Rapid Combinatorial Access to Macrocyclic Ansapeptoids and Ansapeptides with Natural-Product-like Core Structures

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Abstract: 14-Membered ansa-cyclopeptide alkaloids are among the most abundant natural macrocycles and thus valuable templates for diversity-oriented synthesis with biological relevance. A rapid synthesis of the core structure is conceivable by a combination of an Ugi four-component reaction with bifunctional building blocks to form the dipeptoid part, followed by a suitable macrocyclization reaction. The latter step is crucial, and an uncommon macroetherification gave the best results. The use of ammonium salts allows direct access to peptides instead of peptoids. Depending on the substitution pattern, some cyclopeptoids show planar chirality despite free rotation of the phenylene group.

Key words: alkaloids, cyclopeptides, macrocycles, ansa compounds, multicomponent reaction, planar chirality, natural product analogues

The success rate of natural products and products derived therefrom is overproportional in pharmaceutical development.[1–7] Two reasons accepted for this are the evolutionary advantage of natural products with privileged structural elements, and the dominance of conserved structural regions (motifs) in the target protein counterparts.[1,8,9] Furthermore, nature achieves an incredible diversity of products derived from very few basic pathway chemistries.[1,10] However, secondary natural products often show quite complex structures requiring multistep syntheses, and rendering backbone variations for lead discovery or quantitative structure–activity studies a lengthy and costly process. Consequently, only few natural-product-related libraries have been reported, and even fewer utilize rapid high-diversity multicomponent approaches.[7,9,11–16]

The most relevant structural motifs are amino acid side chains, especially in macrocycles.[1] Important recognition or active motifs are often to be found in loops,[17,18] and many mimics of constrained peptides and turns have been described,[19–24] whereby macrocycles with their structural semirigidity allow both conformational control and favorable entropy reduction, with, at the same time, some flexibility.[1,7,11] Conformationally defined, proteolytically stable cyclic peptides of medium ring size consequently have attracted some attention.[25–28] This contribution describes a highly efficient, short, and flexible synthetic route with the potential to generate libraries of natural-product-like cyclic pept(o)ides, which we term ansapeptoids.[29–32]

The basic macrocyclic motif we chose is derived from the unusual ansa structure of the natural 13-, 14-, or 15-membered cyclopeptide alkaloids **1** (Scheme 1).[1,33] In these, a benzene ring is spanned at the 1,3- or, usually, the 1,4-position by a peptide-type bridge, which, besides proteinogenic amino acids, commonly includes decarboxylated, D-, β-hydroxy-, and N,N-dialkylated amino acids and is proteolytically quite stable in blood plasma. A large variety of cyclopeptide alkaloids **1** are used in folk medicine and were isolated by us and others in small amounts from a wide range of (tropical) plants.[34–37] Antifungal and antibacterial activities as well as sedative effects have been attributed to some compounds.[33,38]

Several synthetic studies utilizing conventional approaches have been published.[39–41] In a few cases, multicomponent reactions have been used for the synthesis of some building blocks.[41–47] The efforts have concentrated on the generation of the central 14-membered macrocyclic ansa scaffold, which is most critical, since a strained system is formed. The general approach is to initially synthesize a suitably functionalized linear (di)peptide chain,[40] and then close the ring. Thus far, cyclization has been attempted at positions **A**, **B**, and **D** indicated in Scheme 1 in structure **2**.[48] Cyclization at positions **A** and **B** requires standard peptide-bond-formation methods, e.g. the macrolactamization techniques developed by Pais[49,50] and Rapoport,[51] the pioneering work of Joullié and co-workers,[52,53] and, especially, the excellent work of Schmidt.[54–56] Most cyclization attempts at positions **C** or **D**, induced by the intramolecular formation of an alkyl aryl ether bond were not very successful,[57–59] including unsuccessful biomimetic attempts by Lawton's group.[60,61] However, recently Zhu and co-workers described an efficient macrocyclization procedure based on endocyclic alkyl aryl ether bond formation by a type-**D** S_NAr reaction.[41,46,62] This approach was expanded to other aryl ether macrocycles.[47,62–65]

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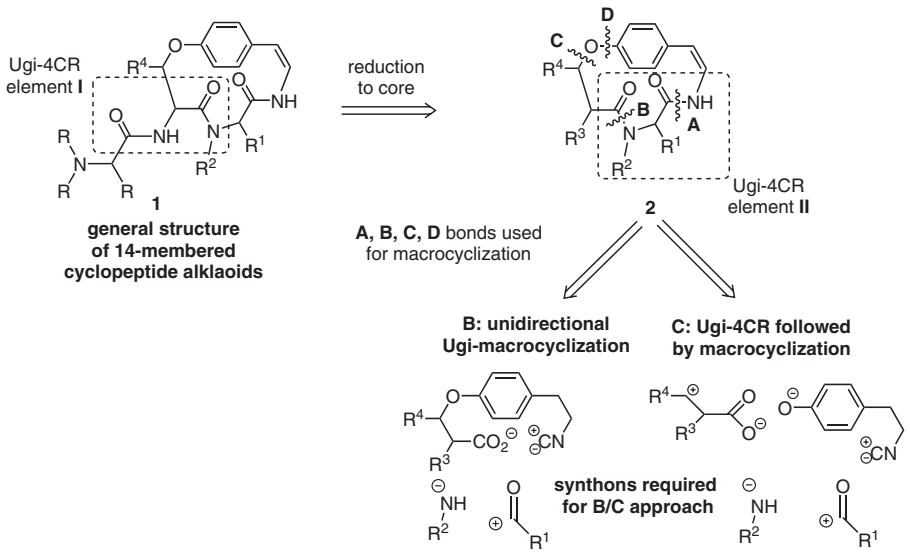

