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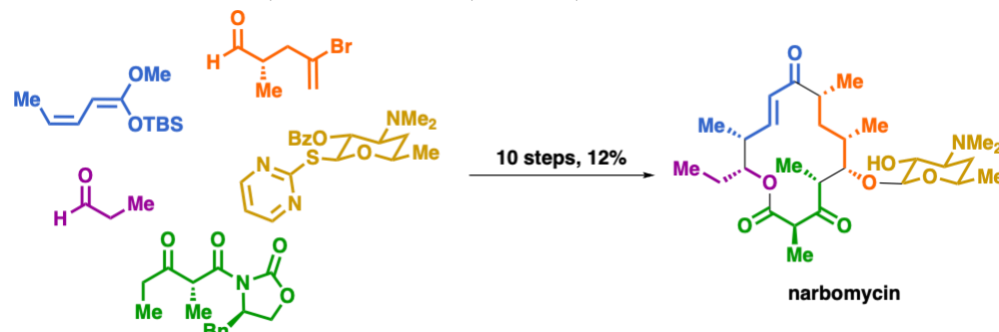
Convergent synthesis of the minimal macrolide antibiotic narbomycin

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ABSTRACT: Macrolide antibiotics are a class of structurally diverse polyketides including essential medicines like erythromycin and azithromycin. Structurally minimal macrolides such as narbomycin lack much of the functionality common to other members of the class and exhibit a distinct mode of action wherein they completely inhibit bacterial growth despite only moderate (~50%) inhibition of global protein synthesis. Unfortunately, lack of availability of these natural products has prevented a thorough investigation of their unusual mechanisms of action. Here we report a 10-step synthesis of narbomycin enabled by a Liebeskind-Srogl fragment coupling, a novel macrolactonization by direct displacement of an Evans auxiliary, and a stereoselective late-stage enone reduction. In addition to accessing the natural product, the route enables access to C8,19-unsaturated variants which could in principle serve as useful precursors for late-stage functionalization by conjugate addition.

Macrolide natural products, predominantly isolated from *Streptomyces* bacteria, are polyketides with 12- to 16-membered macrolactone cores, a variety of oxidation patterns, and at least one pendant sugar.¹ Since their initial discovery and isolation, macrolides such as erythromycin and its semisynthetic derivatives (e.g., clarithromycin, azithromycin) have been indispensable as treatments for a variety of bacterial infections.² Macrolides bind to the nascent polypeptide exit tunnel (NPET) in the 50S subunit of the bacterial ribosome, inhibiting protein synthesis by interfering with the elongation of the growing polypeptide chain via interactions with specific nascent peptide sequence motifs.^{1,3} One of the most widespread resistance mechanisms to the class is methylation of A2058 by methyltransferases encoded by *erm* genes that can be induced by macrolides bearing a cladinose sugar. Ketolides, which harbor a ketone instead of a cladinose-bearing alcohol, do not induce *erm*-mediated resistance, offering a strategy to restore activity against pathogens with inducible *erm*-mediated resistance. This sub-class includes natural ketolides such as narbomycin (**1**)⁴ and pikromycin (**2**)⁵ and semisynthetic ketolides such as telithromycin (**3**) and solithromycin (**4**).⁶

Minimal ketolides such as narbomycin (**1**) or pikromycin (**2**) have distinct mechanisms of action compared to highly functionalized ketolides **3** and **4**. Mankin and coworkers demonstrated that minimal ketolides rapidly halt cellular growth of bacteria, but protein synthesis proceeds at nearly half the level of untreated control even at saturating concentrations

