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Stereogenic α-carbons determine the shape and topology of [13]-macrodilactones†

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The synthesis and characterization of new [13]-macrodilactones substituted at stereogenic centers α- to the carbonyl are reported. When one center is substituted, it directs the topology of the macrocycle; when two centers are substituted, both the shape and the topology are influenced. The findings indicate that the number and configuration of α-centers fine-tune macrocyclic structure.

Shape and topology are intrinsic molecular properties. Shape refers to the geometric collection of features defined by the van der Waals surface of the compound. Topology is related, but nonetheless distinct from shape; it differentiates the interior and exterior surfaces of the compound and the orientation of its features. A hand, for example, defines a shape. Right hand and left hand, by our definitions, are two topologies of the same shape. For a macrocycle, shape and topology are intimately linked with both affinity for biomolecules[1,2,3] and chemical reactivity (i.e., macrocyclic diastereocontrol).[4,5,6] The structural features of the ring organize the arrangement of functionalities at specific locations and in specific orientations in three-dimensional space.[1] One control feature that dictates the preference for one topology over another is the configuration of atoms at strategic positions along the backbone of the acyclic precursor en route to the cyclized compound. This control feature has been used to increase skeletal diversity for chemical library generation.[7] Our efforts are geared at understanding, on a fundamental level, all the factors that dictate the shape and topology of macrocycles.[8,9,10,11] If a series of rules that govern macrocyclic shape and topology can be defined, they can be used to design macrocycles with predictable activities, including protein binding and facial selective reactions.

Using synthesis and structural analysis, we systematically explore the interplay between the arrangement of planar units and stereogenic centers on the shape and topology of macrocycles. We describe the shape of the macrocycle as the geometry adopted by the skeleton while its topology involves its planar chirality[12,13,14] and the associated arrangement of different functional groups in three-dimensional space. Earlier studies on a [13]-macrodilactone showed

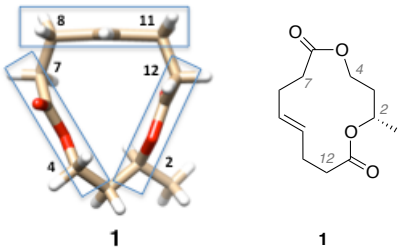

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Figure 1. Structure of the 2*Sp*S [13]-macrodilactone **1** (taken from a racemic crystal).

that multi-atom planar units - two esters and an *E*-alkene (i.e., **1** in Figure 1) - rigidified the ring by reducing the number of freely rotatable bonds in it. The arrangement of the planar units, guided by the C2 stereogenic center (*R* or *S*), defined the planar chirality of the [13]-macrodilactones (p*R* or p*S*). One shape of the backbone ("ribbon") therefore took up two enantiomeric topologies.[8] Because the alkene plane is oriented perpendicular to the molecular plane, similar to other *E*-alkene-containing macrocycles[4], only one face is accessible by reagents leading to highly diastereofacial selective reactions of the embedded alkene.

Here we report on an important development in our understanding of the roles that specific key atoms play in the determination of [13]-macrodilactone structure. We identified another stereogenic center, α to the ester carbonyl (C7 and C12), that influences the shape and topology of this family of [13]-macrodilactones. We observed that these atoms, which are at the junction of two planar units akin to C2 and C4 substituted [13]-macrodilactones we characterized previously, have similarly influenced the planar chirality of [13]-macrodilactones. Further, when these key atoms are stereogenic, they can either work together constructively to reinforce a given fold (ribbon) or against each other, resulting in other macrocyclic shapes and topologies.