Scheme 1 Retrosynthesis and synthons/building blocks required for rapid access to the core structure of 14-membered ansa-cyclopept(o)ids

Despite the impressive achievements, these classical cyclization approaches are often characterized by low yields, or need additional steps such as reduction of an activator nitro group, or suffer from limited versatility or applicability. They are not useful for rapid automated library construction. Also, the required linear cyclization precursors are often synthesized by lengthy routes resulting in low overall yields. Finally, in most cases, there is no flexibility in the choice of starting materials and thus in the substitution pattern of the generated macrocycle.

A closer look at the general structure of cyclopeptides **1** shows that an Ugi four-component reaction (Ugi-4CR)[66] could not only be used to prepare the exocyclic peptide bonds (cf. Ugi-4CR element **I** in Scheme 1),[42,44] but also for the more relevant endocyclic α-acylamino amide moiety with different side-chain functionalities in a highly flexible way (Ugi-4CR element **II** in Scheme 1).

Further retrosynthetic analysis shows that the Ugi-4CR elements, especially element **II**, can be used not only to form the α-acylamino amide, but also to simultaneously macrocyclize the building blocks, to form the desired 14-membered ansa scaffold **2** in a single shot.[7,11] For the production of libraries, this approach is less useful, since the original four-component reaction is reduced to a three-component reaction, limiting the flexibility considerably. The main problems with this setup, however, are (a) the instability of the required bifunctional precursor with a carboxylic acid and isocyanide function in the same molecule,[67] and (b) the increased strain of the Ugi intermediates and transition states en route.[11]

More efficiently, the 14-membered ansa scaffold **2** can be prepared in two consecutive steps, combining the diversity-generating Ugi-4CR with macrocyclization.[7,11,25,68] The versatility of the standard Ugi-4CR can be used to construct a set of linear dipeptoid precursors. The crucial step will be an efficient macrocyclization. Since the Ugi-4CR is normally not sensitive to hydroxy groups, we considered the use of a type-**C** cyclization with a suitable phenol(ate) as functionalized building block to be the most straightforward strategy. Recently, Zhu followed a classical precursor synthesis to use a type-**D** cyclization for an intramolecular ring closure of an alkyl aryl ether by an S_NAr reaction.[41] However, this approach is target-oriented and not diversity-oriented and requires more complex building blocks, which had to be prepared in seven steps, instead of two to arrive at the basic skeleton. No literature precedent for type-**C** macro-etherification is known for 14-membered ansapeptoids.

Noncommercial phenol isocyanides such as **6** (Scheme 2) are crucial to our approach. Isocyanides are most commonly prepared by dehydration of the corresponding *N*-formamide.[66] Isocyanide **6** was obtained by *N*-formylation of commercially available tyramine. Protection of the phenol as acetate and subsequent dehydration with phosphoryl chloride gave *O*-acetyl-**6**. Finally, mild hydrolysis of the acetate protective group with commercial two molar ammonia in methanol gave phenol isocyanide **6** in 69% overall yield. A large selection of the other components required, aldehydes **3**, amines **4**, and carboxylic acids **5** (Scheme 2), are commercially available and affordable. Further acids **5** with an acceptor group in the β-position can be prepared straightforwardly, e.g. by a Baylis–Hillman-type reaction.[69] Thus, the full potential of the original four-component Ugi reaction is maintained, and the efficient and highly variable synthesis of libraries of α-acylamino amides **7** is possible (Scheme 2).

It was envisioned that the subsequent strained macrocyclization reaction with a phenolate as nucleophile might be problematic. Initially, a Michael addition on suitably functionalized α,β-unsaturated linear dipeptides was considered.[70] Despite the problem that the phenolate has low nucleophilicity and is a good leaving group for a retro-reaction, such an approach seemed possible, since it is be-

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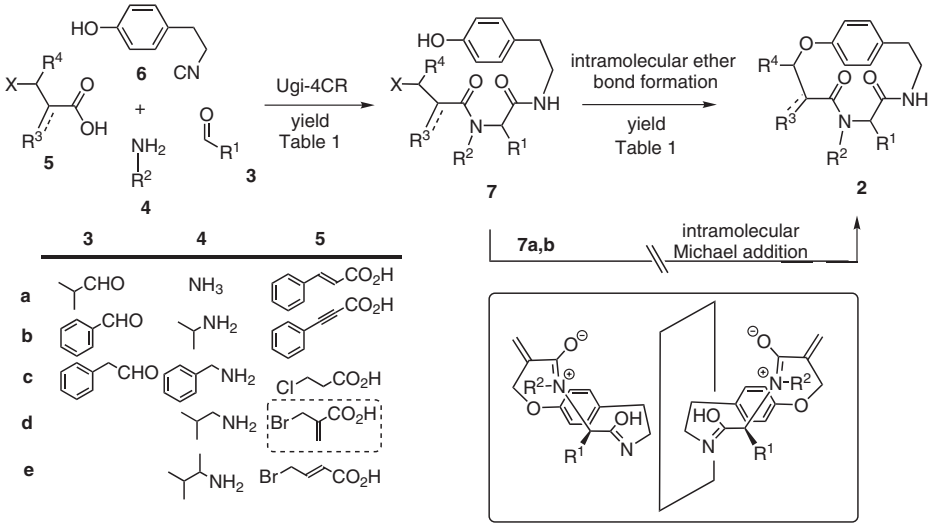