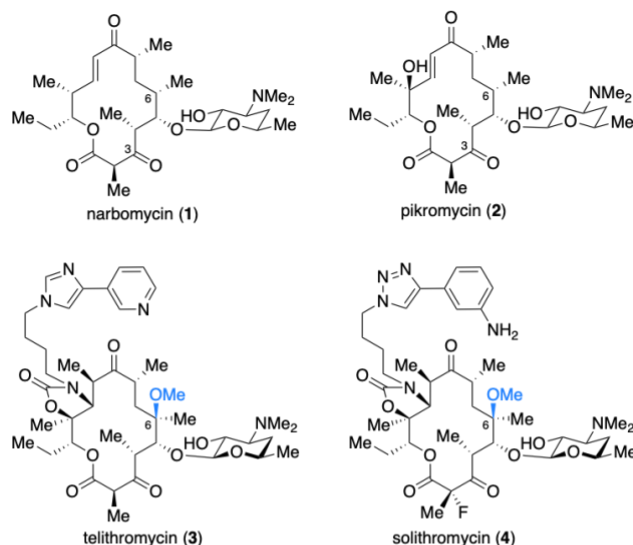
of **2**.⁷ This suggests that the ability of these molecules to inhibit cellular growth stems from selective inhibition of a subset of proteins that are required for proliferation. Unfortunately, lack of access to large quantities of these minimal macrolides, 1.3 mg/L of narbomycin produced from fermentative isolation,⁸ precluded genome-wide studies to grant further insight into this unusual mechanism of action.

Efficient (~14-17 steps), modular chemical syntheses of highly functionalized ketolides such as **4** enabled access to potent members of the class with inhibitory activity against multidrug-resistant strains of Gram-positive⁹ and Gram-negative bacteria.¹⁰ Similarly efficient routes to minimal pharmacophores **1** and **2** have not been reported.¹¹ The only reported total synthesis of **1** by Kang and coworkers used olefin metathesis to cyclize the macrocycle after constructing the macrolactone ester under Yamaguchi conditions, resulting in a longest-linear sequence of 20 linear steps.¹² The same group later reported the first total synthesis of **2** in 20 linear steps.^{12,13} Synthetic routes to the aglycones narbonolide¹²⁻¹⁵ and pikronolide^{12,16-19} which lack the pendant desosamine sugar required for biological activity, have been accomplished in as few as 18 steps.

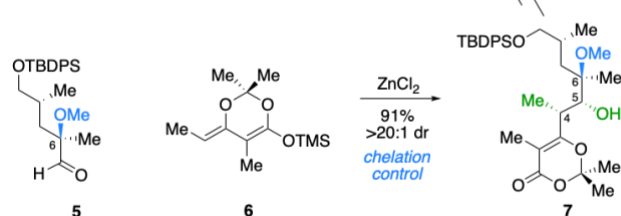
We initially envisioned an efficient synthesis of narbomycin (**1**) using a general macrocyclization strategy initially explored by Boeckman^{20,21} that relies on thermolysis of 1,3-dioxin-4-ones (herein referred to as dioxinones) to produce an electrophilic acylketene²² that is intercepted by the secondary

alcohol to generate the macrocycle.²³ This strategy was

A. Natural and semisynthetic ketolide antibiotics



B. Mukaiyama strategy for C6-methoxy ketolides



C. Failure of Mukaiyama strategy without C6 oxygenation

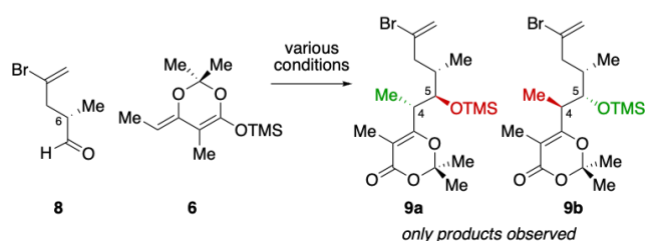


Figure 1. (A) Natural and semisynthetic ketolide antibiotics. (B) Vinylogous Mukaiyama aldol reactions with C6-methoxy aldehyde **5** enabling incorporation of the dioxinone for thermal macrocyclization en route to solithromycin. (C) Similar macrocyclization with the C6-desmethoxy aldehyde **8** yields only undesired *anti* products.

effectively employed by the Myers group in the synthesis of ketolides such as solithromycin (**4**),⁹ wherein the dioxinone was incorporated by means of a highly *syn*-selective vinylogous Mukaiyama aldol reaction between **5** and **6** to reach intermediate **7** (Figure 1B). When we attempted to adapt this strategy to the narbomycin scaffold using aldehyde **8** as an electrophile, we obtained exclusively *trans*-aldol products **9a** and **9b** under a variety of conditions (Figure 1C and Figure S1). We hypothesize that the C6 methoxy group, present in **5** but absent in **8**, plays an important role in the *syn*-selectivity of this transformation, likely due to chelation to the Lewis acid. We next sought alternative nucleophiles that could achieve the desired *syn*-selectivity and serve as functional precursors of the C1-C4 fragment of the natural product.

