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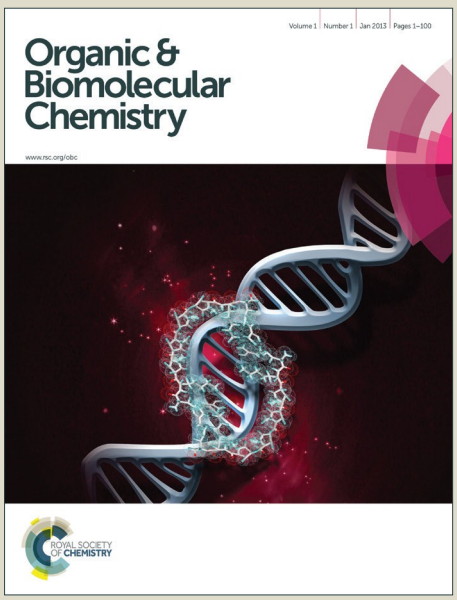

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Synthesis, structure and reactivity of [15]-macrodilactones

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A strategy for utilizing parameters such as ring size, planar units and the connections between them, and the location of asymmetric centers has been applied to the design and synthesis of a new class of 15-membered macrocycles. Interplay between three planar units in combination with a hinge atom and a stereogenic center, introduces a planar chirality that defines the molecular topology of these [15]-macrodilactones.

Macrocycles, cyclic compound of twelve or more atoms with diverse functional groups, play a vital role in drug discovery.[1] They can bind biomolecules with high affinity and selectivity by occupying large surface areas on their targets that enable them to affect various cellular processes primarily by inhibition of protein-protein interactions. At the same time, they satisfy many of the physicochemical criteria necessary for being a good drug candidate. In this connection, natural product macrocycles lead the way and have been in medicinal use for long time.[1a,2] Moreover, recent advances in synthesis and screening technologies have engendered enormous interest in the design of new macrocyclic ligands.[3,4,5] Indeed, several of synthetic macrocycles are currently in advanced stages of preclinical trials.[1b,d]

In this context, we have become interested in illustrating the rules by which structural features such as the ring size, the presence and disposition of multi-atom planar units, and asymmetric centers contribute to the overall structures of macrocyclic molecules.[6] As the structure of a macrocycle is directly related to its function, this information will be helpful for designing new macrocyclic ligands that target specific protein surfaces. Our group recently described some of the structural principles that govern the shape of [13]-macrodilactones[7] like **1** (Figure 1). This macrocycle possesses three planar units - two esters and an (*E*)-alkene - that arrange themselves in a non-coplanar fashion around an sp^3-hybridized atom (C3) which is not a part of planar units. We have called this atom a "hinge" because it can mediate the orientation of the rigid planar units to define the overall structure. As an outcome of such spatial organization, a planar chirality[8] is generated in [13]-macrodilactones and the handedness of the twist is determined by the absolute configuration of asymmetric centers present at specific sites that connect planar units of the macrocycle (i.e., C2, C7, etc. of **1**). Thus, for [13]-macrodilactones a single asymmetric center governed the topology of the macrocycle.

Here we report an important development in our understanding of macrocycle design. We introduce a larger, 15-membered ring

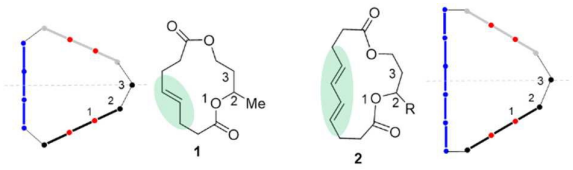

Figure 1. [13]-macrodilactone **1** and [15]-macrodilactone **2**

macrocycle (i.e., **2** in Figure 1) that is an expanded version of [13]-macrodilactone **1**. In **2** an additional alkene unit has been inserted between the existing alkene and its allylic carbon. Motivation for this exercise was twofold. First, we wanted to apply the rules that had emerged during our investigation of the [13]-macrodilactones. Second, we were interested in accessing larger rings because it will be better protein surface binders. A synthetic route to [15]-macrodilactones such as **2** was therefore established to investigate how the extension of one of the planar units would affect the structure and topology of the macrocycle. Compound **2** contains two four-atom ester units, a six-atom diene unit, and an asymmetric center at C2. The design, synthesis and characterization of the new macrodilactones reported here underscore the generality of the fundamental parameters (planar units, hinges, asymmetric centers) that govern macrocycle topology.