Scheme 2 Ugi reaction and subsequent macrocyclization to ansapept(o)ides **2**. *Boxed drawing*: The intrinsic chirality of twisted ansa structures (with $R^1 = H$) results in the formation of enantiomers if the bridge cannot flip. Amide bonds need to be rigid, and behave like *endo* double bonds (*s-trans* tautomeric/mesomeric forms shown for clarity). A stereocenter ($R^1 \neq H$) allows diastereomers to be formed (for details, see text).

lieved that the natural cyclopeptide alkaloids are formed biogenetically by a decarboxylation–Michael addition sequence.[33] With isocyanide **6** and α,β-unsaturated acids **5a**,**b**, Ugi-4CRs gave a selection of Michael-acceptor dipeptoids like **7a**,**b** (Scheme 2, Table 1) and similar Michael-type precursors in good to excellent yields of up to 98%. Cyclization was attempted under various conditions. Amides **7a** and **b** derived from cinnamic and phenylpropargylic acid, respectively, showed no reaction at all in toluene, tetrahydrofuran, or *N*,*N*-dimethylacetamide (DMA) under neutral or basic conditions (py, *t*-BuOK, K_2CO_3, DMAP, NMM) at various temperatures.[70–72]

These rather disappointing results led us to consider an intramolecular nucleophilic substitution reaction to induce cyclization. First, the chloro-substituted α-acylamino amide **7c** (X = Cl; $R^3 = H$) was prepared in 96% yield by an Ugi-4CR from isopropylamine (**4b**), isobutyraldehyde (**3a**), 3-chloropropanoic acid (**5c**), and isocyanide **6** (Scheme 2). Subsequently, an S_N2-induced cyclization was attempted with the use of potassium *tert*-butoxide, alkali carbonates, or 4-(*N*,*N*-dimethylamino)pyridine as bases. Reactions were performed in *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide (DMA), toluene, or acetone at room and reflux temperatures. Unfortunately, no cyclization products were isolated, and only β-elimination of hydrogen chloride to give the corresponding, unreactive α,β-unsaturated amides such as **7c′** could be detected. Various other cyclization attempts with compounds **7** with $R^3 = H$ and X = Cl, Br, OTs, or OH (Williamson ether synthesis or Mitsunobu reaction) also failed. In contrast to this, the reaction of 4-bromocrotonic acid (**5e**) with **3a**, **4b**, and **6** gave a dipeptoid **7k** (60% yield), which could be cyclized to a 15-membered ansa-cyclopeptide in 25% yield and a dimeric 30-membered compound in 50% yield (c = 1 mM, K_2CO_3, cat. KI, acetone).

To avoid β-elimination or a retro-Michael reaction, a combination of the two unsuccessful reaction types was considered as a solution to obtain the 14-membered core compounds. Thus, linear dipeptide **7d** was prepared (55% yield) as described above, from 2-(bromomethyl)acrylic acid (**5d**), isonitrile **6**, aldehyde **3a**, and amine **4d** (Scheme 2). Whereas acids **5a**–**c** generally gave the Ugi products **7** in 80–98% yield, somewhat lower yields resulted with acid **5d** (often around 50%). This can be attributed to the strong electrophilic nature of the allyl bromide moiety. The intermediate imine formed from the aldehyde and amine at the beginning of the reaction is in equilibrium with its enamine tautomer, depending on the substitution pattern. Enamines are susceptible to allylation by **5d**, resulting in undesired side products. Thus, in Ugi reactions with acid **5d**, either suitably substituted imines or acidic conditions should be chosen to favor the direct Ugi reaction over enamine alkylation.

After deprotonation of the phenolic hydroxy function in the linear dipeptoid **7d**, intramolecular nucleophilic substitution of bromine resulted in the desired 14-membered ansa-cyclopeptoid **2a**. Several attempts have been made to optimize the cyclization yield and to counter the moderate nucleophilic activity of the phenolate anions. Reactions have been attempted with sodium hydride, potassium *tert*-butoxide, or potassium carbonate, each in *N*,*N*-dimethylformamide, acetone, methanol, or *tert*-butyl alcohol at room temperature. All experiments were carried out with and without a catalytic amount of either potassium iodide or 18-crown-6. Finally, the use of a vigorously stirred suspension of potassium carbonate and a catalytic amount of 18-crown-6 in acetone proved to be the most successful.

