Solid-phase based synthesis of jasplakinolide analogs by intramolecular azide–alkyne cycloadditions†

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The synthesis of a focused library of jasplakinolide analogs with a 1,2,3-triazole in place of an *E*-configured double bond is described, featuring the Cu(I) catalyzed azide–alkyne cycloaddition reaction as an efficient macrocyclization tool.

Nature remains a constant source for new lead compounds in chemical biology and medicinal chemistry investigations.[1] One approach to exploit this source further is to construct compound libraries derived from natural product scaffolds. In benefiting from evolutionary optimization, these collections can be expected to yield hits at a very much reduced library size or help to uncover new target proteins.[2] Their synthesis furthermore stimulates chemical development.[3]

We have recently introduced *biology oriented synthesis* (BIOS)[2c] as a concept for the synthesis of focused compound collections. Here, efficient methods for the synthesis of natural product inspired compound collections are constantly required.[4] In order to advance such strategies to macrocycles we became interested in chemically interrogating polyketide units, which are common to many bioactive macrocyclic molecules, and opening up diversification strategies for them.

The 19-membered cyclodepsipeptide jasplakinolide (**1**, also named jaspamide) was selected as an exploratory test case (Fig. 1). This natural product was isolated from marine *Jaspis* sponges and is endowed with a remarkable cytotoxicity and antitumor activity profile.[5] The detailed mechanism of its action *in vivo* is believed to involve a disruption of F-actin filaments and the induction of actin polymerisation, rendering **1** a potential chemotherapeutic agent.[6] **1** features a tripeptide (β-Tyr, D-Trp and L-Ala) and a polyketide segment united in a macrocyclic ring. It has been hypothesized that the polypropionate portion may adopt a U-shaped conformation, leading to a β-II-hairpin-type conformation in the tripeptide segment.[7] Recently, syntheses of jasplakinolide analogs were reported[8] where the polyketide part was replaced by simplified building blocks.[9] Interestingly, cyclodepsipeptides closely related to **1** and active in actin modulation have been uncovered also in nature.[10]

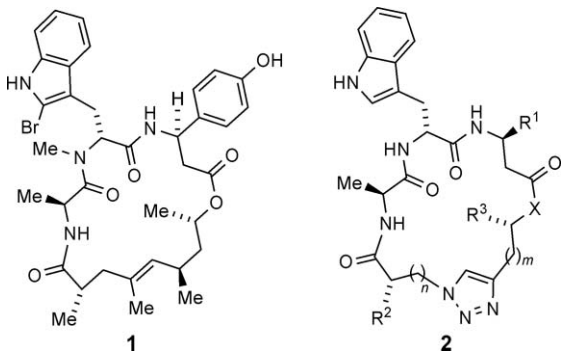
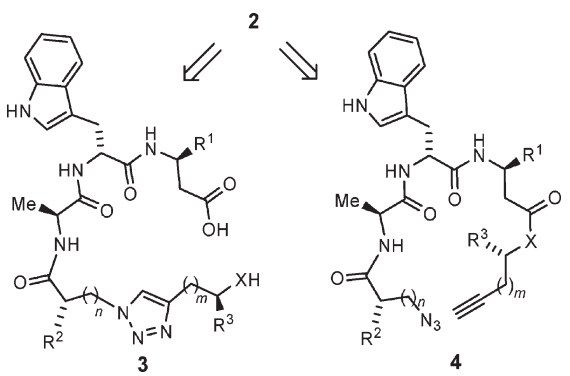


Fig. 1 Jasplakinolide (**1**) and triazole analogs **2**.

We report here on the synthesis of jasplakinolide analogs **2** by utilizing 1,4-disubstituted 1,2,3-triazoles for the diversification of the macrocycle (Fig. 1). Importantly, the efficiency of Cu(I)-catalyzed intramolecular alkyne–azide cycloadditions[11] as a reliable macrocyclization method was demonstrated.

Simple 1,4-disubstituted 1,2,3-triazoles are readily available from Cu(I)-catalyzed 1,3-dipolar cycloadditions of alkynes and azides.[12] A 1,2,3-triazole is found in many pharmaceuticals[13] and was discussed as *trans*-amide bond replacement with enhanced hydrolytic and proteolytic stability.[14] An *E*-configured trisubstituted double bond has similar structural parameters, and hence should be likewise amenable to triazole replacement. In this case, the triazole should confer sufficient lipophilicity to account for the third substituent on the double bond.