Evans β -keto-imides are useful aldol precursors, enabling the synthesis of β -keto- δ -hydroxy imides with control over three

stereocenters.^{24,25} However, access to ketolides using this strategy is complicated by the incompatibility of β -keto- δ -hydroxy imides with hydrolytic cleavage conditions due to rapid decarboxylation of the β -keto acid products.^{26–28} We envisioned a late-stage, direct macrocyclization event in which the oxazolidinone could be displaced by the C13 alcohol to generate the macrocycle, either by nucleophilic acyl-transfer or through an acylketene, analogous to dioxinone-mediated macrocyclizations. This would allow retention of the ketone required for C3 in the ketolide structure while avoiding unnecessary functional group manipulations.

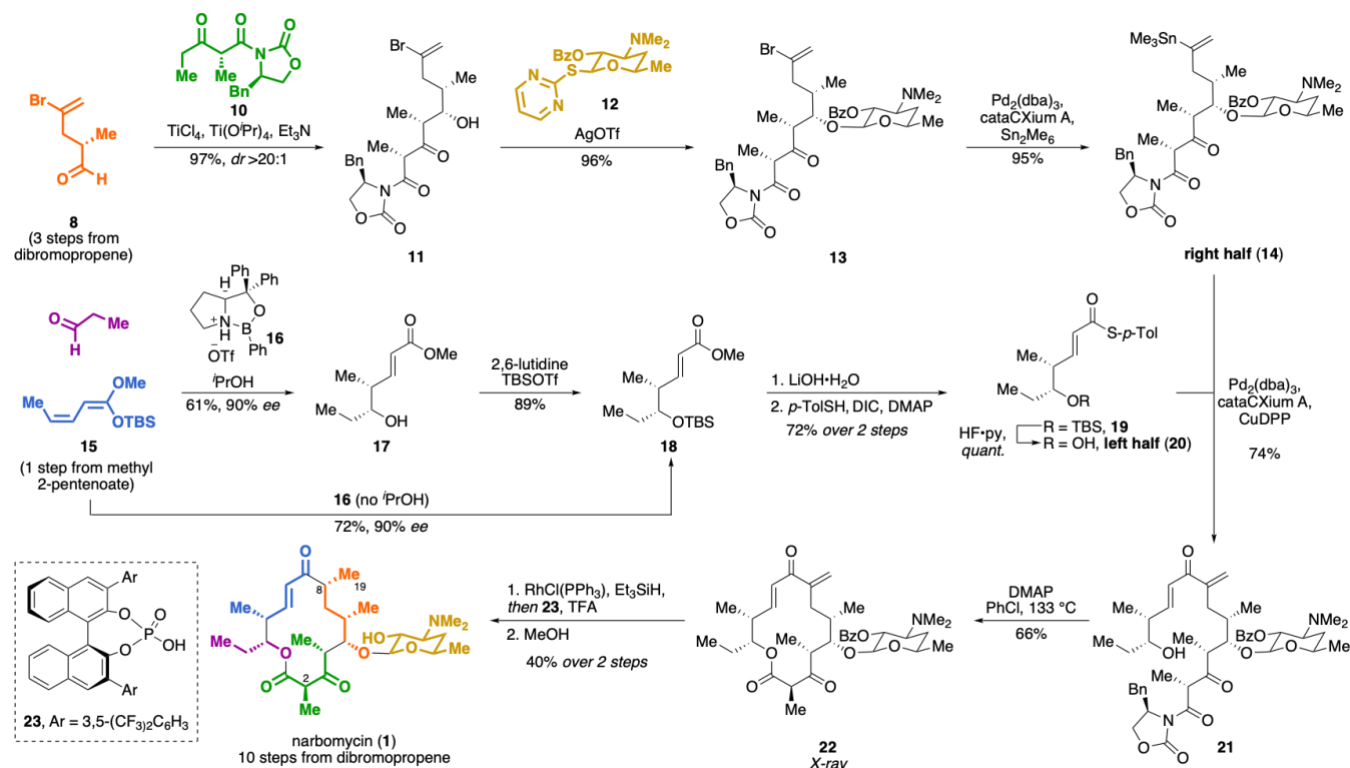
Aldol reaction between aldehyde **8** and β -keto-imide **10** proceeded in 97% yield with high diastereoselectivity, delivering the desired *syn* aldol product **11**.²⁵ Glycosidation with the desosamine glycosyl donor **12**^{29,30} in the presence of silver triflate provided the β -glycoside **13** in 96% yield. Conversion of **13** to the vinyl stannane **14** was only successful with the use of bulky di(adamantyl)-alkyl phosphine ligand cataCXium A in the presence of a palladium precatalyst. The bulky ligand may aid in occluding the multiple coordinating functionalities on **13** from the palladium center. With the fully furnished right half **14** in hand, we next focused our attention on the left half of narbomycin.