In this way, the 14-membered ansa-cyclopeptide **2a** could be isolated in 60% yield under dilution conditions (0.6 mM), to avoid dimer formation. To minimize the required amount of solvent used, the cyclization reaction was also

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Table 1 Linear Ugi Products **7** Obtained from Isonitrile **6** and Subsequent Macrocyclization of **7d–k** to **2**[a]

Starting material	Product	R^1	R^2	CR^3CXR^4 \b	Yield (%)
3a + 4b + 5a + 6	**7a**	*i*-Pr	*i*-Pr	CH=CHPh	87
3a + 4b + 5b + 6	**7b**	*i*-Pr	*i*-Pr	C≡CPh	98
3a + 4b + 5c + 6	**7c**	*i*-Pr	*i*-Pr	CH_2CH_2Cl	96
	7c′	*i*-Pr	*i*-Pr	$CH=CH_2$	
3a + 4b + 5d + 6	**7d**	*i*-Pr	*i*-Pr	$C(=CH_2)CH_2Br$	55
3a + 4e + 5d + 6	**7e**	*i*-Pr	CH(*i*-Pr)Me	$C(=CH_2)CH_2Br$	55
3b + 4a + 5d + 6	**7f**	Ph	H	$C(=CH_2)CH_2Br$	12
3b + 4b + 5d + 6	**7g**	Ph	*i*-Pr	$C(=CH_2)CH_2Br$	45
3b + 4c + 5d + 6	**7h**	Ph	Bn	$C(=CH_2)CH_2Br$	36
3b + 4d + 5d + 6	**7i**	Ph	*i*-Bu	$C(=CH_2)CH_2Br$	50
3c + 4b + 5d + 6	**7j**	Bn	*i*-Pr	$C(=CH_2)CH_2Br$	14
3a + 4b + 5e + 6	**7k**	*i*-Pr	*i*-Pr	$CH=CHCH_2Br$	60
7d	**2a**	*i*-Pr	*i*-Pr	$C(=CH_2)CH_2$	60/95[c]
7e	**2b**	*i*-Pr	CH(*i*-Pr)Me	$C(=CH_2)CH_2$	19
7f	**2c**	Ph	H	$C(=CH_2)CH_2$	87
7g	**2d**	Ph	*i*-Pr	$C(=CH_2)CH_2$	30
7h	**2e**	Ph	Bn	$C(=CH_2)CH_2$	24
7i	**2f**	Ph	*i*-Bu	$C(=CH_2)CH_2$	20
7j	**2g**	Bn	*i*-Pr	$C(=CH_2)CH_2$	mixture
7k	**2k**	*i*-Pr	*i*-Pr	$CH=CHCH_2$	25 (+50[d])

[a] All new compounds gave the expected spectroscopic data.
[b] Corresponds to $–CHR^3CHXR^4$ for products **7** and $–CHR^3CHR^4–$ for products **2**.
[c] Optimized macrocyclization conditions applied with pseudodilution.[11,]
[d] Dimer.

performed under pseudo-dilution, by slow addition (2.5 $\mu L \cdot min^{-1}$) of a rather concentrated solution (50 mM) of linear peptoid **7d** to a suspension of potassium carbonate and 18-crown-6 in acetone. The carbonate concentration proved to be critical: too high concentrations of base resulted in complicated product mixtures whereas too low concentrations gave, next to the desired ansa-macrocycle **2a**, unchanged **7d**. However, optimization of the potassium carbonate content (25 mM in acetone) afforded cyclopeptide **2a** in 95% isolated yield. In this way, solvent consumption was reduced tenfold, dimer formation was negligible, and the conversion was almost quantitative compared to the outcome of the initial cyclization conditions.

To demonstrate the broader synthetic applicability of this highly efficient two-step procedure, seven variably functionalized macrocyclic ansapeptides were prepared manually and characterized. Thus, five different amines **4a–e** and three different aldehydes **3a–c** reacted with 2-(bromomethyl)acrylic acid **5d** and isocyanide **6** to give seven different α-acylamino amides **7d–j** in reasonable to good yields (Scheme 2, Table 1). Crucial for an efficient Ugi-4CR is the initial formation of an imine intermediate.[66] Optimal yields of linear peptoids **7** were obtained with aldehyde–amine combinations resulting in imine intermediates less prone to tautomerization to the corresponding enamines.

Subsequently, all seven linear α-acylamino amides **7d–j** were treated with potassium carbonate and 18-crown-6 as described above to effect cyclization (Scheme 2, Table 1). Cyclic ansapeptides **2** generally formed smoothly and in good yields (up to 95%). The low end is occupied by the cyclic ansapeptoids **2b**, **2f**, and **2g** (Table 1, <20%), owing to significant dimer formation (**2f**) and/or a slow conversion rate.

It should also be noted that, depending on the bulkiness of the substituents, some cyclization products form as diastereomers, although the molecules contain only one asymmetric carbon center (see box in Scheme 2).

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Through cyclization, a chiral plane forms – despite the aryl ring being exclusively 1,4-substituted and able to rotate freely (both rims are equivalent in NMR); i.e., compounds **2** deviate from the usual cyclophane-type planar chirality. Obviously, the tether is twisted by conformational ring strain, and chirality results in a way similar to that observed in *trans*-cyclooctene, but without a double bond in the ring in this case. The amide bonds, if seen in tautomeric and mesomeric forms as shown in the representation, may serve as a substitute. Still, the tethers of the two conformers can flip: the corresponding planar chirality has not been reported for similar natural products with $R^2 = H$ or with small R^1 and R^2. Molecular modeling shows that the tether does not flip over if R^2 can not pass through between R^1 and the *exo*-methylene group. As a consequence, the conformers can not interconvert, and diastereomerism results, which, e.g., in the case of **2d** allows both isomers to be detected by NMR spectroscopy at low temperatures. This quite unusual behavior will be elucidated in more detail elsewhere.

