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Rapid and diverse route to natural product-like biaryl ether containing macrocycles

Pierre Cristau,[a] Jean-Pierre Vors[b] and Jieping Zhu[a,*]

[a]*Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, cedex 91198, France*
[b]*Bayer CropScience, 14-20 Rue Pierre Baizet, Lyon 69009, France*

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Abstract—A two-step sequence involving an Ugi four-component reaction and an intramolecular nucleophilic aromatic substitution (S_NAr) has been developed for the rapid access to biaryl-ether containing macrocycles. In the course of this study, we documented that ammonium chloride can promote the Ugi-4CR in non-polar aprotic solvent (toluene) without the interference of an alternative Passerini reaction. Solid phase synthesis of macrocycles by this two-step sequence was also developed using polymer (Wang resin) supported α-(4′-fluoro-3′-nitro)phenethyl isocyanoacetate as one of the inputs.

1. Introduction

Many macrocycles with a non-symmetrical *endo* biaryl ether bridge have been found in nature. These compounds range from the monocyclic K-13 (**1**) (ACE inhibitor),[1] the bicyclic piperazinomycin (**2**) (antifungal),[2] the RA VII (**3**) (antitumor antibiotics)[3] to the structurally complex polycyclic glycopeptide vancomycin (**4**), an important antibiotic used as a last resort for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive bacteria[4] (Fig. 1). Not surprisingly, non-natural biaryl ether containing macrocycles have been designed and compounds with potent bioactivities have been identified.[5]

Mainly intrigued by the molecular complexity as well as the synthetic challenges posed by vancomycin, a number of new synthetic methodologies have been developed during the past decade that made the construction of the elusive biaryl ether containing macrocycles possible. From the view point of retro-synthetic analysis, two strategies are among the most obvious for the synthesis of above-mentioned macrocycles.[6,7] The first one involves the formation of the functionalized biaryl ether unit, followed by macrolactamization that has been successfully applied to the total synthesis of K-13 (**1**) and OF4949-III.[8] The second strategy consists of the construction of the suitably functionalized peptide backbone followed by the ring closure with concomitant formation of the biaryl ether bridge. To implement this latter strategy, few methodologies including thallium trinitrate promoted intramolecular oxidative coupling,[9] intramolecular Ullmann reaction[10] nucleophilic aromatic substitution (S_NAr) reaction[11] and Cu-assisted O-arylation of arylboronic acid[12] have been developed. The mild cyclization condition in conjunction with the high chemical yield and generality made the S_NAr based cyclization methodology one of the most efficient technologies for the access of aryl-ether containing macrocycles. Indeed, a number of natural products including K-13,[13] RA-VII,[14] aceroside IV,[15] sanjoinine G1,[16] vancomycin,[17] and teicoplanin[18] have been synthesized by using this cycloetherification reaction as a key step.

The development of efficient synthetic tools in conjunction with the emergency of high throughput screening of drug candidates have provided opportunities for the library production of biaryl ether containing macrocycles, inaccessible just a few years back. Since the initial report on the solid phase synthesis of OF-4949 analogs by S_NAr-based macrocyclization reaction,[19] a number of aryl ether containing macrocyclic compound libraries with a peptide tether have been synthesized.[20,21] While on-resin S_NAr macrocyclization worked nicely to provide the expected macrocycles, the cyclization precursors in these studies have been prepared by a stepwise peptide coupling strategy, elongating thus the overall synthetic sequence.

In connection with our ongoing project aimed at the development of step-efficient high throughput synthesis of potentially bioactive molecules,[22] we envisaged the synthesis of the biaryl ether containing macrocycles of generic structure (**5**) by combined use of Ugi-4CR[23] and S_NAr methodology.[24,25] The underlying principle is shown in the Scheme 1. Thus, the Ugi reaction of an aldehyde (**7**), an

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* Corresponding author. Tel.: +33-1-69-82-31-31; fax: +33-1-69-07-72-47; e-mail: zhu@icsn.cnrs-gif.fr

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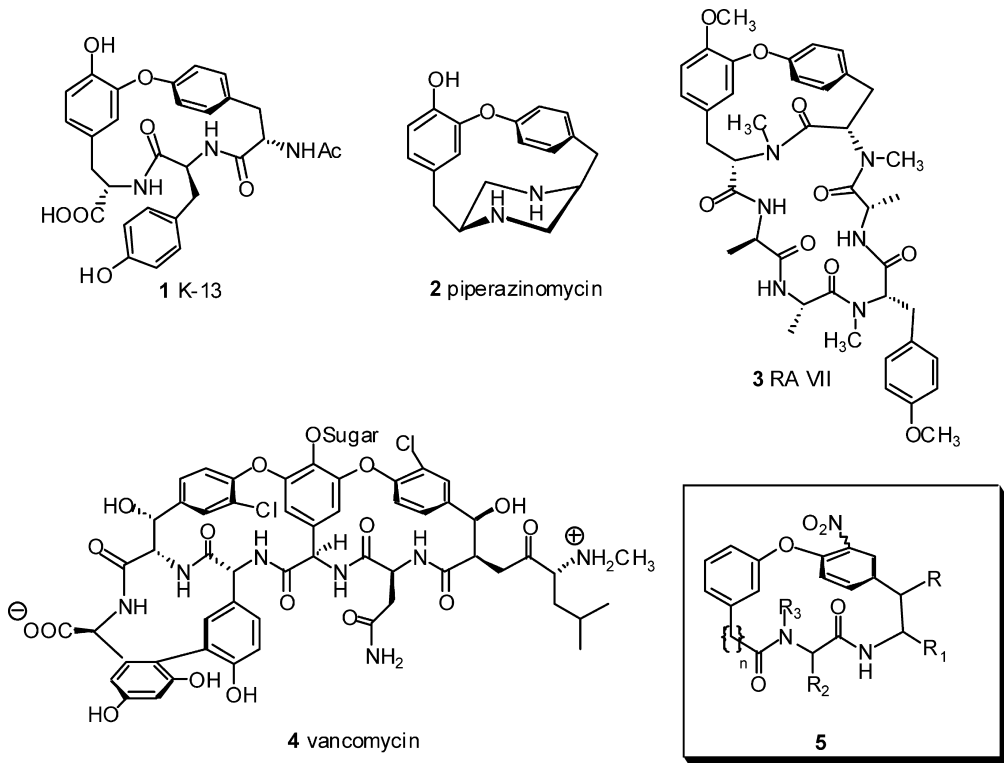
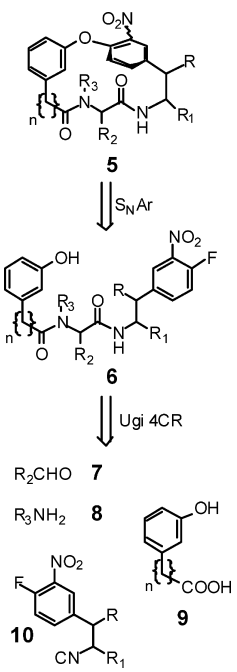


Figure 1. Natural products with *endo* aryl–aryl ether bond.

amine (**8**), a ω-(3′-hydroxyphenyl)alkanecarboxylic acid (**9**), and a suitably functionalized isonitrile (**10**) should give the dipeptide (**6**) which under our previously established conditions, should cyclize to provide the desired *m,p*-cyclophanes (**5**).[26] We detail herein the successful implementation of this strategy using both solution and solid phase synthesis technologies. Tempest, Hulme and their co-workers have independently developed the similar approach for the synthesis of fused 7-membered heterocycles.[27]



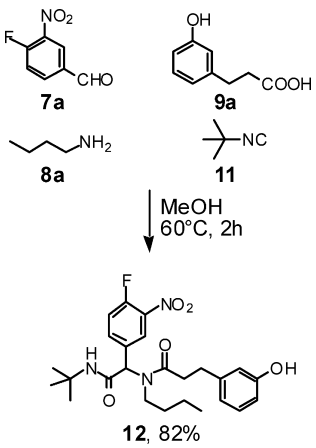
Scheme 1.