We set the C12 and C13 stereocenters by means of an enantioselective vinylogous Mukaiyama aldol between silyl ketene acetal **15** and propionaldehyde using the prolyl-type oxazaborolidine catalyst **16**,³¹ providing **17** in 61% yield and 90% enantiomeric excess. The secondary alcohol was then converted to a *tert*-butyldimethylsilyl ether (**18**). However, it was observed that a small amount of silyl-transfer side product (i.e., **18**) was formed in the aldol reaction (**15** $\rightarrow$ **17**). This is usually circumvented by inclusion of a sacrificial alcohol, like *i*-PrOH, but since the protected alcohol was desired, omitting *i*-PrOH from the otherwise identical aldol conditions yielded **18** directly in 72% yield without any decline in enantioselectivity, bypassing the separate protection step. Thioester **19** was synthesized by saponification and thioesterification of **18** in 72% yield over two steps. Precise control of the temperature of the thioester formation was critical to the outcome of the reaction; even with substoichiometric amounts of thiol, at temperatures above 0 °C, conjugate addition was observed as a byproduct. The final left half **20** was produced upon the removal of the TBS group with HF $\cdot$ pyridine in quantitative yield.

The left (**20**) and right (**14**) halves were successfully coupled with a Liebeskind-Srogl acylative palladium/copper-catalyzed cross coupling reaction³² to provide the linear macrocyclization precursor **21** in 74% yield (Scheme 1). The loading of CuDPP and thioester **20** relative to the vinyl stannane **14** were important in avoiding proto-destannylation side product.^{33,34} This coupling was also successful between **14** and TBS-protected thioester **19**, yielding the TBS-protected linear molecule whose silyl group could subsequently be removed to generate **21** in approximately the same yield (over 2 steps) as the aforementioned coupling (Figure S2). The catalyst and ligand combination used in this transformation is the same employed in the stannylation reaction, and telescoping the two reactions (i.e., **13** and **20** to produce **21**) gave product, albeit in much lower unoptimized yield (13%, Figure S2). In all cases, **21** existed as a 5:1 diastereomeric mixture by ¹H NMR, we hypothesized that the other product was a C2 epimer of **21**. This was of no concern because we anticipated that upon cyclization the C2 methyl group would equilibrate to its natural

configuration avoiding *syn*-pentane interactions, as documented for other macrolides.^{9,35}

Scheme 1. Synthesis of narbomycin (1)



We next turned our attention to macrocyclization strategies. Unlike dioxinones, which are known to thermolyze at 90–130 °C to generate acylketenes that can be captured by nucleophiles, Evans-style imides and β -keto-imides have only been shown to thermolyze under forcing thermal conditions (>133 °C) or with assistance from Lewis acids³⁶ and are always captured with an excess of nucleophile. Intramolecular displacement of the auxiliary has been documented for small ring sizes,³⁷ but macrocyclizations have not been reported to the best of our knowledge. Despite this lack of precedent, we decided to subject the substrate to the same thermal macrocyclization conditions used in the dioxinone acylketene cyclization.²⁰ After 16 h in refluxing chlorobenzene we were able to isolate the macrocycle **22** in 33% yield as a single diastereomer, recovering 66% of remaining starting material. Unfortunately, the yield could not be improved by increasing the temperature or reaction time nor by adding Lewis acids or using microwave irradiation. However, upon addition of a catalytic amount of 4-dimethylaminopyridine (DMAP), the reaction yield could be brought to 66% in a single pass. The structure of macrocycle **22** was supported by X-ray crystallography (Scheme 2), which revealed the correct stereochemical configuration of all stereocenters present.