A retrosynthetic analysis of triazole-containing jasplakinolide analogs **2** is shown in Scheme 1. Two distinct approaches for the macrocyclization were explored: a classical macrolactonization or -lactamization with hydroxy or amino acids **3** as substrates, and furthermore the Cu(I)-catalyzed intramolecular 1,3-dipolar cycloaddition with azidoalkynes **4** as the precursor. For precursor synthesis, a combination of solution phase and solid phase



Scheme 1 Alternative retrosynthetic disconnections of **2**.

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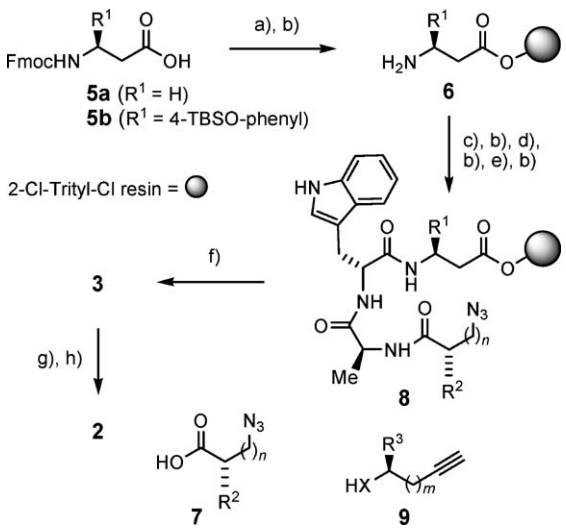
methods was employed, relying on Fmoc protected amino acids and 2-chlorotrityl chloride resin to anchor the growing chain.

The classical macrocyclization strategy with **3** as the linear precursor was explored first (Scheme 2). Fmoc protected β-amino acid **5** was attached to the solid support in the presence of diisopropylethylamine. After release of the Fmoc group with 20% piperidine in DMF, the chain was extended with Fmoc-D-Trp-OH using *N*,*N*′-diisopropylcarbodiimide (DIC) and HOBt as the coupling reagents. Two cycles of Fmoc deprotection and amide bond forming reactions (with Fmoc-L-Ala and an azido acid **7**, respectively) afforded resin-bound azides **8**, which reacted smoothly with alkyne alcohols/amines **9** in the presence of CuI. The progress of this on-resin Cu(I)-catalyzed intermolecular 1,3-dipolar cycloaddition[15] was monitored with on-bead FTIR by the disappearance of the strong absorption of the azido group around 2100 cm^{-1}. Acid mediated cleavage from solid support gave hydroxy/amino acids **3** in greater than 70% overall yield and with greater than 95% purity. The acids **3** were then subjected to modified Yamaguchi cyclization conditions[16] or macrolactamization conditions, respectively, to deliver the target compounds **2**. All results are summarized in Table 1 (entries 1–8, method A). The macrolactones were obtained in moderate yields in the range of 28–59% (**2a**–**d**). For **2e**–**f**, where (*R*)-*N*-Fmoc-*O*-TBS-β-tyrosine **5b** was used in the first step (R^1 = 4-*tert*-butyldimethylsilyloxyphenyl), TBS deprotection of the phenol followed after macrocyclization, and the compounds were obtained in 15–32% yield in these cases (2 steps). Unexpectedly, macrolactamization did not give clean results under conventional conditions (HOBt, EDC), and **2h** could only be isolated in very low yield (entry 8, method A).

Due to the scattered yields observed in the macrolactonization and -lactamization attempts, the intramolecular 1,3-dipolar cycloaddition was investigated as an alternative macrocyclization variant. The resin-bound azides **8** were cleaved from solid support



Scheme 2 Synthesis of analogs **2** by macrolactonization or -lactamization. *Reagents and conditions*: (a) 2-Cl-Trityl-Cl resin, $(i\text{Pr})_2\text{NEt}$, CH_2Cl_2; (b) 20% piperidine in DMF; (c) (i) Fmoc-D-Trp-OH, DIC, HOBt, DMF; (d) (i) Fmoc-L-Ala-OH, DIC, HOBt, DMF; (e) **7**, DIC, HOBt; (f) (i) **9**, CuI, $(i\text{Pr})_2\text{NEt}$, THF; (ii) CH_2Cl_2–AcOH–TFE (8 : 1 : 1), >70% overall yield; (g) 2,4,6-trichlorobenzoyl chloride for hydroxy acids, and EDC, HOBt for amino acids; (h) TBAF, THF, for TBS-protected compounds only, 5–59%.

