Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis, structure and reactivity of a macrocyclic imine: aza-[13]-macrodiolides

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ARTICLE INFO

Article history:
Received 30 April 2014
Revised 15 May 2014
Accepted 16 May 2014
Available online xxxx

Keywords:
Macrocycle
Imine
Synthesis
Structure

ABSTRACT

The in situ synthesis and subsequent reactions of macrocylic imine **2** are reported. The imine was trapped with cyanotrimethylsilane to give α-amino nitrile aza-[13]-macrodiolides in a 1:1 ratio of diastereomers. A crystal structure of the *syn* α-cyano nitrile diastereomer, **7a**, provided insights into the lack of selectivity in reactions of **2** relative to macrocyclic alkene **1**. Reactions to functionalize the *syn* diastereomer **7a** are also reported.

Macrocycles occupy an important niche among organic compounds because they share features with both small molecules and larger ones.[1] The number of atoms in the ring, the presence and positioning of planar units and the stereogenic centers within it all contribute to the overall shape or topology of the macrocycle.[2,3] We have been focusing recently on how these factors interact in the context of some [13]-macrodiolides such as **1** (Fig. 1). Planar units such as esters, amides, and alkenes, for example, help to rigidify macrocyles and thereby reduce the number of low-energy conformations available to them. In the context of **1**, the ester and alkene units simplified its structure to three planar units and one 'hinge' atom.[2b,c] Further, the planar units must orient themselves in a non-coplanar fashion that creates a fold to the ring much like the twist of *E*-cyclooctene. Macrocycle **1** exhibits planar chirality when homochiral starting materials are used; we have shown that the absolute configuration of key stereogenic centers govern the planar chirality[4] of [13]-macrodiolides.[2]

Here we evaluate the substitution of an imine for the alkene unit in **1** (e.g., **2** in Fig. 1).[2,5] Specifically, we thought that the imine functionality, from the α-carbon through the imine carbon and nitrogen to the carbon attached to the nitrogen, would act as a four-atom planar unit (blue atoms in Fig. 1). The investigation aimed to illustrate the imine as another planar unit that would rigidify the [13]-macrodiolide structure and also switch the reactivity from that of a nucleophile to an electrophile. We were also motivated by the beneficial new properties associated with the incorporation of a nitrogen atom into a macrocycle.[6–9] Analysis of products, for example, aza-[13]-macrolide **7** (Scheme 1) that arise from additions to macrocyclic imine **2** would also provide information about the structure of **2**.[10] The structure and reactivity of imine **2** were of interest because we considered it an aza-analog of **1**. We report the in situ synthesis of macrocyclic imine **2** and its subsequent functionalization to novel aza-[13]-macrodiolides.

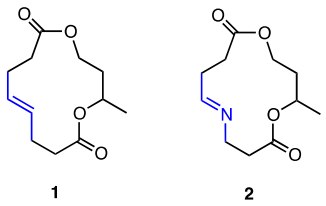

Figure 1. [13]-Macrodiolide **1** and aza-[13]-macrodiolide analog **2**.

The synthesis of imine **2** followed a strategy similar to the synthesis of **1**.[2] Sequential, chemoselective acylations of racemic 1,3-butanediol—first with pentenoic acid then with *N*-Boc-β-alanine—gave diester **3** in 80% over two steps (Scheme 1). Ozonolyis of the terminal alkene of **3** then provided aldehyde **4** (86%). It should be noted that the choice of aldehyde and Boc protected amine groups for the precursor to the macrocycle was made after earlier attempts with alternative protecting group schemes (i.e., Cbz protected amine with the aldehyde) were unsuccessful. With compound **4** in hand, the following steps were done sequentially in one pot in the successful sequence: (i) TFA deprotection of the

