Molecular Knots


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 his 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).

The ketal motif was cleaved in a late stage by using aqueous HBr, thus 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 preorganization, despite its relative simplicity and facile accessibility.

Recently, we reported a strategy using the perpendicular arrangement of a tetrahedral carbon atom for the synthesis of bicyclic molecule 1 showing an inverted spiro architecture, coined as a quasi[1]catenane (see Figure 1).[2] Inspired by the landmark paper by Schill, we report here the 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.

This cyclic ketal ensures the desired perpendicular arrangement of the ring and thread fragments and is acid labile, thus 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 by respective Cu-catalyzed azide alkyne cycloaddition (CuAAC) and ring-closing metathesis (RCM) reactions. Central in our approach is the use of template 5 that is temporarily connected to the tartaric acid containing ring-

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precursor fragment 4 by esterification/lactonization to the acid-cleavable benzyl tethers. This forces both the subsequent CuAAC macrocyclizations as well as the final RCM macrocyclization in a backfolding fashion. Cleavage of the lactones by trans-esterification and protolytic cleavage of the benzyl linkages provides quasi[1]catenane 2. Final hydrolysis of the ketal in 2 liberates the mechanically locked [2]catenane 3.

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

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 through 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.

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]

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 BF3·Et2O in dry CH2Cl2 failed to give conversion. Therefore, the same mode of activation was chosen as for the attempted synthesis of 10.[6–8] As a result, ketone 12 was first transformed into dimethyl acetal 13 with trimethyl orthoformate in dry methanol. Subsequent oxidation of the terminal alkenes towardsthe aldehydes giving 15 was optimized next. Initially, the Lemieux–Johnson reaction,[9] i.e., oxidation with OsO4 and excess NaIO4, was used, but yields of dialdehyde 15 were not satisfactory. Fortunately,
ozonolysis of the terminal alkenes, followed by reduction with PPh3 gave a clean conversion to dialdehyde 15. Reduction of the ozonide intermediate with dimethyl sulfide, thiourea or NMNO gave lower yields and/or more by-products. 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 PPh3 and PPh3O directly in the subsequent Pinnick oxidation step.10,11 Treatment with NaH2PO4 and NaClO2 while using 2-methyl-2-butene as 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 NaHCO3 and washing the water layer with EtOAc to remove the PPh3, PPh3O 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-pentyne12 was optimized (Scheme 5).

Standard coupling conditions between the amine and diacid 16 with DCC and HOBt gave low yields. However, treatment with 2.5 equiv. of PyBOP gave full conversion, yielding 94% of the diamide, 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 1812 with DCC and HOBt as coupling reagents, giving ring-precursor tetra-amide 4 in 61% yield.

With ring precursor 4 in hand, the diazide template 5 had to be synthesized. The synthesis started with bromomethylation of p-xylene 19 to give dibromide 20 in a moderate but acceptable yield of 54% (see Scheme 6).13 Bisbenzylc bromide 20 was transformed into dialdehyde 21 in 75% yield by the Hass-Bender oxidation using 2-nitropropane.14 Further oxidation to the esters with V2O5 and hydrogen peroxide in acidic ethanol yielded the terephthalic ester in 69% yield.15 Because some monocarboxylic 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 diazide as a colorless solid. Saponification with LiOH gave diacid 23 in quantitative yield. Treatment of diacid 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 was set for the final assembly of the quasi[1]catenane 2. Macrocyclization of tetra-amide 4 with template 5 was performed by using optimized transesterification conditions,21 e.g., stirring the two components with 10 equiv. of Cs2CO3 and 4 Å molecular sieves in acetonitrile at high dilution (2 mM), thus giving macrocycle bis-ester 24 in 67% yield (Scheme 7). As observed in our previous work on the synthesis of the structurally similar quasi[1]catenane 1,25 the 1H NMR spectrum of the macrocycle 24 shows a high complexity (see the 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. These are caused by the hindered rotation around the ester single bonds that connect the endocyclic terephthalic core, thus introducing a center of planar chirality as depicted in the cartoon below (Scheme 8). 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 slightly puckered thus further breaking the symmetry also contributing to the 1H NMR spectra complexity.

Subsequent CuAAC reaction with catalytic Cu(CH3CN)4BF4 and TBTA as ligand in dichloromethane gave bistriazole cage molecule 25 uneventfully in 80% yield.16 Subsequent ring closure though olefin metathesis by 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 CH2-truncated product were also observed.26 Cleavage of the lactone esters was achieved by treatment with excess K2CO3 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 NaOCH3 in "anhydrous" methanol. Next, the E/Z-alkene mixture
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+ of the non-hydrogenated analogue of 2, indicating 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 diastereomers as discussed above, the unambiguous assignment of the quasi[1]catenane architecture of 2 by 1H 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 terephthalic, 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, but usually resulted in acid-catalyzed hydrolysis of the methyl esters of the terephthalate moiety instead (see the Supporting 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 synthesize the sterically less encumbered [2]rotaxanes by 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 an imidazolidin-4-one as the perpendicular and cleavable thread/ring connecting moiety, hydrolysis will result in a peptide thus coming closer to the envisaged 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 approach 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 by a fluorene-centered tetrahedral C atom. In this communication we have replaced the fluorene by a tartaric acid derived ketal with 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., macrocyclization, CuAAC macrocyclizations and RCM towards a cycloolefin, worked well. Unfortunately, so far we are unable to hydrolyze the central ketal moiety.
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