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Authors: Jan Herman Van Maarseveen, Luuk Steemers, Martin Wanner, Bart van Leeuwen, and Henk Hiemstra

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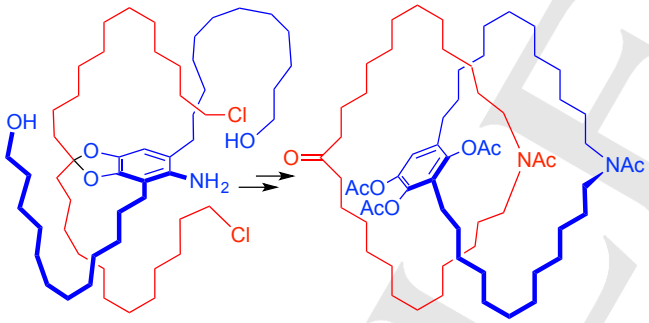
Attempted [2]catenane synthesis *via* a quasi[1]catenane by a templated backfolding strategy

Luuk Steemers,[a] Martin J. Wanner,[a] Bart R. C. van Leeuwen,[a] Henk Hiemstra[a] and Jan H. van Maarseveen*[a]

Abstract: A templated backfolding concept to construct a [2]catenane was attempted via a quasi[1]catenane showing an inverted spiro geometry. The template is covalently connected to the ketal-connected semi-perpendicular arranged linear precursors and spatially directs the sterically congested backfolding macrocyclizations that are required to give a quasi[1]catenane. So far, we are unable to hydrolyze the cyclic ketal to liberate the [2]catenane.

Introduction

To disclose the natural lasso peptide series in the far future, we are currently exploring covalent strategies towards mechanically interlocked molecules that do not contain the supramolecular motifs generally applied in the current synthetic approaches. Back in 1967 Schill reported one of the first [2]catenane syntheses using a covalent approach.[1] Crucial in their approach was the use of a cyclic ketal as motif for preorganization of the ring fragment, ensuring a perpendicular arrangement of the two linear ring precursors before ring-closure (see scheme 1).



Scheme 1. Schill's approach towards a [2]catenane *via* ketal preorganization.

The ketal motif was cleaved in a late stage using aqueous HBr, liberating the ketone and a catechol moiety. To the best of our knowledge, this approach is the only successful synthesis of a mechanically interlocked product employing a cyclic ketal as motif for pre-organization, despite its relative simplicity and facile accessibility.

[a] Van 't Hoff Institute for Molecular Sciences
University of Amsterdam
Science Park 904, 1098XH Amsterdam, The Netherlands
Homepage: http://hims.uva.nl/soc
E-mail: j.h.vanmaarseveen@uva.nl

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Recently, we reported a strategy using the perpendicular arrangement of a tetrahedral carbon atom for the synthesis of bicyclic molecule **1** showing an inverted sipro architecture, coined as a quasi[1]catenane (see Figure 1).[2] Inspired by the landmark paper by Schill we report here our efforts to combine the best of both worlds to arrive at [2]catenanes *via* quasi[1]catenane **2** by introducing scissile bonds at the connecting tetrahedral carbon atom. Figure 1 illustrates a comparison of the design of the two quasi[1]catenanes differing in replacing the permanent central fluorene moiety reported before by a rigid cyclic ketal linkage based on L-(+)-tartaric acid in the current communication.

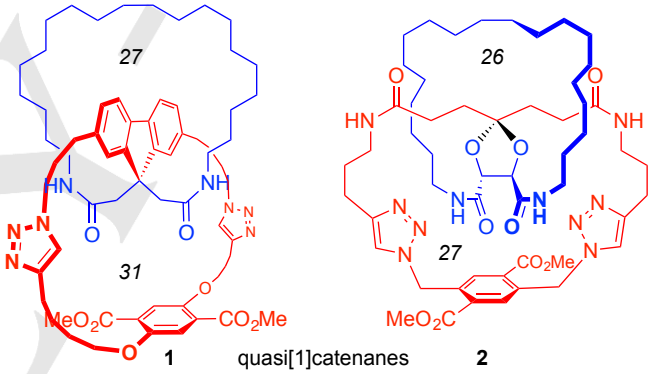

Figure 1. The previously synthesized permanent quasi[1]catenane **1** and analog **2** employing a scissile ketal.