Another special case is **2c** ($R^2 = H$; from **7f** in 87% yield), obtained by the direct use of ammonia in the Ugi-4CR, commonly a difficult problem. Initially, we tried to use 4-methoxyaniline as a masked ammonia equivalent, but this resulted in complex mixtures (enamine formation). The direct use of ammonia was more successful in our system, although the conditions had to be modified to avoid hemiaminal formation, which happens by condensation of an initially formed benzylidene amine, reaction with the alcohol solvent and then with excess benzaldehyde before the Ugi reaction starts. This side reaction can be reduced if an excess of an ammonium salt in a solvent other than an alcohol is used. The thus directly accessible 'normal' dipeptide bond ($R^2 = H$) is of great importance for natural cyclopeptide alkaloids, where N-substitution of the endocyclic amide bond is not common and planar chirality is not described.

In conclusion, we have developed a highly efficient, extremely short, and flexible two-step route to macrocyclic ansapeptoids and peptides amenable to automated synthesis. Macrocyclic dipeptides ($R^2 = H$) prepared in this way are suitable for further synthetic elaboration toward natural cyclopeptide alkaloids. In addition, the method allows rapid access to libraries of variably substituted natural-product-like ansa scaffolds with additional functionalities (e.g., R^2 or with other hydroxy isonitrile building blocks), or new orientation, or a rare form of planar chirality.

All glassware was flame-dried prior to use. All reagents and solvents were purchased from commercial sources and used as supplied or purified by standard methods. Preparations were carried out under a N_2 atmosphere.

^{1}H NMR spectra were recorded in the specified solvents on a Bruker spectrometer at 200 MHz or at 400 MHz operating at ambient probe temperature unless stated otherwise. Coupling constants were measured in Hertz (Hz). ^{13}C NMR spectra were recorded in the specified solvents on a Bruker spectrometer at 50 MHz or at 100 MHz operating at ambient probe temperature unless stated otherwise. NMR assignments were based on 2D NMR experiments. Low-resolution electron-impact mass spectra were determined at 70 eV on a MAT 900 mass spectrometer. LC-MS was carried out on an API-150 apparatus equipped with an Agilent 1100 LC. Separations were carried out by using gradient elution, initiated with MeCN–H_2O (1:1). The MeCN concentration was then increased to 90% over 15 min. Both solvents contained 0.2% AcOH. The negative, as well as the positive electrospray mass spectra were recorded, using a turbo ion spray source for ionization. HRMS-spectra were measured on a Finnigan MAT 90 (EI 70eV or CI with isobutene), or on a Bruker Apex III FT ion cyclotron resonance (ICR) mass spectrometer equipped with an Infinity cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide, and an external ESI source (Agilent, off-axis spray). Some products, if prepared and kept as MeOH soln for ESI reacted by addition to the acrylamide moiety or substitution to the allyl bromide moiety. HPLC other than LC-MS was done on a Shimadzu apparatus (Alltima C18 5 u, 100 × 2.1 mm). Separations were carried out by using isocratic elution with MeCN–H_2O (55:45; containing 1% HCO_2H) at a flow rate of 0.2 mL/min. Detection was done with a diode array detector. Analytical TLC was carried out on precoated plates (Merck TLC aluminum sheets, silica gel 60 F254, Art. No. 5554) and visualized under UV light (254 nm), by treating with either aq $KMnO_4$, or cerium-molybdatophosphate reagent followed by heating. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh). PE (bp 40–60 °C) was used. Whenever a cyclization was performed under pseudo-diluted conditions, a syringe pump (SAGE instruments – 341B) was used to maintain constant flow and tin-foil-wrapped syringes (BD-Plastipack) were equipped with inert peek-tubing (0.010 in/0.25 mm) to prevent the reagent from degrading by exposure to UV light.

Compounds 7 by Ugi-4CR; General Procedure

Freshly distilled amine **4** (2 equiv) and aldehyde **3** (2 equiv) were added to MeOH (final c = 1 M) and the mixture was stirred for 60 min at r.t. in the presence of a drying agent (Na_2SO_4). Then acid **5** (1 equiv) was added and stirring continued for another 30 min (or shorter for **5d**), after which isocyanide **6** (1 equiv) was added. Mostly, reactions were completed after 2 h at r.t. (by TLC, EtOAc–$CHCl_3$, 1:1 or EtOAc–PE, 2:1). The mixture was poured into H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). Isolation of the reaction products was usually by evaporation of excess solvent and reagents. After flash chromatography, the Ugi products **7** could be isolated and characterized (see below for selected examples). The acceptor-substituted allylic bromides are of limited stability, especially in the presence of nucleophiles such as MeOH (e.g., before chromatography, on extended storage, or when used in MeOH in ESI-MS).