2. Results and discussion

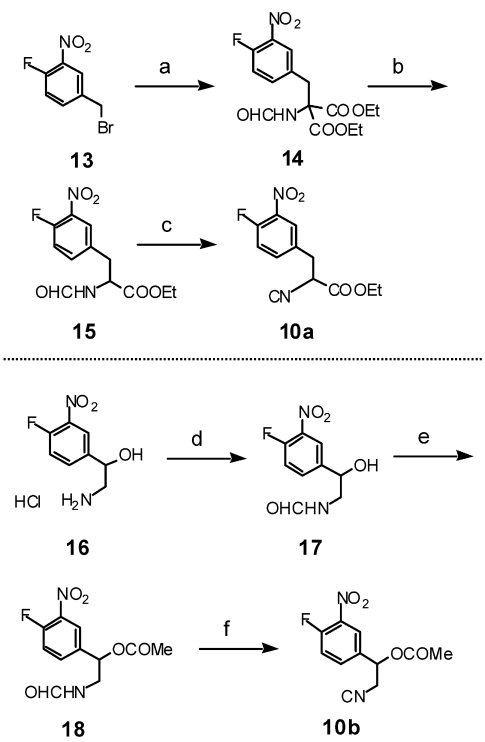
2.1. Solution phase synthesis of biaryl ether containing macrocycles (5)

At the outset of this work, we were unaware of the compatibility of an ortho fluoronitro aromatic compound and an amine under the Ugi's reaction conditions. Indeed, amines and low-molecular-weight alcohols, which are usually the solvent of choice for Ugi-4CR are known to be good nucleophiles for the intermolecular S_NAr reaction.[28] In order to evaluate the feasibility of our approach, the reaction of the known 4-fluoro-3-nitrobenzaldehyde (**7a**),[29] butylamine (**8a**), 3-(3′-hydroxyphenyl) propionic acid (**9a**) and the commercially available *tert*-butyl isocyanide (**11**) in MeOH was carried out. As shown in Scheme 2, Ugi reaction occurred smoothly at the expense of S_NAr process to provide exclusively the α-amino acylamide (**12**) in 82% yield.

To proceed the projected reaction sequence, two unknown isonitriles, namely, ethyl α-(4′-fluoro-3′-nitro)-phenethyl isocyanoacetate (**10a**) and the 2-acetoxy (4′-fluoro-3′-nitro)phenethyl isocyanide (**10b**) have to be synthesized. This is shown in Scheme 3. Alkylation of the commercially available diethyl formamidomalonate with 4-fluoro-3-nitrobenzyl bromide (**13**, NaH, DMF)[30] provided **14** in 92% yield. Selective hydrolysis of one of the carboxylic ester functionalities followed by decarboxylation in 1,4-dioxane[31] afforded the corresponding racemic



Scheme 2.



Scheme 3.

N-formyl α-amino ester (**15**). Dehydration of the *N*-formyl group was performed under Ugi's conditions ($POCl_3$, Et_3N)[32] to provide the desired isonitrile (**10a**) in good overall yield. The isonitrile (**10b**) was synthesized starting from the racemic 2-amino-1-(4′-fluoro-3′-nitro)phenyl-ethanol (**16**).[33] Formylation of the amine function was carried out under standard conditions (HCOOH, EDC) to provide **17** in 90% yield. Acetylation of the hydroxyl group followed by dehydration of the *N*-formyl function afforded the desired isonitrile (**10b**) in good yield.

With these isonitriles in hands, the Ugi-4CR was examined using isonitrile (**10a**), heptanal (**7b**), butylamine (**8a**) and 3-hydroxyphenylacetic acid (**9b**) as inputs. Stirring a methanol solution of **10a**, **7b**, **8a**, and **9b** did provide the desired dipeptide amide (**6a**), but the yield was only moderate (16–34%, entry 1 and 2, Table 1). Therefore, the reaction conditions were re-examined varying the solvent, temperature and additives (Table 1).

Table 1. Survey of conditions for Ugi-4CR

Entries	Solvent	*T* (°C)	Additive	Yield[a] (%)
1	MeOH	rt[b]	None	34[c]
2	MeOH	60	None	16[d]
3	DMF[e]	rt	None	0
4	TFE[e]	rt	None	71
5	Benzene	Reflux[f]	None	76
6	Toluene	60	None	50
7	Toluene	60	NH_4Cl	60
8	Toluene	rt	NH_4Cl	33[g]
9	Toluene	60	LiBr	35
10	THF[e]	60	NH_4Cl	39

2.2 equiv. each of amine, aldehyde, and acid relative to isonitrile was used.
[a] Total yield of two diastereomers in a 1/1 ratio.
[b] Room temperature.
[c] 83% conversion of **10a** after 24 h.
[d] Isonitrile was consumed rapidly, leading to a complex reaction mixture.
[e] DMF=*N*,*N*-dimethylformamide, TFE=2,2,2-trifluoroethanol, HF=tetrahydrofurane.
[f] With Dean–Stark.
[g] 63% conversion of **10a** after 48 h.

As is seen, the reaction did not occur in DMF (entry 3) but proceeded smoothly in 2,2,2-trifluoroethanol (TFE) (entry 4) to provide the desired dipeptide (**6a**) in 71% yield. To our surprise, non-polar solvents such as benzene or toluene gave better results than methanol leading to the desired dipeptide (**6a**) in 76 and 50% yield, respectively (entries 5 and 6). Since aprotic solvents are generally considered to be inappropriate for the Ugi reaction, a more detailed investigation was carried out. In the perspective view of library production, and because Dean–Stark apparatus are not convenient for parallel synthesis, only toluene was investigated further.[34] While lithium bromide (LiBr) had an adverse effect (entry 9), addition of ammonium chloride (entry 7) is, on the other hand beneficial to the reaction. This observed beneficial effect has also been demonstrated in our laboratory where a three-component synthesis of oxazole in toluene was significantly promoted by addition of ammonium chloride.[35] To the best of our knowledge, this was the first example wherein the effect of ammonium chloride in promoting the Ugi reaction in aprotic solvent was demonstrated.[36] Two points deserved further comments. First, the α-acyloxy amide resulting from the potentially competitive Passerini reaction[37] was not isolated although it is known that non-polar solvents favor the latter reaction.[38] Second, ammonium chloride, a potential donor of NH_3,[39] did not participate in the Ugi reaction. Keeping in mind the potential application of the Ugi-4CR/S_NAr sequence to the solid phase synthesis of macrocycles (**5**) and the good swelling property of toluene, we decided to exploit these new conditions for the synthesis of dipeptides (**6**). From five amines, five aldehydes, two acids and three isonitriles inputs (Fig. 2), some representative dipeptides synthesized are listed in Figure 3. As expected, all the dipeptides (**6**) were obtained as a mixture of two

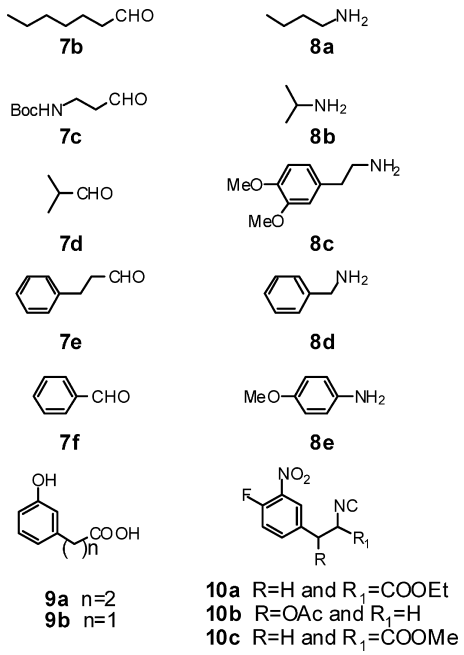


Figure 2. Inputs of Ugi-4CR.

diastereoisomers in a ratio of 1/1, separable by preparative TLC on silica gel.

The ready availability of aldehydes, amines and acids components allow the easy introduction of structural diversity into the newly formed peptide backbone. For the aldehyde part, aromatic and aliphatic aldehyde including sterically hindered, and functionalized aldehyde were suitable substrates. Both aliphatic amine and aniline participated well in this process. Two different spacer sizes between the tertiary amide function and the phenol moiety have been introduced by using either the 3-(3′-hydroxyphenyl) propionic acid (**9a**) (n=2) or the 3-hydroxyphenylacetic acid (**9b**) (n=1).