This cyclic ketal ensures the desired perpendicular arrangement of the ring and thread fragments and is acid labile, allowing hydrolysis during the final acidolytic cleavage step. L-(+)-tartaric acid was chosen as a building block, as it possesses two carboxylic acid moieties and two hydroxyl functionalities, allowing ketal formation. Moreover, tartaric acid chemistry is well developed and starting materials are readily available. As shown in Scheme 2, the design of the linear precursor **4** features terminal alkyne and alkene moieties to allow closure of the macrocyclic rings via respective Cu-catalyzed azide alkyne cycloaddition (CuAAC) and ring-closing metathesis (RCM) reactions. Central in our approach is the use of a template **5** that is temporarily connected to the tartaric acid-containing ring-precursor fragment **4** via esterification/lactonization to the acid cleavable benzylic tethers. This forces both the subsequent CuAAC macrocyclizations as well as the final RCM macrocyclization in a backfolding fashion. Cleavage of the lactones via transesterification and protolytic cleavage of the benzylic linkages provides quasi[1]catenane **2**. Final hydrolysis of the ketal in **2** liberates the mechanically locked [2]catenane **3**.

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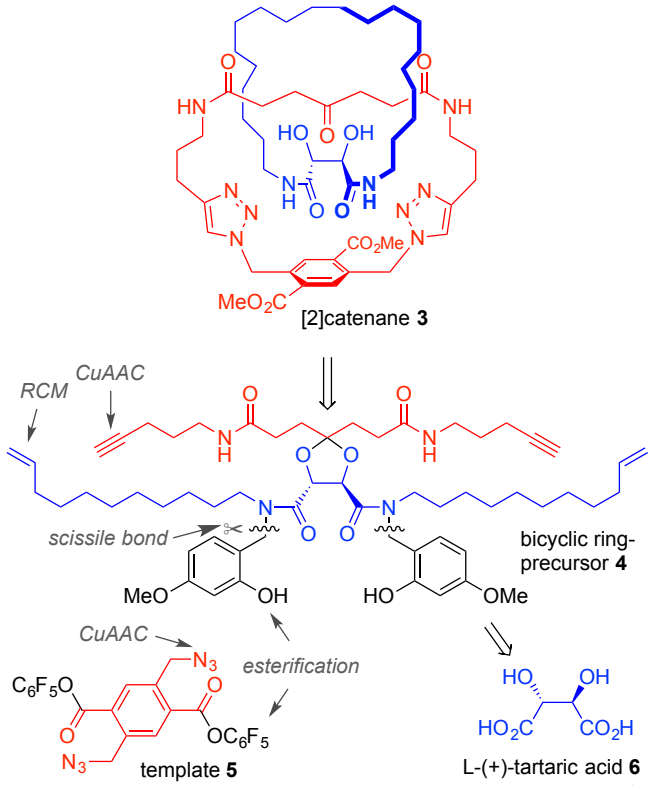
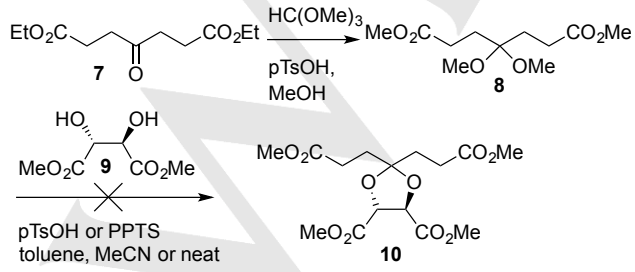


Scheme 2. Outline of the covalent template-directed backfolding strategy.