Ugi Product 7a

R_f = 0.50, 0.59 (EtOAc–$CHCl_3$, 1:1).

t_R = 3.66, 4.44 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.49 (d, J = 6.8 Hz, 3 H), 0.58 (d, J = 6.8 Hz, 3 H), 0.74 (d, J = 6.5 Hz, 3 H), 0.77 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 2.65–2.74 (m, 4 H), 2.80–2.87 (m, 2 H), 3.00 (t, J = 11.1 Hz, 2 H), 3.20–3.28 (m, 2 H), 3.51–3.60 (m, 2 H), 3.85–3.92 (m, 2 H), 5.12 (s, 1 H), 5.16 (s, 1 H), 5.33 (s, 1 H), 5.41 (s, 1 H), 5.48 (s, 1 H), 5.59 (s, 1 H), 6.76–6.80 (m, 4 H), 7.05–7.08 (m, 4 H), 7.17–7.29 (m, 10 H), 8.27 (t, J = 5.4 Hz, 1 H), 8.34 (t, J = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.3, 20.6, 20.6, 20.7, 20.8, 20.8, 20.9, 27.3, 27.4, 35.2, 41.3, 41.4, 52.8, 53.2, 68.7, 68.7, 74.7, 77.0, 112.5, 116.0 (2 C), 116.1 (2 C), 116.4, 126.3 (2 C), 126.8 (2 C), 128.4 (2 C), 128.7 (2 C), 128.9 (2 C), 129.1 (2 C), 130.1 (2 C), 130.2 (2 C), 130.6, 140.9, 141.2, 145.7, 147.4, 155.5, 155.6, 173.0, 173.3, 173.4, 173.7.

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ESI-MS: *m*/*z* = 439.4 [MH$^+$].

Ugi Product 7d

R_f = 0.67 (EtOAc–$CHCl_3$, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.16–1.18 (m, 6 H), 2.67–2.75 (m, 2 H), 2.86–2.92 (m, 1 H), 3.21 (d, *J* = 11.1 Hz, 1 H), 3.41–3.54 (m, 2 H), 4.00 (d, *J* = 10.3 Hz, 1 H), 4.33–4.42 (m, 2 H), 5.17 (s, 1 H), 5.45 (s, 1 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.30 (br s, 1 H), 8.45 (t, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 20.3, 20.5, 21.1, 27.0, 33.0, 34.9, 40.7, 52.3, 68.5, 115.4 (2 C), 116.9, 129.6 (2 C), 130.0, 141.1, 155.1, 171.2, 173.5.

ESI-MS: *m*/*z* = 425.1 [MH$^+$].

Ugi Product 7e

R_f = 0.75 (EtOAc–$CHCl_3$, 1:1).

t_R = 6.91, 7.32 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.94 (m, 24 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.89–1.93 (m, 2 H), 2.70–2.75 (m, 4 H), 2.88 (m, 2 H), 3.17 (d, *J* = 11.1 Hz, 1 H), 3.31(d, *J* = 10.8 Hz, 1 H), 3.42–3.50 (m, 4 H), 3.64 (m, 1 H), 3.86 (m, 1 H), 3.97 (d, *J* = 10.6 Hz, 1 H), 4.03 (d, *J* = 11.0 Hz, 1 H), 4.22 (d, *J* = 11.0 Hz, 1 H), 4.31 (d, *J* = 10.6 Hz, 1 H), 5.24 (s, 1 H), 5.34 (s, 1 H), 5.51 (s, 1 H), 5.62 (s, 1 H), 6.75 (d, *J* = 8.2 Hz, 4 H), 7.03 (d, *J* = 8.2 Hz, 4 H), 8.26 (br s, 1 H), 8.72 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 17.8, 19.4, 19.9, 20.0, 20.35, 20.43, 20.8, 20.9, 21.8, 27.0, 28.3, 31.2, 31.6, 31.8, 32.9, 34.6, 34.7, 40.6, 40.9, 62.4, 63.1, 69.3, 69.7, 115.4 (4 C), 118.6, 120.2, 129.6 (4 C), 130.0, 130.1, 141.0, 141.1, 155.0 (2 C), 171.5, 172.3, 172.7, 174.1.

ESI-MS: *m*/*z* = 453.2 [MH$^+$].

ESI-HRMS: *m*/*z* [M – Br + OMe + Na]$^+$ calcd for $C_{23}H_{36}N_2O_4Na$: 427.25673; found: 427.25675.

Ugi Product 7f

R_f = 0.51 (EtOAc–$CHCl_3$, 1:1).

t_R = 3.38 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54–2.65 (m, 4 H), 3.29–3.42 (m, 3 H), 3.49 (s, 3 H), 3.50–3.55 (m, 1 H), 4.11 (d, *J* = 10.6 Hz, 1 H), 4.17 (d, *J* = 10.8 Hz, 1 H), 4.20 (d, *J* = 10.8 Hz, 1 H), 4.67 (d, *J* = 10.5 Hz, 1 H), 4.82 (s, 1 H), 5.43 (d, *J* = 6.5 Hz, 1 H), 5.72 (s, 1 H), 5.73 (s, 1 H), 5.77 (s, 1 H), 5.84 (t, *J* = 5.5 Hz, 1 H), 5.89 (s, 1 H), 6.03 (t, *J* = 5.8 Hz, 1 H), 6.19 (s, 1 H), 6.65 (dd, *J* = 2.0, 8.4 Hz, 4 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.87–7.33 (m, 15 H), 7.51 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0, 33.0, 34.5 (2 C), 41.3, 41.4, 55.9, 57.5, 63.0, 89.5, 115.4 (2 C), 115.6 (2 C), 120.6, 123.5, 127.2 (2 C), 127.3 (2 C), 127.6, 128.2 (2 C), 128.5 (2 C), 128.6, 128.9 (2 C), 129.1 (2 C), 129.7 (2 C), 129.7 (2 C), 130.8, 135.2, 135.9, 137.6, 139.9, 140.6, 154.6, 154.8, 165.4, 169.3, 169.6, 170.5.