Cycloetherification of the dipeptide amide (**6**) was next examined. Compound **6** cyclized smoothly to afford the *m*,*p*-cyclophane under the conditions we developed previously for natural product synthesis (DMF, 0.01 M, K_2CO_3, room temperature). As shown in Figure 4, both 16- and 17-membered macrocycles (n=1 or 2) were produced in good yields regardless the substitution patterns. Except for **5g**, two atropisomers were generally formed from a diastereomerically pure dipeptide due to the creation of a planar chirality around the biaryl ether linkage. Apparently, the presence of a tertiary amide function did not have a significant influence on the atropstereoselectivity. In most of the cases, the two atropisomers were readily separable by preparative TLC on silica gel. The upfield shift of the proton Ha in a 16-membered macrocycle is characteristic of the cyclic structure and can be used for NMR quantification.[40]

To further increase the structural and functional diversity of the biaryl ether containing macrocycles (**5**), the selective chemical transformation of the nitro group was exploited. As shown in Scheme 4, hydrogenolysis of **5a** under standard conditions (Pd/C, H_2, EtOH) provided the aniline (**19**) in very good yield, which was then converted into the corresponding urea (**20**) and *N*,*N*-dimethylsulfonamide (**21**) by its reaction with benzyl isocyanate and methansulfonyl chloride, respectively. Similarly, macrocycle (**5b**) was transformed into the aniline (**22**), acetamide (**23**) and de-aminated compound **24** in good yield under standard conditions.

The hydroxyl group in benzylic position represents an important structural feature of many natural biaryl ether containing macrocycles like the complex glycopeptide vancomycin (**4**).[4] As shown in Scheme 5 the *m*,*p*-cyclophane (**5e**) prepared from isonitrile (**10b**), could be easily transformed into **25** by mild hydrolysis (K_2CO_3, MeOH/H_2O) of the ester functionality.

2.2. Solid phase synthesis of biaryl ether containing macrocycles (5)

Our next goal was to apply the Ugi-4CR/S_NAr sequence to the solid phase synthesis of macrocycle (**5**). Scheme 6 depicted the synthesis of the resin-bound isonitrile (**28**). Hydrolysis of the *N*-formyl α-amino ester (**15**) under

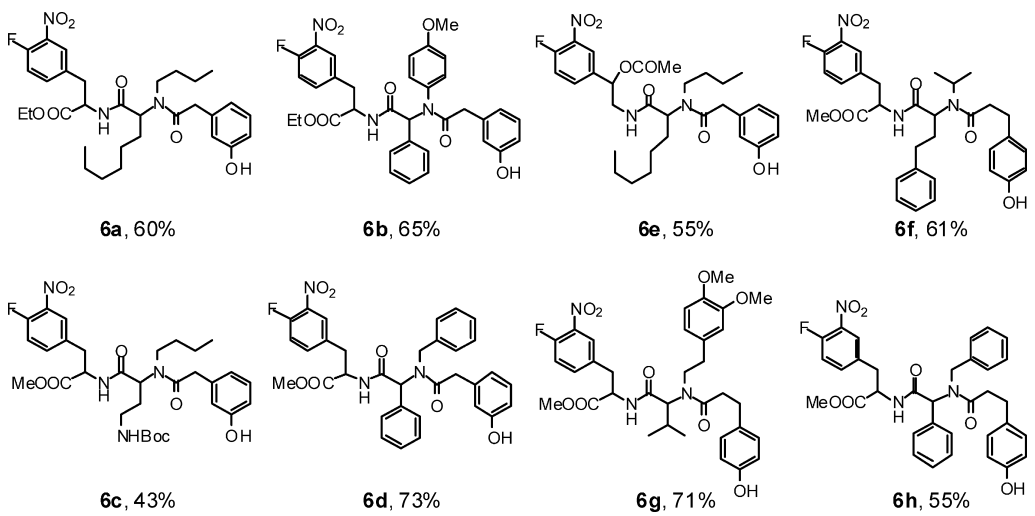


Figure 3. Structure of dipeptides obtained by Ugi-4CR.

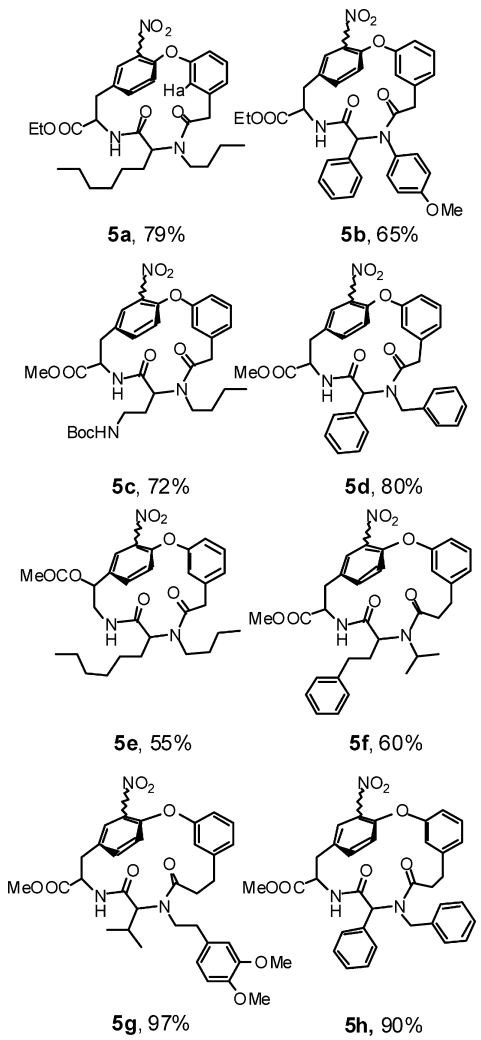
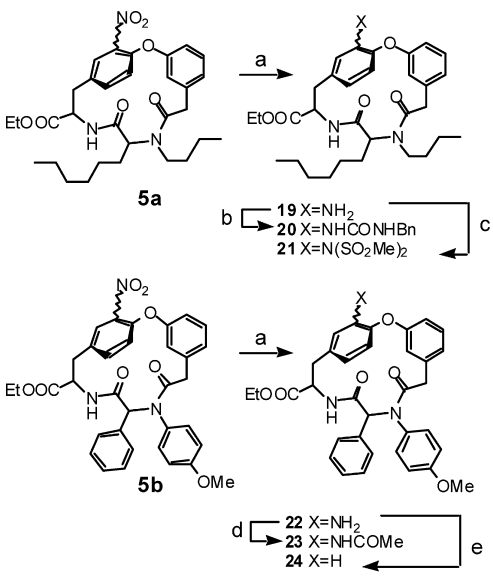
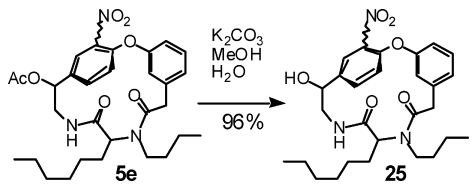


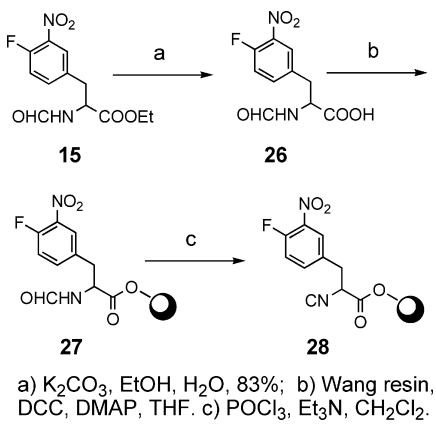
Figure 4. Structure of macrocycles obtained by a sequence of Ugi-4CR and cycloetherification.



Scheme 4.



Scheme 5.