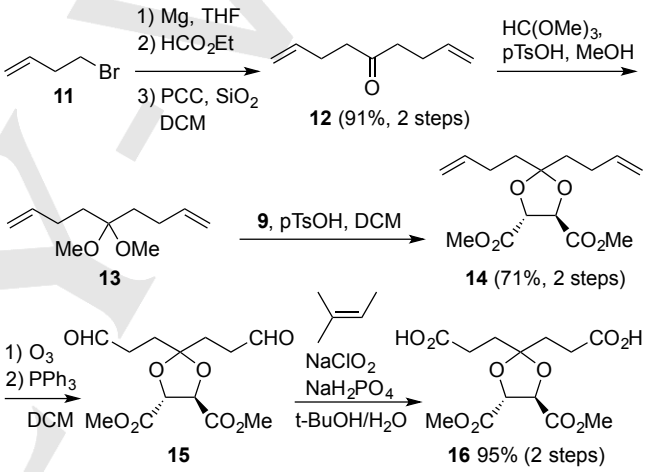
Results and Discussion

The synthesis commenced with the build up of the tartaric acid-based acyclic ring precursor. It was decided to install the pivotal cyclic ketal moiety as early on as possible in the synthesis. The most logical reaction to form the desired skeleton was *via* ketalization of dimethyl tartrate **9** with a diester of 4-oxopimelic acid **7** as this would directly form the desired core **10** with the correct oxidation states. Although orthogonally protected esters would be most desirable, it was decided to first test the ketal formation with dimethyl tartrate **9** and diethyl 4-oxopimelate **7** (both commercially available). To activate the ketone moiety, it was first reacted with excess trimethyl orthoformate in methanol, forming acetal **8** (see Scheme 3).[3] Note that under these conditions the ethyl esters were transformed to methyl esters. Subsequent acid catalyzed trans-acetalization with dimethyl tartrate was conducted next.



Scheme 3. Attempted synthesis of central L-(+)-tartaric acid-based core.

However, under the various reaction conditions tested, only hydrolysis of the acetal was observed (forming the starting ketone **7** again) with no traces of the desired tartaric acid ketal **10**. It is thought that the close proximity of the methyl ester moieties to the acetal prevents the desired reaction to take place, probably by an unwanted but favored 5-*exo-trig* attack of the ester carbonyls at the intermediate oxonium intermediate. Therefore, we chose to mask the ester moieties on the 4-oxopimelic acid side during ketalization. It was decided to use an alkene as a carboxylate synthon, eventually transforming it through sequential oxidation *via* the bis-aldehyde to the bis-carboxylic acid. This synthetic detour started with a Grignard reaction of 4-bromo-1-butene **11** with ethyl formate to give the symmetric secondary alcohol in quantitative yield (see scheme 4.[4] Subsequent oxidation with pyridinium chlorochromate (PCC) gave ketone **12** in 91% yield over the two steps, after column chromatography.[5]



Scheme 4. Synthetic scheme of the L-(+)-tartaric acid based central core.

Next, the acid catalyzed ketal formation of ketone **12** with dimethyl tartrate was tested. Refluxing with p-TsOH in toluene with a Dean-Stark trap gave no conversion and also refluxing with $BF_3{\cdot}Et_2O$ in dry CH_2Cl_2 failed to give conversion. Therefore, the same mode of activation was chosen as for the attempted synthesis of **10**.[6,7,8] As a result, ketone **12** was first transformed into dimethyl acetal **13** with trimethyl orthoformate in dry methanol. Subsequent p-TsOH catalyzed trans-acetalization with two equivalents of dimethyl tartrate **9** in refluxing dichloromethane gave a clean conversion to cyclic ketal **14**, which was isolated in 71% yield over the two steps. Subsequent oxidation of the terminal alkenes towards the aldehydes giving **15** was optimized next. Initially, the Lemieux-Johnson reaction,[9] *i.e.* oxidation with OsO_4 and excess $NaIO_4$, was used, but yields of dialdehyde **15** were not satisfactory. Fortunately, ozonolysis of the terminal alkenes, followed by reduction with PPh_3 gave a clean conversion to dialdehyde **15**. Reduction of the ozonide intermediate with dimethyl sulfide, thiourea or NMMO gave lower yields and/or more byproducts. Because isolated yields of the sensitive dialdehyde after column chromatography were mediocre at best, it was decided to use the crude dialdehyde still contaminated with PPh_3 and PPh_3O directly in the subsequent Pinnick oxidation step.[10,11] Treatment with NaH_2PO_4 and $NaClO_2$ using 2-methyl-2-butene as