ESI-MS: *m*/*z* = 417.4 [MH$^+$], 537.6 [M + 1].

Ugi Product 7g

R_f = 0.38 (EtOAc–$CHCl_3$, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.6 Hz, 3 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 2.63–2.68 (m, 2 H), 3.41–3.48 (m, 2 H), 4.16 (d, *J* = 10.2 Hz, 1 H), 4.31 (d, *J* = 10.2 Hz, 1 H), 4.57 (br s, 1 H), 4.84 (br s, 1 H), 5.34 (s, 1 H), 5.50 (s, 1 H), 6.44 (br s, 1 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 7.27–7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.5, 33.4, 34.5, 41.3, 51.4, 62.2, 115.4 (2 C), 117.3, 127.7, 128.0 (2 C), 128.8 (2 C), 129.6 (2 C), 130.0, 136.1, 140.4, 154.8, 170.0, 170.2.

ESI-MS: *m*/*z* = 459.4 [M + 1].

Ugi Product 7h

R_f = 0.32 (EtOAc–$CHCl_3$, 1:1).

t_R = 6.06 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, $CDCl_3$, 330 K): δ = 2.61–2.65 (m, 2 H), 3.36–3.49 (m, 2 H), 4.10 (d, *J* = 10.2 Hz, 1 H), 4.39 (d, *J* = 10.4 Hz, 1 H), 4.51 (d, *J* = 16.5 Hz, 1 H), 4.90 (d, *J* = 16.5 Hz, 1 H), 5.21 (br s, 1 H), 5.38 (s, 1 H), 5.46 (s, 1 H), 5.73 (br s, 1 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.15–7.27 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$, 330 K): δ = 33.2, 34.4, 41.2, 51.7, 65.9, 115.7 (2 C), 118.7, 119.0, 127.3 (2 C), 128.5 (2 C), 128.7, 128.9 (2 C), 129.5 (2 C), 129.6 (2 C), 130.0, 134.5, 136.8, 139.9, 155.0, 169.1, 170.9.

Ugi Product 7i

R_f = 0.57 (EtOAc–$CHCl_3$, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.42 (br s, 3 H), 0.62 (d, *J* = 6.7 Hz, 3 H), 1.03 (br s, 1 H), 2.60 (t, *J* = 7.1 Hz, 2 H), 3.07 (m, 1 H), 3.29–3.35 (m, 3 H), 4.32 (d, *J* = 6.9 Hz, 1 H), 4.40 (d, *J* = 10.2 Hz, 1 H), 5.11 (br s, 1 H), 5.65 (d, *J* = 15.1 Hz, 2 H), 6.65 (d, *J* = 8.3 Hz, 2 H), 6.96 (d, *J* = 8.3 Hz, 2 H), 7.29–7.49 (m, 5 H), 8.12 (br s, 1 H), 9.14 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.0, 20.1, 26.9, 34.0, 34.2, 40.4, 51.0, 64.3, 115.0 (2 C), 118.2, 128.2, 128.4 (2 C), 129.2, 129.4 (2 C), 129.5 (2 C), 136.3, 140.1, 155.6, 169.0, 169.4.

ESI-MS: *m*/*z* = 473.3 [MH$^+$].

Compounds 2 by Cyclization of 7d–j; General Procedure

To a suspension of commercial, dry K_2CO_3 (70 mg, 0.50 mmol) and 18-crown-6 (20 mg) in dry acetone (20 mL) was added a 50 mM soln of **7** in acetone (2.5 mL) over 18 h by a syringe pump. Then H_2O (25 mL) was added and the aqueous mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). The solvents were evaporated at 40 °C under reduced pressure. The crude reaction product was purified by flash chromatography (silica gel, MeOH–$CHCl_3$, 5:95); this gave pure **2**.[73] The less sterically hindered derivatives, e.g. **2c**, slowly react with nucleophiles, e.g. MeOH (e.g., when used in MeOH in ESI-MS).

Ansapeptoid 2a

R_f = 0.37 (EtOAc–$CHCl_3$, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.26 (m, 24 H), 2.22–2.29 (m, 1 H), 2.33–2.42 (m, 2 H), 2.50–2.57 (m, 1 H), 2.92–3.01 (m, 2 H), 3.07–3,25 (m, 5 H), 3.27–3.36 (m, 1 H), 4.32–4.51 (m, 4 H), 4.67 (d, *J* = 12.1 Hz, 1 H), 4.82 (d, *J* = 11.9 Hz, 1 H), 5.20 (s, 1 H), 5.21 (s, 1 H), 5.40 (s, 1 H), 5.42 (s, 1 H), 6.73 (d, *J* = 8.6 Hz, 4 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 8.28 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (2 C), 20.3 (2 C), 20.4 (2 C), 21.27, 21.33, 22.6, 26.8 (2 C), 31.6, 34.1, 34.5, 39.9, 40.2, 52.3 (2 C), 68.6, 68.7, 68.8, 69.1, 114.2, 114.3, 129.4 (2 C), 129.5 (2 C), 131.8, 131.9, 141.8, 141.8, 156.7, 156.8, 171.8, 171.9, 173.2 (2 C).

MS (EI): *m*/*z* = 344 [M$^+$].