New [13]-macrodilactones were prepared by acylation and ring closing metathesis (RCM) using a route we had previously established (Figure 2).[8,9] 1,3 Propanediol was first acylated with pentenoic acid using DCC and DMAP to yield the 3-hydroxypropyl

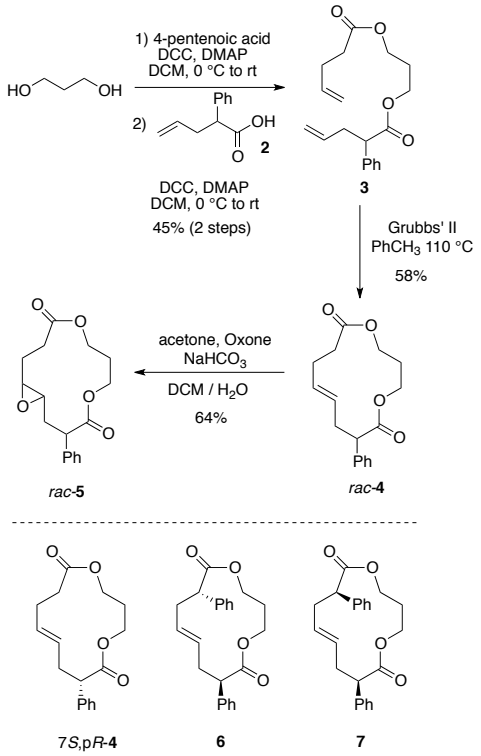

Figure 2. (top) Synthesis and epoxidation of *rac*-**4** that illustrates strategy for preparation of the [13]-macrodilactones. (bottom) Other macrocycles prepared by the method. Note: **6** and **7** were synthesized as racemates; stereochemistry defines *cis/trans* relationship of phenyl groups.

4-pentenoate in 56% yield.[15] A second acylation with racemic 2-phenyl 4-pentenoic acid, **2**,[16] on the remaining free hydroxyl group gave diacylated product **3** (80%). Racemic macrocycle **4** (*rac*-**4**) arose via RCM on **3** using Grubbs' second generation catalyst (58%). Disubstituted macrocycles **6** (*trans*) and **7** (*cis*) were synthesized using the same route except that the dienes were prepared by concurrent acylation of 1,3 propanediol using two equivalents of racemic 2-phenyl 4-pentenoic acid (Figure 2). Note that the *cis/trans* designation refers to the relative relationship of the two pendant phenyl groups and not the alkene geometry.

The configuration at the α-stereogenic center (C7) guides the topology of [13]-macrodilactones. Macrocycle *rac*-**4** was isolated as a crystalline solid, which was subjected to X-ray crystallographic analysis. Since racemic 2-phenyl 4-pentenoic acid was used in the synthesis, the corresponding macrocycle was also racemic. Present in its crystal lattice, therefore, were both enantiomers of the [13]-macrodilactone **4**. The C7 stereogenic center with *R* configuration resulted in a macrocycle with only p*S* planar chirality while the C7 *S* enantiomer gave rise to only p*R* planar chirality (Figure 3).[12,17] Transannular nonbonded interactions where sterically demanding substituents attached to the stereogenic center are situated away from the macrocyclic ring itself are minimized in this conformation. The enantiomers have the same shape but different planar chirality and, thus, different topologies. Here, 'topology' includes the mirror-image orientations of the phenyl substituents and the carbonyl groups in three-dimensional space. It is important to note that the shape adopted by the backbone of **4** was similar to that of C2-substituted macrocycle **1** (RMSD = 0.0454, using 2*R*,p*R*-**1** and 7*S*,p*R*-**4**),[18] suggesting that this shape is generally the most stable conformation for the system. Both C2 and C7 are at the junction of

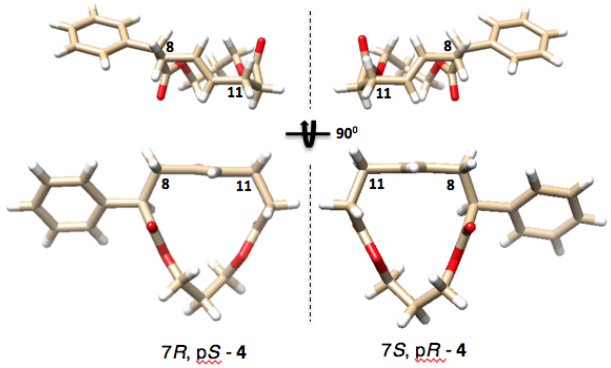

Figure 3. C7 configuration directs the planar chirality of [13]-macrodilactone **4** where C7 *R* resulted in p*S* planar chirality (left) and C7 *S* gave p*R* (right). Top figures show the ribbon view and the bottom show the triangle.

two planar units (Figure 1) corroborating the hypothesis that these positions are key stereogenic centers that direct the planar chirality, and hence the topology of [13]-macrodilactones.