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http://dx.doi.org/10.1016/j.tetlet.2014.05.081
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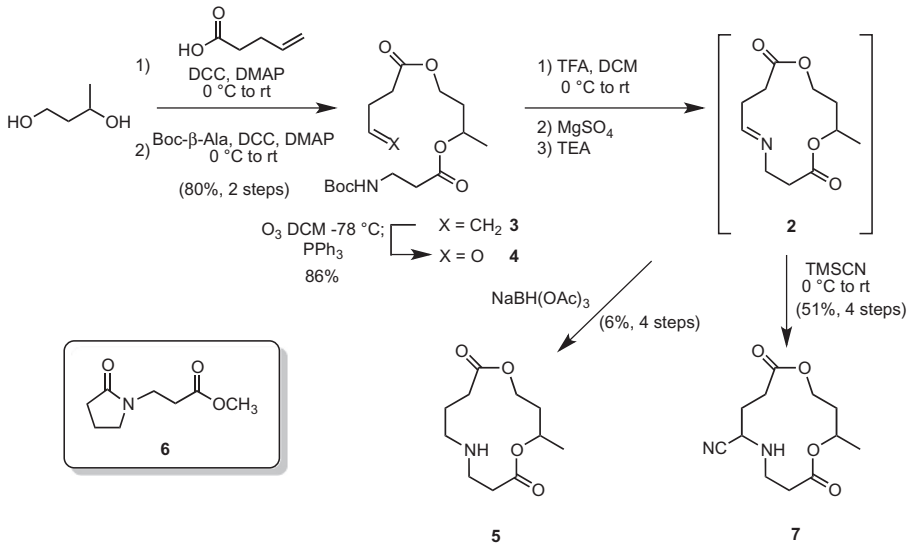


Scheme 1. Synthesis aza-[13]-macrodiolides **5** and **7** via macrocyclic imine **2**.

Boc carbamate; (ii) 20-fold dilution and dehydration using $MgSO_4$[11] and (iii) neutralization by addition of triethylamine. At the outset we had hoped to characterize and potentially isolate imine **2** because there is literature precedence for the formation of other macrocyclic imines.[8,12] Attempts at isolation of **2** were unsuccessful, however. We ultimately resorted to trapping the imine directly with nucleophiles to confirm that it had in fact formed. Sodium cyanoborohydride reduction in methanol[14] did not result in the expected aza-[13]-macrodiolide product **5**; instead, intramolecular amidation and transesterification led to a ring contracted γ-lactam **6** (Scheme 1, inset). The structure of **6** strongly suggested that **5**, and consequently imine **2** itself, were intermediates in the ring contraction (See Supporting information). Hydride reduction using $NaBH(OAc)_3$ did provide aza-[13]-macrodiolide **5**, albeit in only 6% yield as a mixture with other unidentified products.

Addition of cyanotrimethylsilane (TMSCN) after in situ imine formation, on the other hand, yielded cyano aza-[13]-macrodiolides **7** as a ~1:1 mixture of diastereomers, **7a** and **7b** (Scheme 1 and Fig. 2) in a combined 51% yield. It should be noted that each diastereomer of product **7** is itself racemic because the 1,3-butane diol used to start the synthesis was racemic. The yield for the formation of **7** was calculated based on *N*-Boc aldehyde **3** as starting material and formally included four steps.

The *syn* diastereomer, **7a**, was a crystalline solid. Data from X-ray crystallography revealed the structure depicted in Figure 2. Compound **7a** has features that are reminiscent of the X-ray structure collected for **1** and provides clues about macrocyclic imine **2**. First, each ester creates a four atom planar unit that reduces the number of freely rotating bonds in the backbone of the macrocycle. Second, the stereogenic centers at C2 and C9 both put the groups attached to them (methyl at C2 and cyano at C9) in pseudo equatorial positions. Finally, the cyano moiety at C9 is exocyclic to the macrocycle; that is, it points outside the ring. Epoxidations on chiral [13]-macrodiolides akin to **1** were highly diastereoselective.[2a] In those examples, the π-system of the alkene was shown to react exclusively through its exterior face. The position of the cyano group on the periphery of the macrocycle in **7a** suggests that the α-cyano amine arose by nucleophilic attack on a planar imine also from the exterior face.