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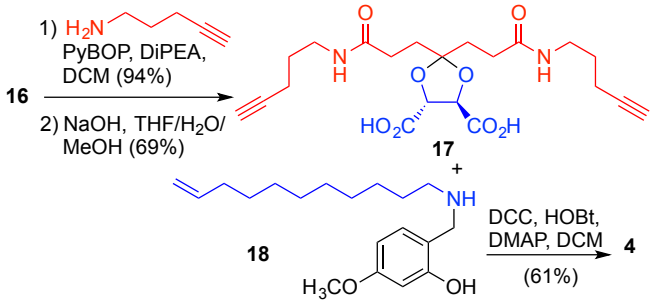
the HOCl scavenger yielded diacid **16** in 95% yield over the two steps. Purification of the diacid was achieved by extracting it into the water layer with $NaHCO_3$ and washing the water layer with EtOAc to remove the PPh_3, PPh_3O and other apolar organic residues. Subsequent careful acidification of the water layer allowed extraction of the product into the organic phase, giving fairly pure diacid **16**.

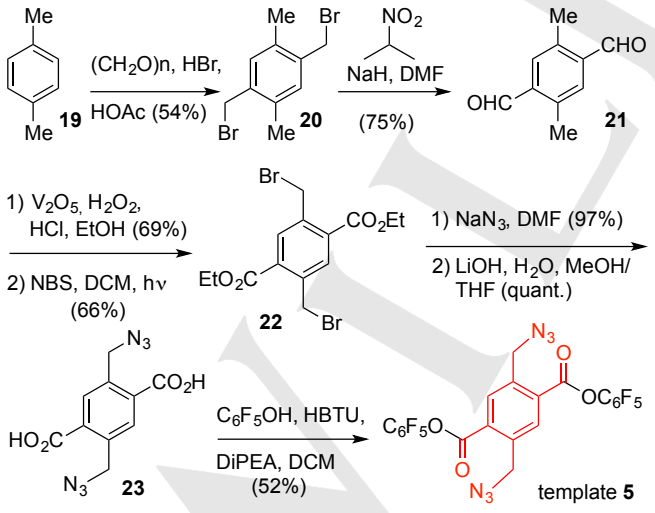
Next, coupling of diacid **16** with 5-amino-1-pentyne[12] was optimized.



Scheme 5. Build up of the ring-precursor fragment.

Standard coupling conditions between the amine and diacid **16** with DCC and HOBt gave low yields. However, treatment with 2.5 equivalents of PyBOP gave full conversion, giving the diamide in 94% yield, which was pure enough for the next step. The two methyl esters were smoothly saponified with aqueous NaOH, giving diacid **17** in 69% yield. Impurities were removed by washing the basic water layer with ethyl acetate. The product was extracted after careful acidification of the water layer. Next, diacid **17** was coupled to amine **18**[2] with DCC and HOBt as coupling reagents, giving ring-precursor tetra-amide **4** in 61% yield.

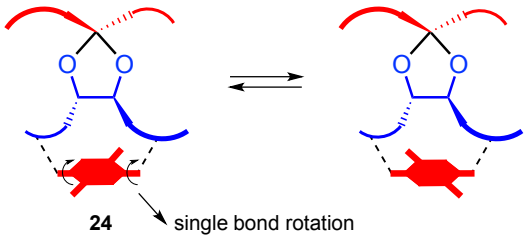
With ring precursor **4** in hand, the di-azide template **5** had to be synthesized.



Scheme 6. Scaffold synthesis.

The synthesis started with bromomethylation of p-xylene **19** to give dibromide **20** in a moderate but acceptable 54% yield (see scheme 6).[13] Bis-benzylic bromide **20** was transformed into di-aldehyde **21** by the Hass-Bender oxidation using 2-nitropropane in 75% yield.[14] Further oxidation to the esters with V_2O_5 and hydrogen peroxide in acidic ethanol yielded the terephthalic ester in 69% yield.[15] Because some mono-carboxylic acid was still present due to hydrolysis this yield may be improved. Fortunately, the subsequent radical bromination went cleanly, giving dibromide **22** in 66% yield after recrystallization. The azides were introduced cleanly and almost quantitatively, giving the di-azide as a colorless solid. Saponification with LiOH gave di-acid **23** in quantitative yield. Treatment of di-acid **23** with pentafluorophenol, DIPEA and HBTU as coupling reagent gave the activated template **5** as a colorless solid in a moderate 52% yield.