To illustrate that it is indeed the configuration at the α-stereogenic center that dictates the planar chirality adopted by the [13]-macrodilactone, an enantioenriched version of **4** (7*S*,p*R*) was synthesized using *S*-2-phenyl 4-pentenoic acid (90% ee).[19] Chiral HPLC profiles of *rac*-**4** and 7*S*,p*R*-**4** are shown in Figure 2. The macrocycle derived from racemic pentenoic acid resulted in a 50:50 mixture of [13]-macrodilactones. The one synthesized from *S*-2-phenyl 4-pentenoic acid was enantioenriched, with an ee of 60%. We attributed the deterioration of enrichment between the acid and macrocycle to racemization of the chiral diester **3** under the acylation conditions during diene formation. Nonetheless, the transfer of point chirality from the starting acid to the planar chirality observed in macrocycle 7*S*,p*R*-**4** corroborated our original conclusion about the control of planar chirality in [13]-macrodilactones by the α-stereogenic center. DMDO epoxidation[7d] of *rac*-**4** gave only one diastereomer of **5** as a pair of enantiomers (Figures 2 and 4). For 7*R*,p*S*-**4**, the enantioenrichment of the alkene was maintained after epoxidation to **5**. Reactions of these [13]-macrodilactones therefore exhibit a high level of macrocyclic diastereocontrol.

Compounds **6** and **7**, substituted at both the C7 and C12 α-carbons (Figure 2), were synthesized to explore how the α-stereogenic centers work together to guide both the shape and topology of [13]-macrodilactones. They were prepared in the same reaction pot because the diastereomeric RCM precursors, an enantiomeric pair and a *meso* compound, could not be separated by chromatography. To our delight, both *trans* diastereomer **6** and *cis* diastereomer **7** were crystalline solids that yielded to structural analysis from X-ray diffraction data. The structures of **6** and **7** revealed the interplay between the key stereocenters and their shapes. Specifically, the relative (*trans* vs. *cis*) configuration of the phenyl groups at the α-stereogenic centers dictated the shape adopted by each diastereomer and the configuration dictated the planar chirality. All four compounds in Figure 5 differ in their topologies by virtue of either the differences in their planar chirality or their shape.

The *trans* isomer was a racemic mixture of 7*R*,12*R*,p*S*-**6** and 7*S*,12*S*,p*R*-**6** with shapes and topologies reminiscent of mono-substituted [13]-macrodilactones **1** and **4** (Figure 5). In fact, the RMSD between 2*R*,p*R*-**1** and 7*S*,12*S*,p*R*-**6** was only 0.0487. This shape was adopted presumably because the two phenyl substituents were oriented outside of the ring and thus minimized transannular nonbonded interactions. The *cis* configured isomers of **7**, on the other hand, adopted a different shape (RMSD 0.49 for 2*R*,p*R*-**1** and

7*S*,12*S*,p*R*-**7**). Inspection of the top, or "triangle" views of **6** and **7** in Figure 3 illustrates the difference. The non-ribbon shape of **7** is more

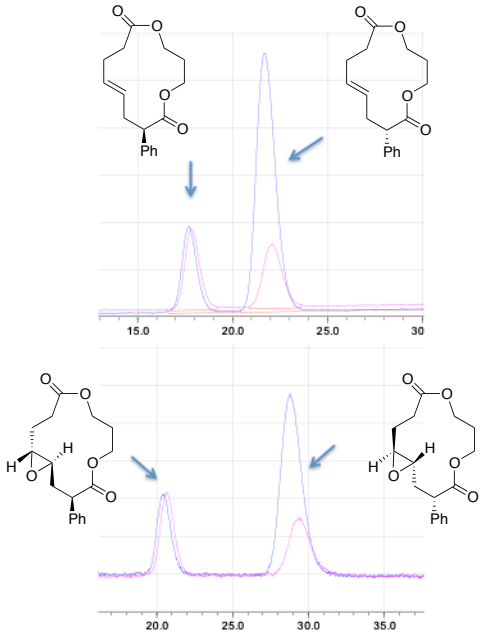

Figure 4. Chiral HPLC profiles of racemic (pink) and chiral (blue) [13]-macrodilactone **4** and the corresponding epoxides **5**.