The structural data from **7a** suggest that imine **2** largely resembles [13]-macrodiolide **1** (Fig. 2). The difference is that the imine of **2** acts as an electrophile rather than as a π nucleophile as does the alkene in **1**. Conversion of **2** to a ~1:1 mixture of diastereomers **7** shows that there is an absence of diastereofacial selectivity for reactions of this π-system, however. This result is in contrast to other compounds where macrocyclic diastereocontrol was operative.[2a,13] The dichotomy indicates a further difference in the nature of macrocycles **1** and **2**. The lack of stereoselectivity for TMSCN addition to **2** could be explained by at least four different models: (i) Imine **2** could take up a rigid geometry that is different than the configuration of **1** in Fig. 2 that would allow attack of nucleophiles from either diastereoface. This is unlikely based on the structural requirements of **1** and **2**. Specifically, we have only observed the formation of *E* alkenes (e.g., **1**) which suggests that the *E* configuration of the π-system is best accommodated based on the architecture of the 13-membered ring macrocycle. (ii) The α-amino nitrile products could equilibrate after they are formed and the reaction is under thermodynamic control. Epimerization of α-amino nitriles is known but under conditions that are more robust (either acidic or basic) than those used in the formation of **7a** and **7b**.[14,15] As reported here, imine **2** arose by TFA deprotection of a Boc group and then the acid was neutralized by one equivalent of TEA prior to addition of TMSCN. Moreover, exposure of **7a** to di-isopropylethylamine for 12 h at 70 °C showed no epimerization. (iii) The macrocyclic imines could interconvert via an aminal intermediate. Such a process could interconvert an *E* imine to *Z* or it could interconvert alternate *E* imines (Fig. 3A). Although we cannot rule it out, the *Z* imine is unlikely based on the ring size and the rigidifying units. The interconversion of *E* imines, however, is on equal footing as the proceeding imine rotational model. (iv) The imine unit is freely rotating within the [13]-macrodiolide. We argue that the lack of selectivity is due to facile rotation of the imine unit in **2** in contrast to the stationary alkene unit of **1** (Fig. 3B and C). In this scenario, rapid rotation of the imine exposes each diastereoface outward toward solution and therefore makes each available for attack by nucleophiles. The nearly 1:1 ratio of diasteromeric products is consistent with the model. Similar bond lengths for both the alkene and the imine imply that the removal of the hydrogen is sufficient to allow facile rotation of the planar unit.[16] Although somewhat speculative, the rotational model is consistent with the structures and reactivity we have observed for this group of macrocycles.

Our next objective was to modify the newly prepared aza-[13]-macrodiolides using **7a** as the example compound. Alkylation of

