (300.1 MHz, 290 K, $CDCl_3$): $\delta$ 7.20−7.18 (m, 3H), 7.04−7.01 (m, 2H), 5.61−5.59 (m, 2H), 3.98 (d, $J$ = 13.8 Hz, 1H), 3.92 (q, $J$ = 6.2 Hz, 1H), 3.77 (s, 3H), 3.14 (d, $J$ = 13.8 Hz, 1H), 2.04 (s, 3H), 1.32 (d, $J$ = 6.2 Hz, 3H). $^{13}$C NMR (75.4 MHz, 290 K, $CDCl_3$): $\delta$ 171.7, 168.9, 136.5, 133.7, 130.7, 128.0, 127.5, 126.3, 77.3, 61.7, 52.7, 37.2, 22.5, 21.1. IR (film): $\nu$ 2951, 1735, 1649, 1402, 1253 cm$^{-1}$. HRMS (EI) Calcd for $[M]^+$ $C_{16}H_{19}N_1O_3$: 273.1365. Found: 273.1354. MS (EI) *m*/*z* (relative intensity in %): 273 (1), 182 (32), 140 (100), 91 (57).

**General Procedure for the *N*-Benzoylation of 14{*1*−*5*} (Protocol C).** 3-Pyrroline **14**{*2*} (0.20 g, 1.4 mmol, 1 equiv), triethylamine (0.60 mL, 4.3 mmol, 3 equiv), and benzoyl chloride **12**{*2*} (0.40 mL, 2.8 mmol, 2 equiv) were dissolved in dichloromethane (4 mL) and irradiated in an Emrys Optimizer microwave reactor (250 W) at 100 °C for 10 min. After the contents of the tube were cooled to room temperature, the reaction mixture was diluted by the addition of dichloromethane (25 mL), washed with saturated sodium bicarbonate solution (10 mL) and saturated ammonium chloride solution (10 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified by chromatography on an ISCO Companion system (12 g, Redisep cartridge) using a gradient of hexane/ethyl acetate (100/0 to 80/20) to yield 0.23 g (66%) of the *N*-benzoyl-3-pyrroline **15**{*2,2*}.

***rac*-1-Benzoyl-2-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (15{*2,2*}).** Colorless solid. mp: 105−106 °C. $^1$H NMR (300.1 MHz, 290 K, $CDCl_3$): $\delta$ 7.50−7.40 (m, 5H), 5.87−5.82 (m, 1H), 5.73−5.68 (m, 1H), 4.35 (d, $J$ = 14.8 Hz, 1H), 4.24 (d, $J$ = 14.8 Hz, 1H), 3.77 (s, 3H), 1.82 (s, 3H). $^{13}$C NMR (75.4 MHz, 290 K, $CDCl_3$): $\delta$ 172.1, 169.4, 136.8, 131.7, 129.8, 128.4, 126.6, 126.5, 73.1, 56.6, 52.6, 21.5. IR (film): $\nu$ 2948, 1740, 1642, 1625, 1404, 1260, 1118 cm$^{-1}$. HRMS (EI) Calcd for $[M - COOCH_3]^+$ $C_{12}H_{12}N_1O_1$: 186.0919. Found: 186.0910. MS (EI) *m*/*z* (relative intensity in %): 186 (57), 105 (100), 77 (45).

**General Procedure for the *N*-Methoxycarbonylation of 14{*1*−*5*} (Protocol D).** 3-Pyrroline **14**{*5*} (0.21 g, 0.46 mmol, 1 equiv) in dichloromethane (20 mL) was treated with powdered potassium carbonate (0.38 g, 2.7 mmol, 3 equiv) and cooled to 0 °C. Methyl chloroformate **12**{*3*} (0.14 mL, 0.93 mmol, 2 equiv) in dichloromethane (5 mL) was added dropwise over a period of 15 min. The reaction mixture was allowed to warm to room temperature, stirred overnight, filtered through Celite, and concentrated in vacuo. Purification by chromatography on an ISCO Companion system (12 g, Redisep cartridge) using a gradient of hexane/ethyl acetate (100/0 to 80/20) afforded 0.24 g (92%) of the *N*-methoxycarbonyl-3-pyrroline **15**{*5,3*}.

***rac*-(2*R*/*S*,5*R*/*S*)-2-Benzyl-5-methyl-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylic Acid Dimethyl Ester (15{*5,3*}).** Colorless oil. $^1$H NMR (500 MHz, 363 K, DMSO-$d_6$): $\delta$ 7.23−7.15 (m, 3H), 7.04−7.00 (m, 2H), 5.69−5.66 (m, 2H) 3.85−3.78 (m, 1H), 3.70−3.67 (m, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.17 (d, $J$ = 14.8 Hz, 1H), 1.21 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (75.4 MHz, 290 K, $CDCl_3$, two rotamers 2:3): $\delta$ 172.3, 172.0, 154.3, 153.8, 136.3, 135.9, 134.2, 134.1, 131.0, 130.7, 130.5, 127.8, 127.6, 127.4, 126.5, 126.3, 76.3, 62.5, 61.5, 52.8, 52.3, 52.2, 39.5, 37.7, 19.9, 18.6. IR (film): $\nu$ 2953, 1740, 1704, 1454, 1380, 1255 cm$^{-1}$. HRMS (EI) Calcd for $[M]^+$ $C_{16}H_{19}NO_4$: 289.1314. Found: 289.1322: MS (EI) *m*/*z* (relative intensity in %): 289 (1), 198 (100), 91 (75).