compressed, or kinked, relative to **6** and its molecular plane is also more twisted. While the diene precursor of **7** was *meso*, **7** itself is a mixture of enantiomers defined by the planar chirality (p*S* or p*R*) introduced to the molecules by cyclization. The relative stereochemistry at C7 and C12 prevents formation of the ribbon shape because minimization of transannular interactions in this case requires reconfiguration of the backbone and hence a different shape. We previously observed that other key stereogenic centers (C2 and C4) can work constructively to reinforce the ribbon or against each other resulting in alternative shapes. For the C2, C4 compounds, the *trans* series adopted the ribbon conformation akin to **1**, **4**, and **6** whereas the *cis* series gave rise to a different macrocyclic shape that was coincidentally distinct from the shape of **7**.[9] The ribbon conformation seems to be of the lowest energy for these [13]-macrodilactones but, based on relative stereochemistry, alternative shapes and consequently topologies are available. Together the structural observations from this study suggest that shape and the topology of this family of [13]-macrodilactones can be fine-tuned based on specific combinations of configuration on α-carbon stereogenic centers.

In conclusion, we have systematically explored the effect of mono- and di-substituted α-stereogenic centers on the shape and topology of a class of [13]-macrodilactones. The monosubstituted macrocycles adopted the same ribbon shape (which appeared to be the most stable conformation) but different or enantiomeric planar chirality - dictated by the configuration at the α-stereogenic center. Disubstituted [13]-macrodilactones, on the other hand, adopted two different shapes - ribbon plus non-ribbon – with each shape existing in two enantiomeric planar chirality. The relative configurations at the α-stereogenic centers, in addition to other parameters (four-atom planar units and their connectivity), governed the shape as well as its topology. The fundamental information discovered in this study implies that the interplay between planar units and stereogenic centers in macrocycles can be used to fine-tune the macrocyclic topology. Data from both solid state and solution experiments (particularly the diastereofacial epoxidations of **4**) paint a consistent

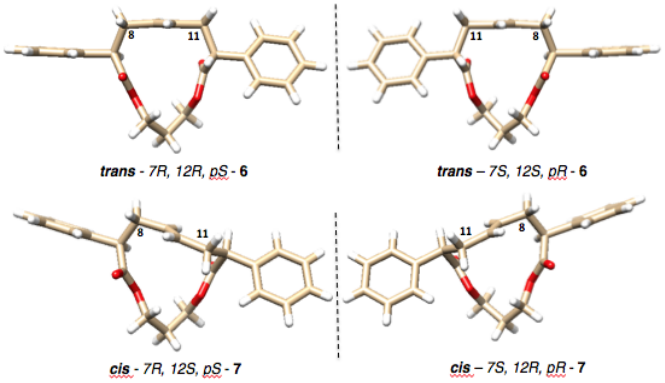

Figure 5. Crystal structure of diastereomeric trans and cis [13]-macrodilactones, 6 and 7 (6/trans = 7R,12R,pS and 7S,12S,pR; 6/cis = 7S,12R,pR and 7R,12S,pS).

picture where the planar units of the macrocycle are not freely rotating but rather are rigid.[9] This results in a planar chirality that gives rise to the macrocyclic diastereocontrol observed in the epoxidation reaction. Systematic combinations of other stereogenic centers in [13]-macrodilactones are currently being investigated in our lab. Understanding these parameters on a fundamental level has useful implications in medicinal chemistry, pharmacology and chemical biology, where macrocyclic shapes and topologies can be used as a scaffold to orient reactive functionalities at specific position in spaces, and in generating compound libraries with diverse skeletons.

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