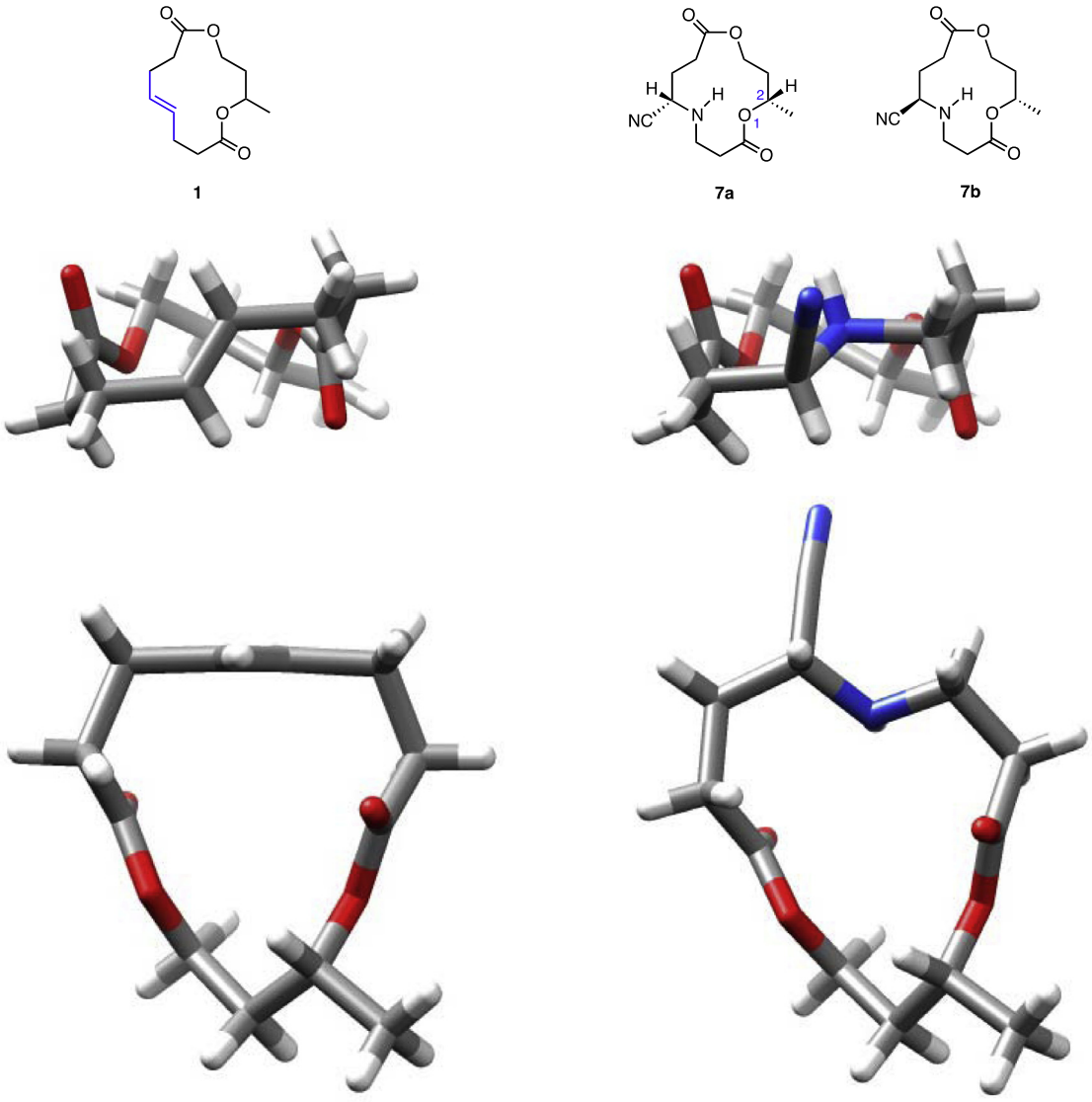


Figure 2. Structures of **1** and **7a** from X-ray crystallography data.

the amine nitrogen of **7a** under standard conditions gave *N*-alkylated macrocycles **8**–**10** in 67–86% yields (Scheme 2). Products **8**–**10** were isolated as an inseparable mixture of diastereomers despite the fact that the starting material, **7a** was of only one (*syn*) diastereomeric series. NMR data for **8**–**10** indicated unique chemical ^{1}H and ^{13}C NMR signals for the α-amino nitrile methine proton and carbon, respectively, and implicated epimerization of this center under the reaction conditions. We reasoned that, after alkylation of the amine, the α-amino nitrile could epimerize via deprotonation-reprotonation[15] or by transient iminium formation through loss of cyanide followed by a rapid recapture.[10] While either mechanism is formally viable, cyanide loss and recapture seemed more plausible based on the reaction conditions and the requirement of a stronger base to deprotonate in other cases. To confirm the site of epimerization, we attempted to reduce the α-amino nitrile moiety of macrocycle **9**. Reduction would remove the stereogenicity of the C9 carbon and the expected product **11**, would then simply return to being a racemic mixture based on the presence of a single stereogenic center (the original center from 1,3-butane diol) at C2. Attempted reduction of **9** with sodium cyanoborohydride at room temperature and at 70 °C did not result in any observable reaction. Potassium borohydride in ethanol at room temperature affected partial reduction of the α-amino nitrile and was coincident with transesterification to give a mixture of **12** and **13** (68%). At a higher temperature (70 °C) in ethanol, reduction occurred along with transesterification to give **13** (59%).[17] The NMR data on **8**–**10** and the products of reduction of **9** were both consistent with epimerization at the α-amino nitrile carbon. The reduction also underscored the lability of the ester units in these 13-membered ring macrocycles.

Akin to the reduction of the α-amino nitrile carbon, which presumably went through an iminium intermediate, we attempted a Bruylants reaction on compound **9**.[10,18,19] Upon the addition of AgOTf to **9**, an iminium salt is presumably produced; subsequent addition of allylzincbromide to this species gave an inseparable, 1:1 diastereomeric mixture of C9-allyl aza-[13] macrodiolide **14** in 47% yield. These reactions underscore the variety of structures that may be derived from the parent aza-[13]-macrodiolides by standard procedures.