Synthesis of the [15]-macrodiolides required a slightly different strategy than was employed previously for [13]-macrodiolides.[7,9] In the earlier route, acylations were followed by a ring closing metathesis (RCM) reaction to form the macrocycle. In the new synthesis, an intramolecular Stille coupling[10] was devised for the macrocyclic ring closure. Using this strategy, [15]-macrodiolides **3**, **4**, and (–)-**4** (Figure 2) were synthesized as shown in Scheme 1. Three different monosubstituted 1,3-diols **5**-**7** were selected as starting materials. Although they are commercially available, 1-phenyl-1,3-butandiols **6** and **7** were synthesized from cinnamyl alcohol following known procedures.[11] Chemoselective acylation of 1,3-diols **5**-**7** with 4-pentynoic acid **8** afforded esteralkynes **9**-**11** (62-70% yield). Ester-alkynes **9**-**11** were subsequently converted to vinyl stannanes **15**-**17** following a two-step protocol[12]; first bromination with *N*-bromosuccinimide provided bromoalkynes which were then subjected to Pd-mediated reduction with $n\text{Bu}_3\text{SnH}$. Our initial attempts at the direct hydrostannation of esteralkyne **9** were not pursued further as they resulted in poor regioselectivity. Acylation of the vinyl stannanes with 4*E*-5-iodo-pentenoic acid[13,14] **18** resulted the iodostannanes **19**-**21** (71-82% yield). These were the desired precursors for intramolecular Stille coupling. In the event, Pd(0)-catalyzed intramolecular Stille coupling[10c,d] in the presence of Ph_3As provided the [15]-macrodilactones **3**, **4**, and (–)-**4** (59-65% yield). While macrodilactone **3** was a clear colorless oil, macrolide (–)-**4** and

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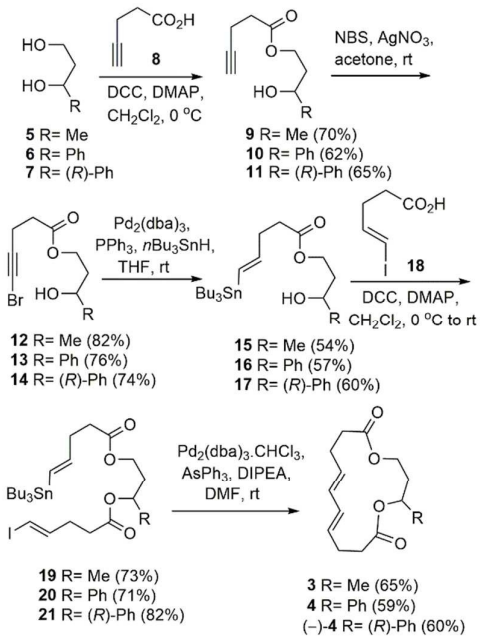
Electronic Supplementary Information (ESI) available: Characterization data including ^{1}H and ^{13}C NMR spectra of all new compounds and crystallographic data of (–)-**4** CCDC 1055302. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x.



Scheme 1. Syntheses of [15]-macrodilactones

4 were isolated as white crystal-line solids. Compound (–)-**4** was recrystallized from hexanes-ethyl acetate to provide crystals of sufficient purity for X-ray crystallography. From ^{1}H NMR data for the [15]-macrodilactones, it was clear that the newly formed conjugated diene adopted a trans-trans geometry[10a,e] but the conformation (*s*-cis vs *s*-trans) of the dienes still remained ambiguous.

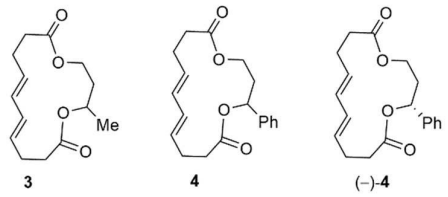


Figure 2. [15]-macrodilactones **3** and **4** and (–)-**4**.