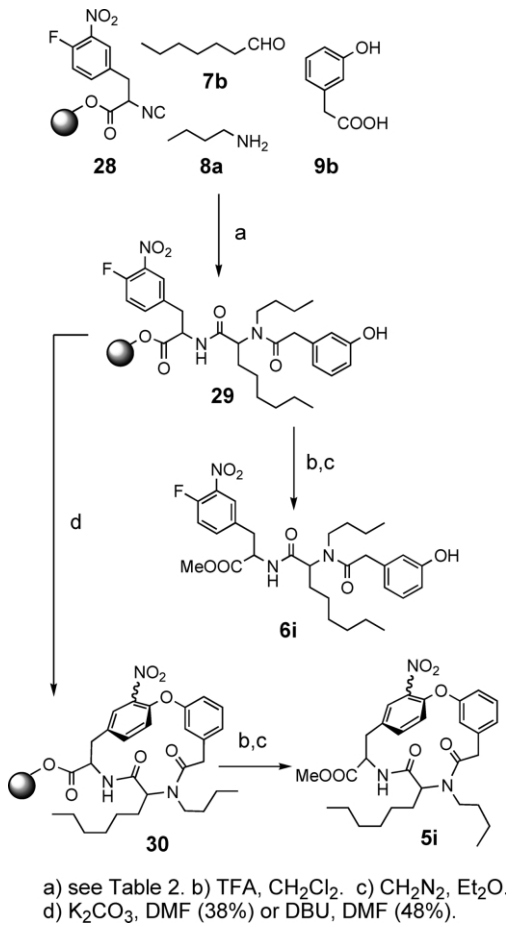


Scheme 6.

standard conditions (K_2CO_3, EtOH, H_2O) followed by esterification with the commercially available Wang resin[41] (loading 0.9 mmol/g) afforded **27**. Dehydration of the *N*-formyl function ($POCl_3$, Et_3N) provided the supported isonitrile (**28**). This last reaction could be easily monitored by Infrared spectra. Indeed, as the reaction progressed, the intensity of the amide carbonyl absorption at 1685 cm^{-1} decreased with concomitant appearance of isonitrile signal at 2145 cm^{-1}. Microanalysis of this resin-bound isonitrile (**28**) indicated a loading of 0.74 mmol/g (theoretical: 0.75 mmol/g).[42] It is interesting to note that this light yellow resin could be easily prepared in large scale and has a long shelf life without any particular precautions.

With the supported isonitrile (**28**) in hands, its reaction with heptanal (**7b**), butylamine (**8a**), and 3-hydroxyphenylacetic acid (**9b**) was examined (Scheme 7).[43] The reaction was followed by Infrared spectra until complete disappearance of the sharp and strong signal at 2145 cm^{-1} of the isonitrile function. The efficiency of the on-resin Ugi-4CR was evaluated by quantification of dipeptide ester (**6i**), in turn obtained by resin cleavage (TFA, CH_2Cl_2) and esterification reactions (diazomethane, ether).

As shown in Table 2, Ugi-4CR conducted in toluene in the presence of NH_4Cl (entry 1) was not investigated due to the poor solubility of the acid component **9b** in toluene and by the presence of ammonium chloride that entail a multi-phases reaction medium, unfavorable to the polymer-supported reactions. Therefore, the solvent system was investigated. Addition of methanol to toluene (entry 2) dissolved all monomeric reagents and the Ugi reaction proceeded to afford dipeptide (**6i**) in 12% yield (calculated for five steps starting from the Wang resin). The yield of dipeptide increased slightly using chloroform instead of toluene as solvent (entries 3 and 4). To our delight, using 2,2,2-trifluoroethanol instead of methanol as co-solvent



Scheme 7.

Table 2. On-resin Ugi-4CR, survey of conditions

Entries	Solvent	Yield[a](%)
1	Toluene/NH_4Cl	NC[b]
2	Toluene/MeOH (1/1)[c]	12
3	$CHCl_3$/MeOH (1/1)[c]	15
4	$CHCl_3$/MeOH (3/1)	17
5	$CHCl_3$/TFE[d] (3/1)[e]	38
6	$CHCl_3$/TFE (5/1)	26[f]

[a] Isolated yield, calculated from the Wang resin.
[b] Not calculated due to very poor solubility of the acid component and ammonium chloride: these conditions are not suitable to solid phase.
[c] The reaction was completed after two runs of 48 h.
[d] TFE=2,2,2-trifluoroethanol.
[e] The reaction was completed after one run of 72 h.
[f] Not optimized.

accelerated the reaction rate to afford **6i** in a very good overall yield (38%, entry 5).[44] The higher acidity of TFE may be responsible for the improved reaction outcome. The ratio of chloroform to TFE (3/1) seems to be an important factor because an increased proportion of chloroform has an adverse effect (entry 6).

Ring closure via the intramolecular S_NAr reaction on solid support has been reported and is known to be very efficient due to a pseudo-dilution effect of the resin. As shown in Scheme 7, the cycloetherification of polymer-supported dipeptide (**29**) in DMF in the presence of potassium carbonate proceeded smoothly to provide the desired macrocycle (**5i**) as a mixture of four diastereoisomers **5i1**, **5i2**, **5i3** and **5i4** separable by chromatography on silica gel. The overall yield of this six-step synthesis was 38% starting from the Wang resin. The low solubility of potassium carbonate in DMF prompted us to use a soluble organic base. Gratefully, under otherwise identical conditions, the cyclization promoted by DBU[20] (DMF, room temperature, 3 days) furnished the macrocycle **5i** in 48% overall yield. To our surprise only two diastereoisomers **5i1** and **5i3** were formed. Thermal equilibrium experiments conducted in DMSO at 160°C indicated that **5i1** and **5i3** are two atropisomers. Moreover, when the diastereoisomerically pure **5i1** was resubmitted to the cyclization conditions, no equilibrium to **5i3** was observed. On the other hand, the diastereoisomer **5i2**, obtained from potassium carbonate promoted cyclization, was readily converted into **5i1** upon treating with DBU in DMF at room temperature. These control experiments indicated that the cyclization step carried out with DBU is under kinetic control leading to two atropisomers. However, the chiral centers of the peptide backbone were epimerized to provide the thermodynamically more stable compounds. While no detailed studies have been carried out, the relative stereochemistry of **5i1** and **5i3** was tentatively assigned as is P*R*R* and M*R*R*, respectively, according to NOE experiments (Fig. 5).

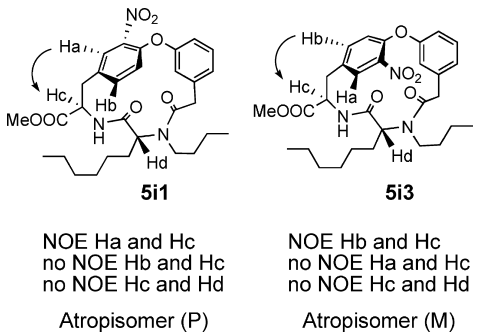


Figure 5. Stereochemistry of two atropisomers.

Figure 6 listed the macrocycles synthesized on polymer support using DBU as base. As is seen, the sequence is generally applicable to various types of amines and aldehydes. In most of the cases, macrocycles were isolated as a mixture of two atropisomers in good overall yields.[45] For macrocycle **5m**, a diketopiperazine derivative **31** was isolated in 4% yield. Although an intramolecular transamidation can account for the formation of **31**, no experiments have been designed to probe whether the diketopiperazine unit was produced before or after the macrocyclization.

3. Conclusion

The novel Ugi-4CR/S_NAr cycloetherification sequence reported in this article allowed the rapid access to a wide range of functionalized biaryl ether containing macrocycles starting from readily available inputs. Moreover, the presence of nitro group in the macrocycles allowed the introduction of further structural diversities. Thus, our

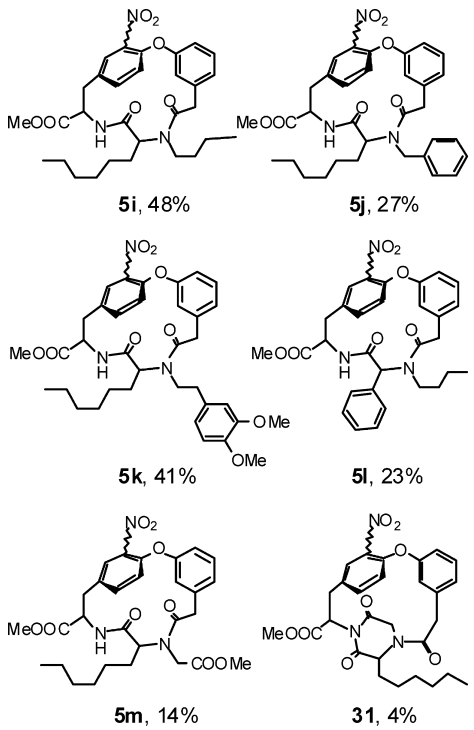


Figure 6. Macrocycles synthesized by a sequence of on-resin Ugi-4CR and cycloetherification.

synthesis allowed the introduction of at least four-point of diversity and generated significant molecular complexity in an operationally simple two-step sequence.