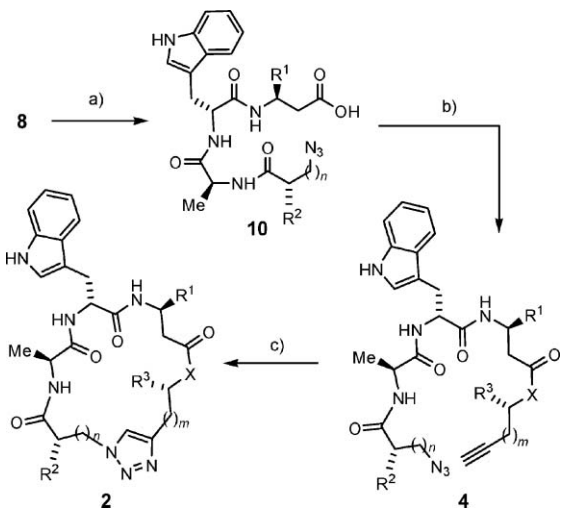
Table 1 Comparison of two different macrocyclization methods

Entry	Compound	R^1	R^2	R^3	X	*m*	*n*	Method A (%)[a]	Method B (%)[b]
1	**2a**	H	H	H	O	0	1	37	87
2	**2b**	H	H	H	O	0	2	28	65
3	**2c**	H	H	H	O	1	1	45	92
4	**2d**	H	H	H	O	1	2	59	82
5	**2e**	Z[c]	H	H	O	0	1	15[d]	—
6	**2f**	Z[c]	H	H	O	1	1	32[d]	—
7	**2g**	Z[c]	H	H	O	1	2	26[d]	—
8	**2h**	H	H	H	NH	0	1	5	70
9	**2i**	Z[c]	H	H	O	0	2	—	63[d]
10	**2j**	H	Me	H	O	1	1	—	75
11	**2k**	H	Me	Me	O	1	1	—	70
12	**2l**	H	H	H	NH	0	2	—	57

[a] Macrolactonization or -lactamization (**3** → **2**). [b] Intramolecular cycloaddition (**4** → **2**). [c] Z = 4-hydroxyphenyl. [d] Combined yield for cycloaddition and TBS ether deprotection (TBAF).

under acidic conditions, and the resulting peptide acids **10** then appended with alkynes **9** in the presence of coupling reagents to give terminal azidoalkynes **4** in 50–82% yields (Scheme 3). To our delight, the Cu(I)-catalyzed intramolecular alkyne–azide reaction of **4** proceeded cleanly and gave analogs **2** in good to excellent yields when a mixture of CH_3CN and THF were used as solvent and 2,6-lutidine as an additive. **2a**–**d** were obtained now in 65–92% yields (Table 1, method B). The 63% yield for β-tyrosine containing analog **2i** (entry 9, method B) also improved when compared with those of **2e**–**g** (entries 5–7, method A). The difference was even more striking for the lactam cases. **2h** was isolated in 70% yield, while the cyclization method described before only gave a trace amount of the same compound. Furthermore, it is worth noting that the intramolecular 1,3-dipolar cycloaddition reaction was exceptionally clean and that in our experiments the formation of dimers was not observed.[17]

In summary, 12 jasplakinolide analogs with varied substitution patterns and ring sizes (18–20 membered) have been synthesized, and an interesting triazole unit was successfully incorporated into the analogs **2** by a Cu(I)-catalyzed alkyne–azide cycloaddition



Scheme 3 Synthesis of **2** by intramolecular cycloaddition. *Reagents and conditions*: (a) CH_2Cl_2–AcOH–TFE (8 : 1 : 1); (b) **9**, EDC, DMAP (or HOBt), CH_2Cl_2–DMF, 50–82%; (c) CuI (0.1–0.5 eq.), $(i\text{Pr})_2\text{NEt}$, 2,6-lutidine, CH_3CN–THF, (then TBAF), 57–92%.

reaction. Applying this cycloaddition in an intramolecular fashion was much more efficient for inducing macrocycle formation than standard macrolactonization and -lactamization attempts. It tolerated a variety of substitution patterns, chain lengths, and stereochemical determinators on the linear precursor, and afforded the desired monomeric macrocycle as the only product.

The stunning efficiency for macrocyclic ring closure in this case must certainly have its roots in the mechanism of the Cu(I)-mediated reaction. It has become increasingly clear that intermediate Cu(I) acetylide–azide complexes are majorly involved in the cycloaddition reaction.[18] The precoordination of both termini of compound **4** to Cu(I) will template the macrocycle and kinetically favor ring closure. Furthermore, for inducing ring closure in this fashion no activated esters need to be generated, which are typically prone to several decay pathways and do not tolerate nucleophilic functional groups—neither in the medium nor in the substrate. It is therefore anticipated that Cu(I)-catalyzed cycloadditions will prove generally useful for accessing large, diversified natural product-like macrocyclic compound collections.

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