The possible mechanisms of the macrocyclization merit further discussion, given the efficiency of this reaction and lack of literature precedent. Direct attack of the C13 alcohol to displace the Evans auxiliary is a possibility, although this seems unlikely given the steric constraints of the system. Alternatively, formation of an acylketene from **21**, which could occur through a concerted proton transfer/fragmentation, would be in good agreement with previous reports on the thermolysis of *tert*-butyl- β -keto-esters.³⁸ The role DMAP plays in

increasing the conversion and yield of the reaction is not yet clear, but it could serve as a catalyst for direct acyl transfer or for more efficient formation of an acylketene. Several possible reaction pathways are outlined in the Supporting Information (Figure S3). Beyond its use in the present application, this direct macrocyclization approach could be greatly enabling in the synthesis of other β -keto-macrolactone-containing natural products.^{39–41} Exploration of scope, mechanistic investigation, and application to other systems will be the subject of future studies.

The final steps remaining to access narbomycin were 1) chemo-, regio-, and stereoselective reduction of the C8 methylene, and 2) removal of the benzoyl group on the desosamine C2'-OH. The first transformation was notably difficult to achieve in any capacity due to the nature of intermediate **22**. The macrocycle has two α,β -unsaturated systems that share the common C9 carbonyl, both of which adopt an *s-cis* conformation with the carbonyl in the crystal structure, though this may not accurately reflect the configuration in solution. Although these alkenes differ in substitution pattern, most attempts to effect this transformation resulted in products of predominantly incorrect chemo-, regio-, and stereoselective reduction (Figure S4). A rhodium-catalyzed conjugate hydrosilylation approach^{42–45} using Wilkinson's catalyst and triethylsilane, followed by protonolysis of the silyl enol ether with a mixture of the chiral Brønsted acid **23** and trifluoroacetic acid and final benzoyl deprotection step in warm methanol provided narbomycin (**1**) in 40% yield over two steps. The spectral data for synthetic narbomycin (**1**) matched reported literature data¹² as well as that of an authentic sample of narbomycin from fermentative isolation.

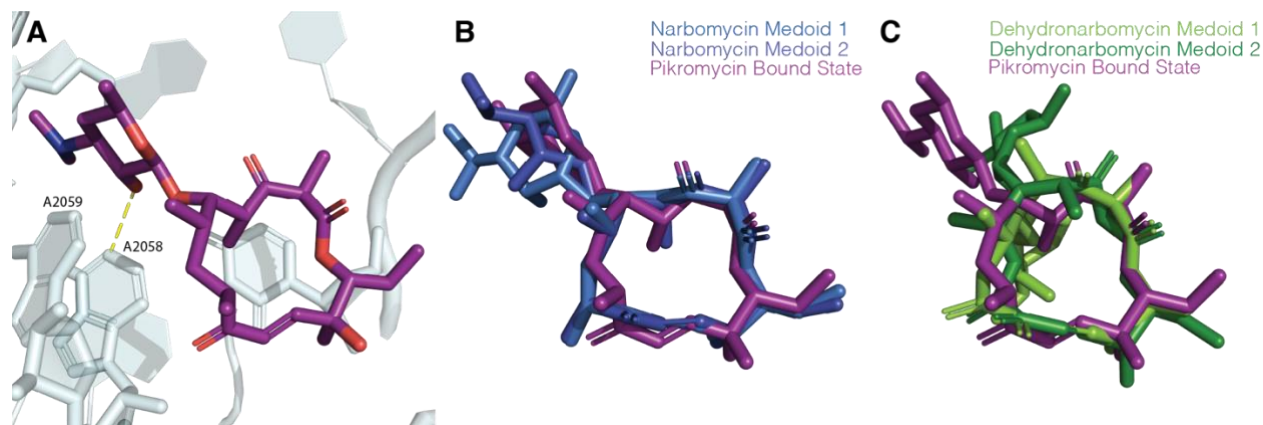
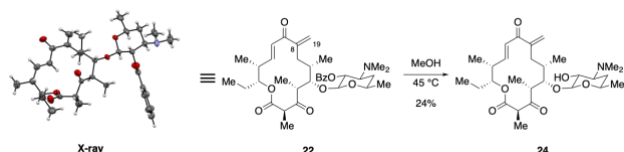