The development of chemistry amenable to the introduction of multiple diversities while still creating molecules of drug-like properties in minimum steps remained a challenging task to synthetic chemists. The combination of multicomponent reaction with other highly efficient transformation, especially cyclization methodologies, has been demonstrated to be one of the highly promising approaches to the problem.[46] Indeed, such a step-economic approach introduced naturally the molecular diversity, complexity and drug likeness of the compounds (heterocycles, macrocycles). Further application of MCR/S_NAr cycloetherification sequence to the synthesis of other natural product-like compound libraries is in progress and will be reported in due course.[47]

4. Experimental

4.1. General procedure of dehydration

To a solution of **15** (1.88 g, 6.62 mmol) and Et_3N (4.59 mL, 33.2 mmol) in dry CH_2Cl_2 (90 mL) was added dropwise at −25°C $POCl_3$ (0.94 mL, 9.96 mmol). The reaction mixture was stirred for 5 h at −25°C. A saturated solution of Na_2CO_3 was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude residue was purified by flash chromatography (SiO_2, Heptane/EtOAc=70/30) to afford 3-(4-fluoro-3-nitro-phenyl)-2-isocyano-propionic acid ethyl ester (**10a**).

4.1.1. Compound 10a. 1.6 g, 91% as a yellow solid: IR ($CHCl_3$) 2995, 2153, 1746, 1624, 1540, 1353, 998 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.96 (dd, 1H, *J*=6.9, 2.2 Hz), 7.57 (ddd, 1H, *J*=8.4, 4.1, 2.2 Hz), 7.30 (dd, 1H, *J*=10.4, 8.5 Hz), 4.51 (dd, 1H, *J*=6.1, 5.7 Hz), 4.29 (q, 2H, *J*=7.1 Hz), 3.28 (dd, 1H, *J*=14.1, 5.7 Hz), 3.26 (dd, 1H, *J*=14.1, 6.1 Hz), 1.31 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 165.2, 161.8, 155.0 (d, *J*=264 Hz), 137.1 (d, *J*=6 Hz), 136.7 (d, *J*=9 Hz), 131.5 (d, *J*=3 Hz), 126.7, 118.8 (d, *J*=21 Hz), 63.2, 57.2, 37.1, 13.8; MS (IE): *m/z* 267 $(M+H)^+$.

4.1.2. Acetic acid 1-(4-fluoro-3-nitro-phenyl)-2-isocyano ethyl ester 10b. IR ($CHCl_3$) 3029, 3013, 2155, 1753, 1624, 1544, 1351, 1226 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 8.11 (dd, 1H, *J*=6.8, 2.4 Hz), 7.71 (ddd, 1H, *J*=9.0, 4.1, 2.4 Hz), 7.37 (dd, 1H, *J*=10.3, 8.5 Hz), 5.97 (t, 1H, *J*=5.4 Hz), 3.82 (d, 2H, *J*=5.4 Hz), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.3, 160.4, 155.7 (d, *J*=264 Hz), 137.6, 133.8 (d, *J*=9 Hz), 133.1, 124.3, 119.2 (d, *J*=22 Hz), 70.5, 46.1, 20.8; MS (ES^+): *m/z* 275 $(M+Na)^+$, 291 $(M+K)^+$.

4.1.3. 3-(4-Fluoro-3-nitro-phenyl)-2-isocyano-propionic acid methyl ester 10c. IR ($CHCl_3$) 3072, 3021, 2958, 2888, 2151, 1752, 1624, 1593, 1537, 1503, 1439, 1355, 1255, 1220, 1137, 1090, 1051, 1024 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.96 (dd, 1H, *J*=6.9, 2.4 Hz), 7.57 (ddd, 1H, *J*=8.5, 4.1, 2.4 Hz), 7.29 (dd, 1H, *J*=10.5, 8.5 Hz), 4.57 (dd, 1H, *J*=7.6, 4.9 Hz), 3.82 (s, 3H), 3.30 (dd, 1H, *J*=14.2, 4.9 Hz), 3.19 (dd, 1H, *J*=14.2, 7.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 165.7, 161.8, 154.9 (d, *J*=263 Hz), 137.1, 136.7 (d, *J*=8 Hz), 131.4 (d, *J*=3 Hz), 126.7, 118.9 (d, *J*=21 Hz), 57.1, 53.6, 37.1; MS (IE): *m/z* 253 $(M+H)^+$.

4.2. General procedure of Ugi-4CR

To a solution of heptanal (58 μL, 0.416 mmol) in dry toluene (1 mL), butylamine (41 μL, 0.416 mmol) was added. The resulting mixture was stirred at room temperature for 1 h then 3-hydroxyphenyl acetic acid (63.3 mg, 0.416 mmol) followed by isonitrile **10a** (50.3 mg, 0.189 mmol) and NH_4Cl (22.2 mg, 0.416 mmol) were added. The reaction mixture was stirred at 60°C for 20 h. The reaction mixture was cooled to room temperature then water was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2, Heptane/EtOAc=60/40) to afford **6a** (67 mg, 60%) as a mixture of two diastereoisomers.

4.2.1. Compound 6a. Mixture of two diastereoisomers (50/50): IR ($CHCl_3$) 3027, 2954, 1732, 1687, 1621, 1542, 1497, 1456, 1353, 1332, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.87 (dd, 0.5H, *J*=7.0, 2.3 Hz), 7.79 (dd, 0.5H, *J*=7.0, 2.3 Hz), 7.72 (s broad, 0.5H), 7.44 (ddd, 0.5H, *J*=8.6, 4.2, 2.3 Hz), 7.39 (ddd, 0.5H, *J*=8.6, 4.2, 2.3 Hz), 7.28 (d, 1H, *J*=8 Hz), 7.07–7.26 (m, 2H), 6.90 (s broad, 0.5H), 6.83 (s broad, 0.5H), 6.68–6.75 (m, 2H), 6.51 (s broad, 0.5H), 4.73–4.88 (m, 2H), 4.16–4.26 (m, 2H), 3.62–3.79 (m, 2H), 2.93–3.26 (m, 4H), 1.00–1.99 (m, 17H), 0.73–1.00 (m, 6H); MS (IE): *m/z* 587 $(M)^+$.

4.3. General procedure of S_NAr cycloetherification

To a solution of dipeptide **6a** (327 mg, 0.557 mmol) in dry DMF (56 mL) was added K_2CO_3 (384 mg, 2.78 mmol). The reaction mixture was stirred at room temperature for 3 h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash chromatography (SiO_2, Heptane/AcOEt=70/30) to afford 9,12-dioxo-2-oxa-10-butyl-11-hexyl-14-ethoxycarbonyl-18-nitro-10,13-diazatricycle[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (**5a**) (250 mg, 79%) as a brown oil. The four diastereoisomers were separated by preparative TLC (SiO_2, Toluene/EtOH=95/5).

4.3.1. Diastereoisomer 5a1. IR ($CHCl_3$) 3424, 3020, 2959, 2931, 1738, 1679, 1624, 1591, 1536, 1490, 1445, 1351, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.91 (d, 1H, *J*=1.7 Hz), 7.18–7.25 (m, 2H), 7.04 (dd, 1H, *J*=8.1, 2.6 Hz), 6.98 (d, 1H, *J*=8.5 Hz), 6.79 (d, 1H, *J*=7.7 Hz), 6.49 (d, 1H, *J*=8.1 Hz), 5.69 (s, 1H), 4.97 (t, 1H, *J*=7.7 Hz), 4.79 (m, 1H), 4.20 (q, 2H, *J*=7.3 Hz), 3.81 (d, 1H, *J*=15.8 Hz), 3.46 (dd, 1H, *J*=13.2, 12.8 Hz), 3.41 (m+d, 2H, *J*=15.8 Hz), 3.06 (dt, 1H, *J*=15.8, 7.7 Hz), 2.64 (t, 1H, *J*=13.2 Hz), 1.70 (m, 1H), 1.48 (m, 1H), 1.03–1.30 (m+t, 15H, *J*=7.3 Hz), 0.72–0.82 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 172.0, 171.1, 171.0, 160.0, 148.3, 143.2, 137.4, 136.1, 134.4, 129.9, 125.8, 125.6, 123.2, 115.9, 113.5, 61.9, 55.7, 52.8, 45.2, 39.4, 37.2, 33.4, 31.6, 31.2, 29.1, 26.1, 22.5, 20.2, 14.2, 14.0, 13.5; MS (IE): *m/z* 567 $(M)^+$, 568 $(M+H)^+$.