In conclusion, we have identified a synthetic route to aza-[13]-macrodiolides with a novel macrocyclic imine as a key intermediate. Compound **2** is the nitrogen analog of macrocyclic alkene **1**, although the high levels of macrocyclic diastereocontrol exhibited by **1** are absent for **2**. We argue that the structures of **1** and **2** are

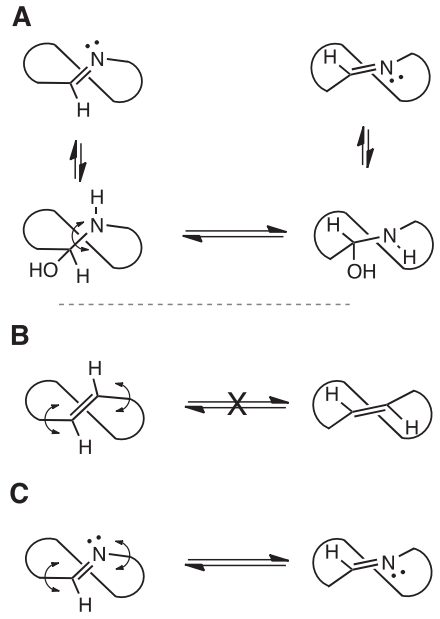
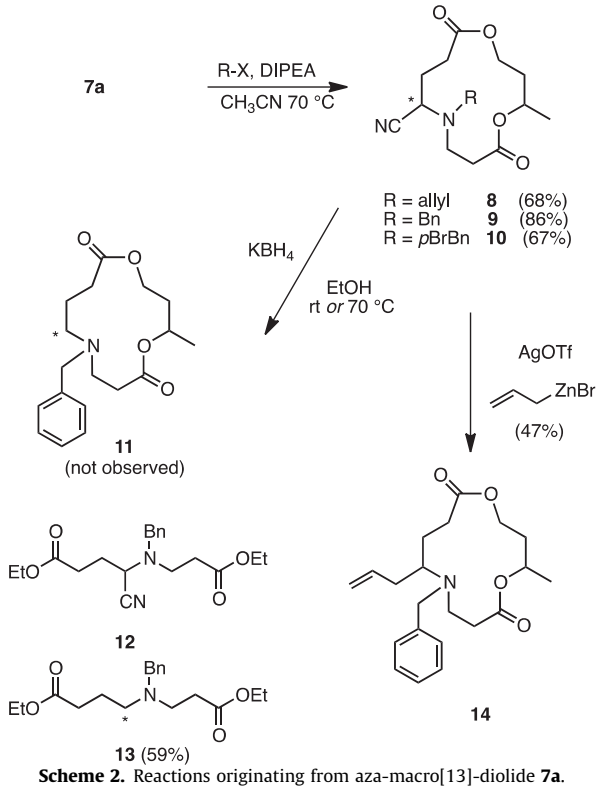


Figure 3. Mechanisms for interconversion of imines. (A) interconversion via bond rotation in a hemi-aminal intermediate. (B) Rotation of the alkene unit in [13]-macrodiolides such as **1** has not been observed. **C**: Proposed free rotation of the imine (i.e., **2**).



Scheme 2. Reactions originating from aza-macro[13]-diolide **7a**.

essentially the same but, because the nitrogen lone pair in imine **1** is smaller than the CH group of alkene **2**, the π-system of the imine is freely rotating. The rotation of the imine therefore provides access to incoming nucleophiles via both diastereofaces and results in a ~1:1 mixture of *syn* and *anti* diastereomeric aza-[13]-macrodiolides **7a** and **7b**. A significant implication of this investigation is that the ester units of macrocylic imine **2** are responsible for unwanted transannular and other side reactions. Current efforts are focused on replacing the esters with more robust planar units that will still enable the formation of a macrocyclic imine that may be more thoroughly characterized in terms of its structure and reactivity. Results from these investigations will be reported in due course.

Acknowledgments

The authors thank Vittorio Saggiomo for helpful email correspondence. The NSF supported this work through a grant to MWP (CHE-0957626) and an NSF-REU Grant (CHE-0754580). 400 MHz/100 MHz NMR spectra were collected on an instrument that was upgraded by an NSF-CRIF Grant (CHE-0947019). Michael Takase at the Chemistry Instrumentation Center at Yale University is acknowledged for collection of X-ray data on **7a**.

Supplementary data

Supplementary data (experimental details for the synthesis of new compounds and corresponding characterization data. Crystallographic Data Centre (CCDC), No. 993642. Copies of this information may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; web: www.ccdc.cam.ac.uk/conts/retrieving/html; email: deposit@ccdc.cam.ac.uk)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.081.

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