With all building blocks in hand the scene is set for the final assembly of the quasi[1]catenane **2**. Macrocyclization of tetra-amide **4** with template **5** was performed using optimized transesterification conditions[2] by stirring the two components with 10 equiv of Cs_2CO_3 and 4Å molecular sieves in acetonitrile at high dilution (2 mM), giving macrocycle bis-ester **24** in 67% yield (Scheme 8). As observed in our previous work on the synthesis of the structurally similar quasi[1]catenane **1**,[2] the ^{1}H-NMR spectrum of the macrocycle **24** shows a high complexity (see supporting information). Besides rotamers emerging from the tertiary amides the complexity of the NMR spectrum of **24** might be further increased due to the presence of two diastereomers caused by hindered rotation around the endocyclic terephthalic core connecting ester single bonds introducing a center of planar chirality, as depicted in the cartoon below (Scheme 7). The 27-membered ring probably does not allow free rotation of the ester bonds as was the case in the similar precursor towards the synthesis of quasi[1]catenane **1**. In contrast to the perfect flat central five-membered ring within the fluorene core as in **1**, the 1,3-dioxolane ring as in **24** is slighlty puckered thus further breaking the symmetry also contributing to the ^{1}H-NMR spectra complexity.



Scheme 7. Possible diastereomer formation due to hindered rotation at the terephthalic single bond ester connections.

Subsequent CuAAC reaction with catalytic $Cu(CH_3CN)_4BF_4$ and TBTA as ligand in dichloromethane gave bis-triazole cage molecule **25** uneventfully in 80% yield.[16] Subsequent ring closure *via* olefin metathesis using Grubbs 2nd generation catalyst was unexpectedly difficult. Despite various experiments, the macrocyclic olefin **26** was obtained in 25% yield only. Moreover, as observed in our previously reported quasi[1]catenane synthesis, trace amounts of the CH_2-truncated product were also observed.[2] Cleavage of the lactone esters was achieved by treatment with excess K_2CO_3 in methanol, giving the diester **27** in 82% yield. These conditions suppress unwanted saponification due to trace amounts of water in the reaction mixture as observed occasionally when employing $NaOCH_3$ in 'anhydrous' methanol.

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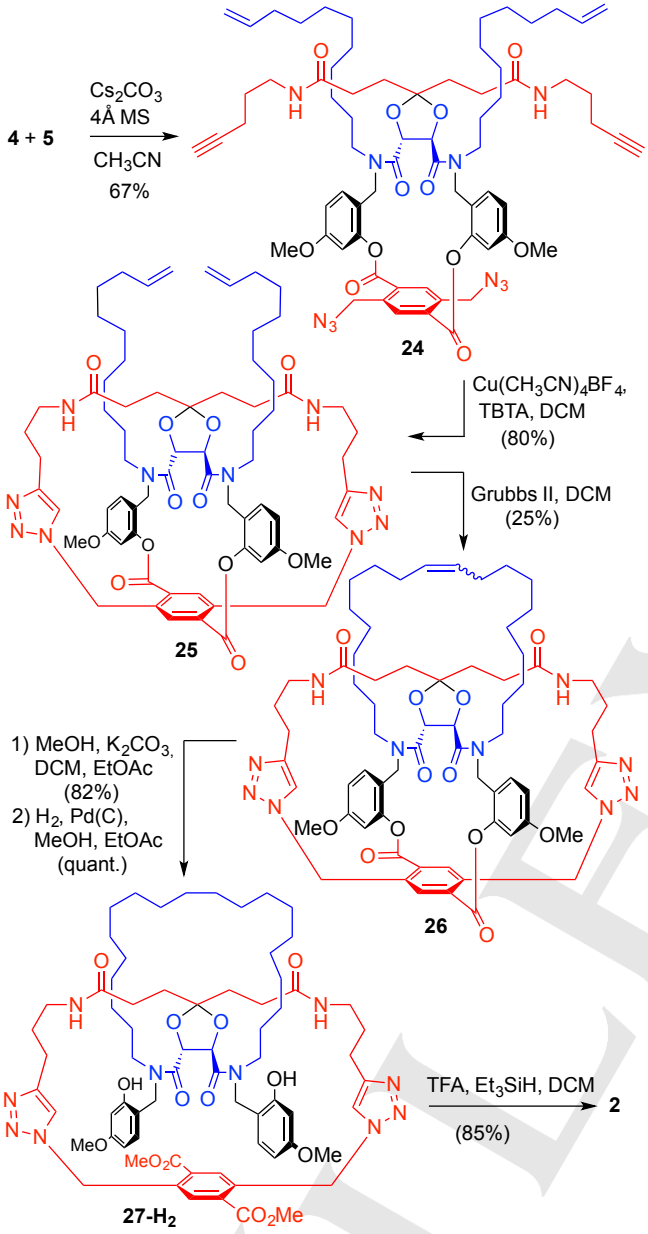
Next, the alkene E/Z-mixture was removed by catalytic hydrogenation to give **27-H$_2$**. The final steps of the attempted synthesis of [2]catenane **3** included acidolytic cleavage of the benzyl groups and acidic hydrolysis of the ketal moiety.