Figure 2. Structures of pikromycin, narbomycin and dehydronarbomycin (**24**). (A) X-ray crystal structure of pikromycin bound to *Thermus thermophilus* 70S ribosome (PDB code 5WIT; 2.6 Å). Hydrogen bonds are shown as yellow dashed lines. (B) Two representative conformations of narbomycin (blue) overlayed on the crystal structure of pikromycin (purple). (C) Two representative conformations of dehydronarbomycin (green) overlayed on the crystal structure of pikromycin (purple). The narbomycin and dehydronarbomycin structures represent two major clusters of conformers observed in annealing refinement MD simulations in MOE using Amber10 forcefield in water at room temperature.

Natural macrolide antibiotics usually harbor a methyl group (C19) at the C8 position of the macrocycle, and fluorination of C8, as in flurithromycin, increases acid stability, a major

Scheme 2. X-ray crystal structure of macrocyclization product **22 and the synthesis of dehydronarbomycin (**24**).**



drawback to the class prior to the development of azithromycin and clarithromycin.⁴⁶ We were interested to see how sp^2 hybridization at C8 (such as that found in intermediate **22**) would affect the antimicrobial activity of narbomycin-based macrolide scaffolds. We removed the benzoyl group from **22** to provide dehydronarbomycin (**24**, Scheme 2).

We then evaluated **1** and **24** for inhibitory activity against *Enterococcus faecium* Com15. While **1** inhibited growth at 8 $\mu\text{g/mL}$, **24** failed to inhibit growth at concentrations up to 256 $\mu\text{g/mL}$. These data show that a C8-C19 double bond greatly decreases narbomycin's antimicrobial activity, potentially due to the consequences of the additional sp^2 hybridization on the macrocycle's conformation. To explore this, we used a simulated annealing procedure in Molecular Operating Environment (MOE)'s dynamics module and modeled conformational ensembles for **24**, **1** and **2** (Figure 2, Figure S5). The conformation of pikromycin (**2**) in its cocrystal structure

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedures for each step in Schemes 1, 2, selected conditions screened for dioxinone vinyllogous Mukaiyama aldol, and C8-C19 reduction, simulation calculations, X-ray crystallographic information, and characterization of all intermediates and final compounds (PDF)

bound the *Thermus thermophilus* 70S ribosome⁷ was used as a proxy since structural data for **1** is not available. The conformational ensembles generated were then processed to find representative structures for each cluster of conformations (medoids). We found that while **1** closely matched the pikromycin ribosome-bound conformation, **24** adopted two notably different conformations that position the desosamine sugar away from its cognate binding groove in the A-site cleft. Given the importance of the desosamine for macrolide binding,^{47–49} these data are consistent with the reduction of activity of **24** arising from poor conformational preorganization for binding compared to **1** and **2**.

In summary, we have developed a short chemical synthesis of narbomycin (**1**) that proceeds in 10 steps (longest-linear sequence) with a high degree of convergency. The route is enabled by a vinyllogous Mukaiyama aldol reaction with efficient silyl transfer, a strategic Liebeskind-Srogl fragment coupling, and a direct macrolactonization from a β -keto-imide linear precursor. This research demonstrates the utility of β -keto-imides as precursors for macrocyclization, which may find application in the synthesis of diverse natural and unnatural macrocycles. We also found that C8–C19 unsaturation greatly decreased antibiotic activity against *E. faecium*, consistent with calculated changes to ground-state conformations relative to binding conformations. Finally, intermediate **22** could in theory serve as a useful precursor for the synthesis of ketolides with substitution at C8 to increase acid stability and overcome other common ketolide resistance mechanisms.

Deposition Numbers 2402906, 2402907, 2402908 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC).

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Author Contributions

All authors have given approval to the final version of the manuscript.

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