**General Procedure for Hydrolysis of the Methyl Esters 15{*1*−*5,1*−*3*} (Protocol E).** 3,4-Dehydroproline ester **15**{*4,1*} (0.19 g, 0.69 mmol, 1 equiv) and lithium hydroxide (0.14 g, 3.5 mmol, 5 equiv) were dissolved in THF (2.5 mL) and water (2.5 mL). The reaction mixture was irradiated in an Emrys Optimizer microwave reactor (250 W) at 100 °C for 30 min. The solution was cooled to room temperature, diluted with water (10 mL), acidified with 1 N HCl (1 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine and dried over sodium sulfate. After evaporation of all volatile components in vacuo 0.17 g (97%) of the carboxylic acid **16**{*4,1*} was obtained.

***rac*-(2*R*/*S*,5*R*/*S*)-1-Acetyl-5-benzyl-2-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid (16{*4,1*}).** Colorless solid. mp: 134−136 °C. $^1$H NMR (300.1 MHz, 290 K, $CDCl_3$): $\delta$ 7.34−7.27 (m, 3H), 7.11−7.08 (m, 2H), 5.94 (dd, $J$ = 6.5, 1.7 Hz, 1H), 5.74 (dd, $J$ = 6.4, 2.1 Hz, 1H), 4.87−4.82 (m, 1H), 3.06 (dd, $J$ = 13.4, 4.2 Hz, 1H), 2.81 (dd, $J$ = 13.4, 8.5 Hz, 1H), 2.27 (s, 3H), 1.71 (s, 3H). $^{13}$C NMR (75.4 MHz, 290 K, $CDCl_3$): $\delta$ 173.2, 172.9, 135.4, 131.9, 129.3, 128.9, 127.5, 127.2, 75.3, 68.3, 42.5, 22.6, 22.2. IR (film): $\nu$ 2939, 1732, 1640, 1595, 1410 cm$^{-1}$. HRMS (ES+) Calcd for $[M + Na]^+$ $C_{15}H_{17}N_1O_3Na$: 282.1106. Found: 282.1097. MS (ES+) *m*/*z* (relative intensity in %): 282 (100).

**General Procedure for the Amide Coupling of 16{*1*−*5,1*−*3*} (Protocol F).** A 5 mL microwave tube was charged with 3,4-dehydroproline **16**{*1,2*} (20 mg, 0.073 mmol, 1 equiv), PS-carbodiimide (11 mg, 0.15 mmol, 2 equiv), 1-hydroxybenzotriazole (9.9 mg, 0.073 mmol, 1 equiv), and methylamine **13**{*1*} (33 wt % in water) (0.021 mL, 0.22 mmol, 3 equiv) in dichloromethane (1 mL) and capped. The suspension was irradiated in an Emrys Optimizer microwave reactor (250 W) at 60 °C for 30 min (for nonvolatile amines irradiation was performed at 100 °C for 10 min). After it was cool to room temperature, the reaction mixture was filtered through an SPE-cartridge (prepacked with 500 mg silica-bound carbonate and preconditioned with 2 mL of $CH_2Cl_2$) and washed with dichloromethane (3 × 2 mL). The eluants were collected via gravity filtration. Evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amide **10**{*1,2,1*} (21.0 mg, 99%).

***rac*-1-Benzoyl-2-isobutyl-*N*-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (10{*1,2,1*}).** Colorless oil. $^1$H NMR (300.1 MHz, 290 K, $CDCl_3$): $\delta$ 7.82 (bs, 1H), 7.47−7.37

(m, 5H), 6.01 (d, $J = 6.2$ Hz, 1H), 5.76 (d, $J = 6.4$ Hz, 1H), 4.25 (d, $J = 15.1$ Hz, 1H), 4.13 (d, $J = 15.2$ Hz, 1H), 2.83 (d, $J = 4.7$ Hz, 3H), 2.71 (dd, $J = 14.3$, 5.8 Hz, 1H), 2.00 (dd, $J = 14.5$, 5.2 Hz, 1H), 1.70−1.63 (m, 1H), 0.97 (d, $J = 8.0$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (125 MHz, 290 K, $CDCl_3$): $\delta$ 173.8, 171.1, 137.5, 132.6, 129.7, 128.6, 125.7, 123.1, 79.2, 58.5, 41.0, 26.4, 24.8, 24.4, 23.5. IR (film): $\nu$ 3350, 2955, 1659, 1640, 1622, 1531, 1409 cm$^{-1}$. HRMS (EI) Calcd for $[M - CONHCH_3]^+$ $C_{15}H_{18}NO$: 228.1388. Found: 228.1387. MS (EI) *m*/*z* (relative intensity in %): 228 (41), 105 (100).

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**Supporting Information Available.** Experimental procedures and spectroscopic data for compounds **14**{*3*}, **14**{*5*}, **15**{*3,2*}, **15**{*3,3*}, **15**{*4,2*}, **16**{*2,2*}, **16**{*3,2*}, **16**{*3,3*}, **16**{*4,2*}, **16**{*4,3*}, **16**{*5,1*}, **16**{*5,2*}, **16**{*5,3*}, **10**{*2,1,7*}, **10**{*2,2,8*}, **10**{*3,2,4*}, **10**{*3,3,6*}, **10**{*4,2,4*}, **10**{*5,1,1*}, **10**{*5,1,9*}, **10**{*5,1,10*} **10**{*5,2,5*}, **10**{*5,2,9*}, and **10**{*5,3,2*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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