4.3.2. Diastereoisomer 5a2. IR ($CHCl_3$) 3300, 3019, 2960, 2932, 1738, 1662, 1623, 1535, 1501, 1465, 1444, 1351, 1298, 1238 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.66 (d, 1H, *J*=2.6 Hz), 7.44 (dd, 1H, *J*=8.5, 2.6 Hz), 7.30 (dd, 1H, *J*=8.5, 7.2 Hz), 7.18 (dd, 1H, *J*=8.5, 2.4 Hz), 7.13 (d, 1H, *J*=8.5 Hz), 6.81 (d, 1H, *J*=7.2 Hz), 5.47 (s, 1H), 4.73 (m, 1H), 4.56 (m, 1H), 4.33 (m, 2H), 3.77 (d, 1H, *J*=16.6 Hz), 3.48 (dd, 1H, *J*=14.1, 4.3 Hz), 3.47 (d, 1H, *J*=16.6 Hz), 3.28 (dd, 1H, *J*=14.1, 5.5 Hz), 3.06 (m, 2H), 1.95 (m, 1H), 1.64 (m, 1H), 1.38 (t, 3H, *J*=7.3 Hz), 1.26 (m, 12H), 0.84 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 172.4, 171.9, 170.5, 160.9, 150.6, 143.9, 136.7, 136.1, 133.9, 129.8, 127.2, 125.1, 123.2, 116.5, 116.2, 62.1, 53.6, 47.1, 40.4, 35.8 (2C), 31.9, 31.5, 29.0, 28.7, 26.3, 22.5, 20.1, 14.2, 14.0, 13.5; MS (IE): *m/z* 568 $(M+H)^+$.

4.3.3. Diastereoisomer 5a3. IR ($CHCl_3$) 3418, 3011, 2931, 1734, 1683, 1623, 1537, 1490, 1458, 1445, 1352, 1281 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.84 (d, 1H, *J*=2.2 Hz), 7.60 (dd, 1H, *J*=8.3, 2.2 Hz), 7.27 (dd, 1H, *J*=8.0, 7.3 Hz), 7.14 (d, 1H, *J*=8.3 Hz), 7.11 (dd, 1H, *J*=8.0, 2.4 Hz), 6.80 (d, 1H, *J*=7.3 Hz), 6.60 (d, 1H, *J*=9.0 Hz), 5.66 (s, 1H), 4.96 (m, 1H), 4.84 (t, 1H, *J*=7.3 Hz), 4.26 (q, 2H, *J*=7.1 Hz), 3.74 (d, 1H, *J*=15.8 Hz), 3.59 (dd, 1H, *J*=13.9, 5.1 Hz), 3.55 (d, 1H, *J*=15.8 Hz), 3.46 (m, 1H), 3.00 (m, 1H), 2.86 (dd, 1H, *J*=13.9, 14.3 Hz), 1.78 (m, 1H), 1.60 (m, 1H), 1.08–1.36 (m+t, 15H, *J*=7.1 Hz), 0.77–0.89 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 171.6, 171.1, 170.7, 160.1, 148.7, 142.8, 136.9, 134.9, 134.6, 129.9, 127.1, 126.4, 122.8, 115.8, 113.0, 62.0, 56.6, 52.1, 45.2, 40.1, 36.7, 33.2, 31.5, 31.1, 29.1, 26.2, 22.5, 20.3, 14.2, 14.0, 13.6; MS (IE): *m/z* 567 $(M)^+$, 568 $(M+H)^+$.

4.3.4. Diastereoisomer 5a4. IR ($CHCl_3$) 3027, 2931, 1739, 1662, 1624, 1591, 1534, 1444, 1349, 1241 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.90 (d, 1H, *J*=2.0 Hz), 7.18–7.30 (m, 4H), 7.14 (dd, 1H, *J*=8.2, 2.3 Hz), 6.76 (d, 1H, *J*=7.3 Hz), 5.50 (s, 1H), 4.65 (m, 1H), 4.31 (m+q, 3H, *J*=7.2 Hz), 3.61 (s, 2H), 3.51 (dd, 1H, *J*=14.6, 4.9 Hz), 3.38 (dd, 1H, *J*=14.6, 5.3 Hz), 2.98 (m, 2H), 1.75–2.00 (m, 2H), 1.07–1.40 (m+t, 15H, *J*=7.2 Hz), 0.77–0.89 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 172.1, 171.8, 170.9, 160.4, 149.7, 143.1, 136.3, 134.9 (2C), 129.9, 127.3, 126.7, 122.6, 116.2, 114.2, 62.0, 54.2, 49.7, 41.3, 35.8 (2C), 31.6, 31.0, 29.7, 29.0, 26.5, 22.5, 19.9, 14.3, 14.0, 13.5; MS (IE): *m/z* 567 $(M)^+$, 568 $(M+H)^+$.

4.4. Procedures for post-transformations

4.4.1. 9,12-Dioxo-2-oxa-10-butyl-11-hexyl-14-ethoxycarbonyl-18-amino-10,13-diazatricycle[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (19a). To a solution of **5a2** (22.1 mg, 0.039 mmol) in EtOH (0.8 mL) was added a catalytic amount of Pd/C (10%). The reaction mixture was purged several times with argon then stirred under H_2 atmosphere for 20 min. The mixture was filtered on celite and the solvent removed under vacuum to afford aniline **19a** (20.7 mg, Yield: 99%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.22 (d, 1H, *J*=7.6 Hz), 7.07 (dd, 1H, *J*=8.1, 2.4 Hz), 6.85 (d, 1H, *J*=8.1 Hz), 6.78 (d, 1H, *J*=7.6 Hz), 6.57 (dd, 1H, *J*=8.1, 2.4 Hz), 6.40 (d, 1H, *J*=2.4 Hz), 5.61 (s, 1H), 4.64–4.75 (m, 2H), 4.26 (m, 2H), 3.82 (d, 1H, *J*=16.2 Hz), 3.77 (s, 2H), 3.42 (d, 1H, *J*=16.2 Hz), 3.34 (dd, 1H, *J*=14.3, 3 Hz), 3.01–3.18 (m, 3H), 1.93 (m, 1H), 1.65 (m, 1H), 1.11–1.50 (m+t, 15H, *J*=7.1 Hz), 0.84 (m, 6H).

4.4.2. Compound 19b (prepared from 5a3 in 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.25 (m, 1H), 7.04 (m, 1H), 6.86 (d, 1H, *J*=8.5 Hz), 6.78 (d, 1H, *J*=7.3 Hz), 6.66 (d, 1H, *J*=7.9 Hz), 6.63 (s, 1H), 6.09 (d, 1H, *J*=7.3 Hz), 5.81 (s, 1H), 5.02 (t, 1H *J*=7.3 Hz), 4.63 (m, 1H), 4.24 (q, 2H, *J*=7.3 Hz), 3.84 (d, 1H, *J*=15.9 Hz), 3.78 (s, 2H), 3.50 (d, 1H *J*=15.9 Hz), 3.31–3.44 (m, 2H), 3.11 (m, 1H), 2.56 (t, 1H, *J*=13.4 Hz), 1.82 (m, 1H), 1.49 (m, 1H), 1.05–1.35 (m+t, 15H, *J*=7.3 Hz), 0.77–0.88 (m, 6H).

4.4.3. 9,12-Dioxo-2-oxa-10-(4′-methoxyphenyl)-11-phenyl-14-ethoxycarbonyl-18-amino-10,13-diazatricycle[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (22) (prepared from 5b3 in 91% yield). IR ($CHCl_3$) 3041, 1737, 1693, 1645, 1603, 1511, 1443, 1372, 1337, 1297, 1265 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 6.89–7.23 (m, 9H), 6.56–6.62 (m+s, 4H), 6.53 (d, 1H, *J*=7.4 Hz), 6.42 (s broad, 1H), 6.27 (s, 1H), 6.06 (m+d, 2H, *J*=8.8 Hz), 5.00 (m, 1H), 4.14 (m, 2H), 3.68 (s, 3H), 3.43 (m, 1H), 3.41 (d, 1H, *J*=15.8 Hz), 3.26 (d, 1H, *J*=15.8 Hz), 2.59 (dd, 1H, *J*=13.4, 12.5 Hz), 1.20 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 171.8, 171.3, 168.8, 159.7, 159.0, 141.6, 139.8, 137.8, 134.8, 133.9, 131.5, 129.9 (4C), 129.2, 128.41, 128.35 (3C), 123.1, 122.1, 121.1, 116.9, 114.8, 113.9, 113.3, 61.6, 60.4, 55.2, 53.2, 40.3 39.0, 14.1; MS (ES^+): *m/z* 580 $(M+H)^+$, 602 $(M+Na)^+$, 618 $(M+K)^+$.