Scheme 8. End game towards quasi[1]catenane **2**.

Treatment with excess triethylsilane as a cation scavenger in TFA gave quasi[1]catenane **2** in ca. 85% yield. HRMS of the product showed the presence of the desired mass (m/z 1039, M+Na$^+$), however also trace amounts of m/z 1037 were observed, corresponding to the M+Na$^+$ signal of the non-hydrogenated analogue of **2**, meaning that the hydrogenation step had not reached completion yet. Surprisingly, no hydrolysis of the ketal was observed during the LCMS analysis. Most probably due to the presence of multiple conformations and two diasteromers as discussed above, the unambiguous assignment of the quasi[1]catenane architecture of **2** by ^{1}H-NMR is still severely hampered. Heating up the NMR sample in deuterated DMSO to 120 °C resulted in a less complex spectrum in which the peaks of the conformers coalesced. At that temperature in the 7-8 ppm region the terephtalic, triazole and two different amide-N protons gave four broad but discrete signals. Also noteworthy are the ester methyl signals that now gave one peak. Disappointingly, various attempts to hydrolyze the ketal in **2** failed to give any of the desired [2]catenane, usually resulting in acid catalyzed hydrolysis of the methyl esters of the terephthalate moiety only (see supplementary information). We reason that the electron withdrawing esters of the tartaric acid moiety thwart protonation of the dioxolane oxygen. In addition, the severe steric hindrance around the endocyclic ketal hampers hydrolysis. After a landmark publication by the Sauvage group mentioning the catenand effect, various other reports describe the inert environment inside the core of interlocked molecules due to steric isolation.[17] Therefore, the fact that **2** is completely reluctant to hydrolysis can be seen as an indirect proof of the structure. Currently, work is in progress to to synthesize the sterically less encumbered [2]rotaxanes using the same strategy. In addition, a more electron-rich ketal will be installed in combination with replacing the aliphatic chains for peptidic chains allowing water molecules to enter the quasi[1]catenane cavity to facilitate hydrolysis. Furthermore, by replacing the ketal for a imidazolidin-4-one as the perpendicular and cleavable thread/ring connecting moiety, hydrolysis will result in a peptide thus coming closer to the far future lasso peptide series.

Conclusions

Previously we have developed a template-directed covalent strategy in which a linear chain is forced to backfold enabling macrocyclization over another linear molecule. This appoach led to a fascinating compound class coined as quasi[1]catenanes and characterized as bicyclic compounds with an inverted spiro architecture in which the rings are connected via a fluorene-centered tetrahedral C-atom. In this communication we have replaced the fluorene by a tartaric acid derived ketal having a similar geometry. Hydrolysis of the ketal liberates the mechanically locked [2]catenane skeleton. All steps towards the ketal centered quasi[1]catenane, *i.e.* macrolactonization, CuAAC macrocyclizations and RCM towards a cycloolefin, worked well. Unfortunately, so far we are unable to hydrolyze the central ketal moiety.

Acknowledgements

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Keywords: catenanes • templated synthesis • synthetic methodology • spiro compounds •

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Catenanes

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Attempted [2]catenane synthesis *via* a quasi[1]catenane by a templated backfolding strategy

A tartaric acid derived ketal-centered quasi[1]catenane is prepared by a template-directed covalent strategy forcing backfolding macrocyclizations. All key steps towards the quasi[1]catenane, *i.e.* macrolactonization, CuAAC macrocyclizations and RCM towards a cycloolefin, worked well. Unfortunately, all attempts to hydrolyze the ketal liberating the [2]catenane architecture failed.

Molecular knotting