Ansapeptide 2c

t_R = 13.24, 14.23 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.60–2.65 (m, 2 H), 2.72–2.78 (m, 2 H), 3.09–3.49 (m, 4 H), 4.67–4.79 (m, 4 H), 5.48 (d, *J* = 8.2 Hz, 1 H), 5.52 (d, *J* = 8.2 Hz, 1 H), 5.77 (s, 1 H), 6.06 (s, 1 H), 6.07

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(s, 1 H), 6.78–6.83 (m, 4 H), 7.04–7.07 (m, 4 H), 7.21–7.45 (m, 10 H), 8.13 (t, *J* = 5.5 Hz, 1 H), 8.21 (t, *J* = 5.5 Hz, 1 H), 8.38–8.42 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.4 (2 C), 39.4 (2 C), 56.5 (2 C), 67.1 (2 C), 114.5 (4 C), 122.9, 127.0 (4 C), 128.2 (4 C), 129.8 (4 C), 131.9 (2 C), 137.3 (2 C), 138.6 (2 C), 139.1 (2 C), 156.3 (2 C), 165.1 (2 C), 169.5 (2 C).

MS (EI): *m*/*z* = 336 [M$^+$].

Ansapeptoid 2d

R_f = 0.28 (EtOAc–MeOH, 19:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.0 Hz, 6 H), 2.54 (m, 1 H), 2.63–2.69 (m, 1 H), 3.30–3.40 (m, 1 H), 3.40–2.59 (m, 1 H), 4.44 (d, *J* = 12.4 Hz, 1 H), 4.56 (br s, 1 H), 4.65 (d, *J* = 12.1 Hz, 1 H), 4.97 (br s, 1 H), 5.28 (s, 1 H), 5.44 (s, 1 H), 6.66 (d, *J* = 7.6 Hz, 2 H), 6.98 (d, *J* = 8.3 Hz, 2 H), 7.23–7.33 (m, 5 H), 7.69 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 21.3, 34.4, 40.5, 51.9, 62.9, 69.0, 114.4 (2 C), 115.0, 126.3, 127.4, 128.4, 128.7, 129.7 (2 C), 131.9, 136.1, 141.3, 156.6, 170.5, 170.8, 171.4.

MS (EI): *m*/*z* = 378.2 [M$^+$].

HRMS: *m*/*z* [M]$^+$ calcd for $C_{23}H_{26}N_2O_3$: 378.1943; found: 378.1944.

Ansapeptoid 2e

t_R = 32.69, 36.17 min (MeCN–1% HCO_2H in H_2O, 55:45).

^{1}H NMR (400 MHz, DMSO-d_6, 330 K): δ = 2.44–2.73 (m, 4 H), 3.03–3.57 (m, 4 H), 4.39–4.43 (m, 2 H), 4.55–4.69 (m, 4 H), 4.78–4.83 (m, 2 H), 5.18 (s, 1 H), 5.23 (s, 1 H), 5.38 (s, 1 H), 5.39 (s, 1 H), 5.74 (s, 1 H), 5.77 (s, 1 H), 6.65–7.23 (m, 28 H), 7.77 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6, 330 K): δ = 33.6, 39.7, 63.2, 67.9, 114.6 (2 C), 115.7, 126.7 (4 C), 127.5 (2 C), 127.9, 128.3 (2 C), 129.0, 129.5 (2 C), 131.7, 135.8, 138.4, 141.0, 156.4, 169.0, 170.9.

MS (EI): *m*/*z* = 426 [M$^+$].

ESI-HRMS: *m*/*z* [M + MeOH + Na]$^+$ calcd for $C_{28}H_{30}N_2O_4Na$: 481.2103; found: 481.21085.

Ansapeptoid 2f

R_f = 0.41 (EtOAc–MeOH, 19:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.82 (m, 6 H), 1.89 (br s, 1 H), 2.65–2.76 (m, 2 H), 3.22–3.31 (m, 1 H), 3.41–3.52 (m, 3 H), 4.51–4.66 (m, 2 H), 5.31 (m, 2 H), 5.53 (s, 1 H), 6.69–6.74 (m, 2 H), 6.96–7.00 (m, 2 H), 7.29 (d, *J* = 9.2 Hz, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.5, 27.8, 34.7, 41.0, 59.2, 67.2, 69.7, 115.1 (2 C), 117.6, 128.6 (2 C), 128.9 (2 C), 130.2 (2 C), 132.0, 135.6, 135.66, 141.1, 157.3, 170.2, 171.7.

MS (EI): *m*/*z* = 392 [M$^+$].

HRMS: *m*/*z* [M]$^+$ calcd for $C_{24}H_{28}N_2O_3$: 392.2100; found: 392.2102.

ESI-HRMS: *m*/*z* [M_2 + Na]$^+$ calcd for $C_{48}H_{56}N_4O_6Na$: 807.4092; found: 807.4083.

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(73) Broad signals in the ^1H NMR spectrum and the presence of additional signals in the ^{13}C NMR spectrum suggest coexisting conformers. Spectral data refer to major isomer.
(74) Some recent relevant references (added in proof): (a) Cristau, P.; Vors, J.-P.; Zhu, J. *QSAR & Comb. Sci.* **2006**, 25, 519. (b) Cristau, P.; Temol-Laib, T.; Bois-Choussy, M.; Martin, M.-T.; Vors, J.-P.; Zhu, J. *Chem. Eur. J.* **2005**, 11, 2668. (c) Tan, N.-H.; Zhou, J. *Chem. Rev.* **2006**, *106*, 840.

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