4.4.4. Compound 20. To a solution of **19a** (19 mg, 0.035 mmol) in dry CH_2Cl_2 (0.8 mL) was added at 0°C benzyl isocyanate (5 μL, 0.040 mmol). The reaction mixture was stirred at room temperature for 1 h. Water was added at 0°C and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting crude solid was purified by preparative TLC (SiO_2, Toluene/EtOH=90/10) to afford **20** (17.2 mg, 73%) as a brown oil: IR ($CHCl_3$) 3621, 3416, 3006, 2976, 2933, 1735, 1684, 1629, 1601, 1532, 1506, 1446, 1391, 1347, 1242 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.64 (d, 1H, *J*=1.9 Hz), 7.15–7.26 (m, 7H), 7.04 (dd, 1H, *J*=7.6, 1.9 Hz), 6.93 (d, 1H, *J*=8.1 Hz), 6.88 (dd, 1H, *J*=8.1, 1.9 Hz), 6.76 (d, 1H, *J*=7.6 Hz), 6.65 (s, 1H), 5.47 (s broad, 2H), 4.70 (m, 1H), 4.40 (dd, 1H, *J*=15.3, 6.2 Hz), 4.22–4.39 (m, 4H), 3.63 (d, 1H, *J*=16.7 Hz), 3.33 (m, 2H), 2.93–3.11 (m, 3H), 1.91 (m, 1H), 1.63 (m, 1H), 1.07–1.41 (m+t, 15H, *J*=7.2 Hz), 0.80–0.88 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 172.19, 171.50 (2C), 160.4, 154.9, 145.9, 139.0, 137.1, 133.5, 133.2, 129.5, 128.5 (2C), 127.3 (2C), 127.1, 125.4, 124.0, 122.9, 121.3, 115.8, 115.5, 61.8, 54.6, 52.9, 47.3, 44.2, 39.5, 36.4, 32.2, 31.6, 29.0, 28.9, 26.2, 22.6, 20.1, 14.2, 14.0, 13.6; MS (ES^+): *m/z* 693 $(M+Na)^+$, (ES^-): *m/z* 670 $(M)^-$, 669 $(M-H)-$.

4.4.5. Compound 21. To a solution of **19b** (26 mg, 0.048 mmol) in dry CH_2Cl_2 (0.8 mL) was added at 0°C Et_3N (50 μL, 0.361 mmol) followed by methanesulfonyl chloride (15 μL, 0.193 mmol). The reaction mixture was stirred at room temperature for 20 h then a saturated solution of Na_2CO_3 was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude residue was purified by preparative TLC (SiO_2, Heptane/EtOAc=60/40) to afford **21** (16.3 mg, 49%) as a brown oil: IR ($CHCl_3$) 3621, 3461, 3010, 2976, 1734, 1676, 1630, 1603, 1504, 1488, 1447, 1391, 1373, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.26–7.36 (m, 2H), 7.18 (m, 2H), 7.06 (d, 1H, *J*=8.5 Hz), 6.84 (d, 1H, *J*=7.5 Hz), 6.19 (d, 1H, *J*=7.2 Hz), 5.91 (s, 1H), 4.78–4.88 (m, 2H), 4.28 (m, 2H), 3.79 (d, 1H, *J*=15.9 Hz), 3.58 (dd, 1H, *J*=14, 6.1 Hz), 3.50 (d, 1H, *J*=15.9 Hz), 3.41 (s, 3H), 3.06–3.38 (m, 2H), 3.01 (s, 3H), 2.96 (dd, 1H, *J*=14, 10.4 Hz), 1.77–1.86 (m, 1H), 1.40–1.58 (m, 1H), 1.12–1.37 (m+t, 15H, *J*=7.3 Hz), 0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 170.8, 170.3, 160.4, 153.9, 137.7, 133.8, 133.3, 131.8, 130.1, 127.2, 125.3, 123.3, 116.0, 114.7, 61.9, 56.2, 52.2, 44.7, 43.6, 42.5, 39.8, 35.4, 33.2, 31.5, 31.0, 29.0, 25.8, 22.5, 20.2, 14.2, 14.0, 13.7; MS (ES^+): *m/z* 716 $(M+Na)^+$, 732 $(M+K)^+$.

4.4.6. 9,12-Dioxo-2-oxa-10-(4′-methoxyphenyl)-11-phenyl-14-ethoxycarbonyl-18-acetamido-10,13-diazatricycle[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (23). To a solution of **22** (11 mg, 0.019 mmol) in dry CH_2Cl_2 (0.6 mL) was added Et_3N (6 μL, 0.043 mmol) followed by acetic anhydride (4 μL, 0.042 mmol). The reaction mixture was stirred at room temperature for 17 h. Water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting crude solid was purified by preparative TLC (SiO_2, Heptane/EtOAc=50/50) to afford **23** (9.6 mg, 81%) as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) 8.57 (s, 1H), 7.72 (s broad, 1H), 7.50 (s broad, 1H), 7.07–7.23 (m, 5H), 6.86–6.98 (m, 4H), 6.68 (m+d, 2H, *J*=7.6 Hz), 6.60 (s, 1H), 6.43 (m+s, 2H), 6.10 (m, 1H), 5.96 (d, 1H, *J*=7.6 Hz), 4.83 (m, 1H), 4.14 (m, 2H), 3.67 (s, 3H), 3.49 (d, 1H, *J*=15.7 Hz), 3.46 (dd, 1H, *J*=12.9, 3.3 Hz), 3.18 (d, 1H, *J*=15.7 Hz), 2.51 (dd, 1H, *J*=12.9, 12.4 Hz), 2.23 (s, 3H), 1.22 (t, 3H, *J*=7.2 Hz); MS (ES^+): *m/z* 622 $(M+H)^+$, 644 $(M+Na)^+$.

4.4.7. 9,12-Dioxo-2-oxa-10-(4′-methoxyphenyl)-11-phenyl-14-ethoxycarbonyl-10,13-diazatricycle-[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (24). To a solution of **22** (24 mg, 0.041 mmol) in a 1:1 mixture of THF/H_2O (0.8 mL) was added at 0°C a solution of aqueous H_3PO_2 (50%) (16 μL, 0.154 mmol), followed by a catalytic amount of Cu_2O and $NaNO_2$ (3.7 mg, 0.054 mmol) dissolved in water (0.2 mL). The reaction mixture was stirred at room temperature for 2 h. A saturated solution of Na_2CO_3 was added and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude residue was purified by preparative TLC (SiO_2, Heptane/EtOAc=50/50) to afford **24** (20 mg, 86%) as a brown oil: IR (KBr) 3032, 2930, 1686, 1653, 1588, 1536, 1508, 1489, 1442, 1372, 1352, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.54 (dd, 1H, *J*=8.4, 2.2 Hz), 7.38 (m, 1H), 7.11–7.24 (m, 6H), 6.98 (m, 4H), 6.50–6.63 (m+s, 3H), 6.37 (m, 1H), 6.26 (s, 1H), 6.04 (m+d, 2H, *J*=8.6 Hz), 4.95 (m, 1H), 4.13 (m, 2H), 3.66 (s, 3H), 3.42 (m+d, 2H, *J*=15.9 Hz), 3.20 (d, 1H, *J*=15.9 Hz), 2.56 (dd, 1H, *J*=13.2, 12.6 Hz), 1.19 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) 171.9, 169.7, 169.7, 161.7, 159.9, 155.9, 139.5, 137.2, 135.1, 133.5, 133.3, 133.1, 132.1, 131.6, 130.7 (2C), 129.9, 128.9 (2C), 128.7, 123.1, 122.8, 122.7, 116.3, 115.5, 114.0, 113.7, 61.6, 60.9, 55.6, 53.9, 40.7, 38.5, 14.4; MS (ES^+): *m/z* 565 $(M+H)^+$, 587 $(M+Na)^+$, 603 $(M+K)^+$.

4.4.8. 9,12-Dioxo-2-oxa-10-butyl-11-hexyl-14-ethoxycarbonyl-15-hydroxyl-18-nitro-10,13-diazatricycle-[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (25). To a solution of **5e** (23.6 mg, 0.0426 mmol) in a mixture of methanol and water (0.5 mL, methanol/water: 8/2), K_2CO_3 (11.7 mg, 0.0852 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was acidified with a solution of HCl 10% then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The resulting crude solid was purified by preparative TLC (SiO_2, Heptane/EtOAc=50/50) to afford **25** (21 mg, 96%) as a colorless oil: IR ($CHCl_3$) 3284, 2961, 2930, 2859, 1649, 1617, 1591, 1535, 1489, 1458, 1444, 1360, 1232, 1084 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) 8.28 (d, 1H, *J*=1.9 Hz), 7.99 (broad d, 1H, *J*=8.3 Hz), 7.60 (dd, 1H, *J*=8.5, 1.9 Hz), 7.31 (t, 1H, *J*=7.8 Hz), 7.14 (d, 1H, *J*=8.5 Hz), 7.07 (dd, 1H, *J*=7.8, 1.9 Hz), 6.88 (d, 1H, *J*=7.8 Hz), 5.73 (s, 1H), 5.18 (broad s, 1H), 4.88 (m, 1H), 4.12–4.23 (m, 1H), 3.88 (d, 1H, *J*=16.4 Hz), 3.43–3.56 (m+d, 2H, *J*=16.4 Hz), 3.20 (dd, 1H, *J*=14.4, 2.7 Hz), 3.05 (ddd, 1H, *J*=15.6, 10.5, 5.1 Hz), 1.56–1.77 (m, 2H), 1.11–1.42 (m, 12H), 0.88 (t, 3H, *J*=7.3 Hz), 0.84 (t, 1H, *J*=7.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) 173.8, 173.2, 161.4, 149.0, 144.0, 142.1, 138.6, 134.3, 131.0, 126.4, 124.4, 123.9, 116.5, 113.5, 70.8, 57.5, 47.1, 46.8, 40.7, 34.2,

32.8, 32.3, 30.1, 27.3, 23.6, 21.3, 14.4, 13.9; MS (ES^+): *m/z* 512 $(M+H)^+$, 534 $(M+Na)^+$, 550 $(M+K)^+$, 573 $(M+Na+K)^+$.

4.4.9. Procedure for the preparation of the resin-bound isonitrile (28). To a suspension of Wang resin (100 mg, loading: 0.9 mmol / g) in dry THF (2.5 mL), DCC (92.8 mg, 0.45 mmol), followed by DMAP (2.2 mg, 0.018 mmol) and **26** (115.2 mg, 0.45 mmol) were added. The resulting suspension was stirred for 2 days at room temperature. After filtration, the resulting yellow resin **27** was washed four times with THF, then DMF/water (2/1) (to remove excess DCC and DCU), methanol and ether: IR (KBr) 3386, 3060, 3026, 2924, 1736, 1686, 1611, 1541, 1509, 1492, 1451, 1382, 1349, 1248, 1171, 1114, 1028, 819, 756, 697 cm^{-1}.

To a suspension of resin **27** (106.1 mg) in dry CH_2Cl_2 (3 mL), Et_3N (0.163 mL, 1.179 mmol) was added. Then $POCl_3$ (37 μL, 0.397 mmol) was added dropwise at 0°C. The resulting suspension was stirred for 5 h 30 min at 0°C. The yellow resin **28** was filtered and washed four times with CH_2Cl_2, then methanol and ether. Microanalysis of this resin-bound isonitrile indicated a loading of 0.74 mmol/g based on the percentage of nitrogen (theoretical: 0.75 mmol/g): IR (KBr) 3483, 3060, 3026, 2923, 2145, 1752, 1611, 1541, 1511, 1492, 1451, 1350, 1172, 1113, 818, 757, 698 cm^{-1}.

4.5. General procedure for the solid supported Ugi-4CR/S_NAr sequence

To a suspension of resin **28** (100 mg, 0.074 mmol) in a mixture of chloroform and 2,2,2-trifluoroethanol (3/1, 1 mL), 3-hydroxyphenyl acetic acid (225.1 mg, 1.48 mmol) was added. A solution of preformed imine (1 mL of a solution 1.48 M of heptanaldehyde and butylamine in chloroform and 2,2,2-trifluoroethanol: 3/1) was added and the suspension was stirred 3 days at room temperature. After filtration, the resin was washed successively with CH_2Cl_2, methanol, ether and dried under vacuum. The dry resin was suspended in DMF (3 mL), and DBU (55 μL, 0.37 mmol) was added. The suspension was stirred for 3 days at room temperature then filtered. The resin was washed four times with CH_2Cl_2, then methanol and ether. The solid supported macrocycle was suspended in dry CH_2Cl_2 (1.5 mL) and TFA (150 μL) was added. The mixture was stirred at room temperature for 30 min then methanol was added. The resin was filtered and washed four times with methanol. The crude filtrate was treated at 0°C with an excess of diazomethane (solution in ether) and purified by preparative TLC (SiO_2, Heptane/EtOAc=50/50) to afford 6.9 mg of diastereoisomer **5i1** and 13.0 mg of diastereoisomer **5i3** (total yield: 48%).

4.5.1. Diastereoisomer 5i1. IR ($CHCl_3$) 2957, 2930, 2858, 1743, 1685, 1623, 1537, 1491, 1445, 1352, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.99 (d, 1H, *J*=2.2 Hz), 7.34 (dd, 1H, *J*=8.5, 2.2 Hz), 7.31 (d, 1H, *J*=8.1 Hz), 7.12 (m+d, 2H, *J*=8.5 Hz), 6.86 (d, 1H, *J*=7.7 Hz), 6.18 (d, 1H, *J*=8.8 Hz), 5.76 (s, 1H), 5.00 (t, 1H, *J*=7.7 Hz), 4.88 (ddd, 1H, *J*=12.5, 8.1, 4.8 Hz), 3.87 (d, 1H, *J*=15.8 Hz), 3.85 (s, 3H), 3.56 (dd, 1H, *J*=14.3, 4.8 Hz), 3.36–3.50 (m+d, 2H, *J*=15.8 Hz), 3.13 (m, 1H), 2.76 (dd, 1H, *J*=13.2, 12.9 Hz), 1.76–1.83 (m, 1H), 1.36–1.65 (m, 1H), 1.12–1.38 (m, 12H), 0.81–0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.0, 171.4, 171.2, 159.9, 148.4, 143.3, 137.4, 135.9, 134.3, 129.9, 126.0, 125.7, 123.2, 115.9, 113.6, 55.9, 52.8 (2C), 45.3, 39.4, 37.3, 33.4, 31.6, 31.1, 29.1, 26.2, 22.5, 20.3, 14.0, 13.5; MS (ES^+): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 1129 $(2M+Na)^+$.

4.5.2. Diastereoisomer 5i3. IR ($CHCl_3$) 3021, 3015, 1744, 1677, 1624, 1535, 1444, 1350, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.84 (d, 1H, *J*=1.8 Hz), 7.61 (dd, 1H, *J*=8.1, 1.8 Hz), 7.29 (m, 1H), 7.14 (m+d, 2H, *J*=8.5 Hz), 6.82 (d, 1H, *J*=7.7 Hz), 6.51 (d, 1H, *J*=7.7 Hz), 5.67 (s, 1H), 4.98 (ddd, 1H, *J*=12.9, 8.8, 5.5 Hz), 4.82 (t, 1H, *J*=7.4 Hz), 3.84 (s, 3H), 3.75 (d, 1H, *J*=16.2 Hz), 3.54–3.63 (m+d, 2H, *J*=16.2 Hz), 3.37–3.51 (m, 1H), 2.96–3.03 (m, 1H), 2.90 (dd, 1H, *J*=14.0, 12.5 Hz), 1.79–1.88 (m, 1H), 1.52–1.70 (m, 1H), 1.07–1.45 (m, 12H), 0.82–0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.6, 171.2, 171.1, 160.1, 148.7, 142.8, 136.9, 134.9, 134.6, 129.9, 127.1, 126.4, 122.8, 115.8, 113.0, 56.7, 52.7, 52.1, 45.3, 40.1, 36.6, 33.2, 31.6, 31.2, 29.1, 26.2, 22.5, 20.2, 14.0, 13.6; MS (ES^+): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 1129 $(2M+Na)^+$.

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