The structure of [15]-macrodilactone (–)-**4** derived from the X-ray data is shown in Figure 3. It bears a resemblance to the crystal structure of [13]-macrodilactone **1** as revealed by reviewing their similarities. First, the two ester groups of each compound produce four-atom planes that restrict bond rotations in the cyclic structure. Also, the carbonyls of the esters are pointed in opposite directions - perhaps to minimize dipolar interactions between them. Each of the esters adopts an *s*-trans conformation.[15] As a consequence, the C2 of (–)-**4** is eclipsed with its corresponding carbonyl oxygen and positions the phenyl ring outward, away from the macrocyclic ring. The sp^3-hybridized C3 atom acts as a hinge between the two planar ester units and enables them to orient themselves in the macrocycle. Finally, the planar units present in the cyclic array arrange themselves angularly rather than in a coplanar fashion. This gives rise to a planar chirality, and hence, a twist in the macrocyclic structure. The major point of distinction between two macro-cycles is the presence of the conjugated diene, which forms a plane of six atoms in [15]-macrodilactone (–)-**4** in place of the four atom alkene in [13]-

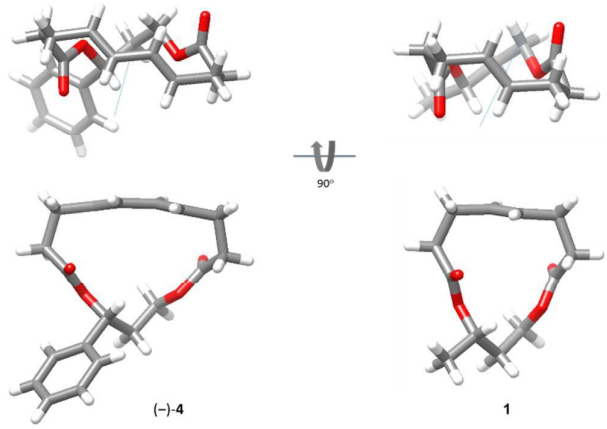
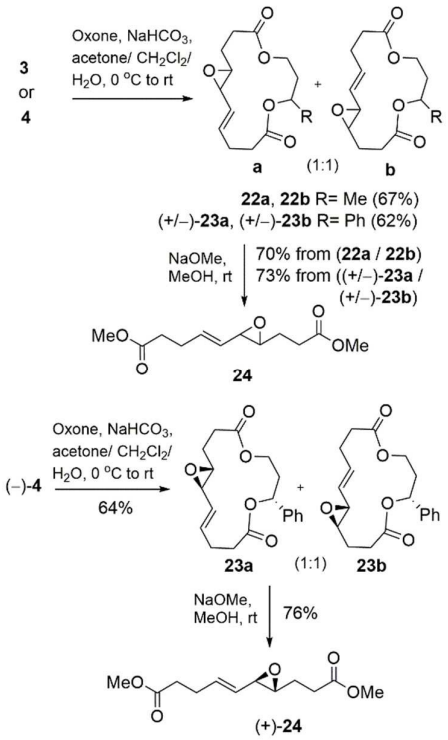


Figure 3. X-ray crystallographic structure of [15]-macrodilactone (–)-**4** and [13]-macrodilactone **1**

macrodilactone **1**. Here, the 1,3-dienyl moiety exists in energetically favourable *s*-trans conformation. Furthermore, due to the conformational rigidity of the macrocyclic ring, only one face of the conjugated diene is exposed to the exterior environment and the other face is blocked by the macrocyclic ring.[16] It should also be noted that in [15]-macrodilactone (–)-**4**, the diene unit isn't strictly planar. Rather, it adopts a subtle curvature, or bend, with an average RMSD between the atoms and the plane being 0.1328 (see supporting information). Overall, considering all the structural features of both the macrocycles, it can be inferred that [15]-macrodilactone (–)-**4** largely resembles [13]-macrodilactone **1**, except in the region of alkenes. Compounds 3 and 4 are, in essence, expanded versions of the original [13]-macrodilactone and consequently the parameters identified capture the essential aspects that define their overall shapes.

Our prior studies on [13]-macrodilactones[7] demonstrated that the asymmetric center at C2 plays a vital role in governing the planar chirality of those compounds. That is, the absolute configuration at C2 decided the handedness of the twist and thereby controlled the topology of the compound. Here, for [15]-macrodiolide (–)-**4**, the *R*-configuration of C2 favours a right-handed, p*R*[15] twist over the left-handed p*S* twist. In the context of the [15]-macrodilactones, only one of the two faces of the diene is expected to be exposed to the outer environment; which one is dependent solely on the absolute configuration of the specific asymmetric center at C2. That's because the size and rigidity of the ring do not allow facile rotation of the planar units. Based on the X-ray crystallographic structure of [15]-macrodilactone (–)-**4**, the *R*-configuration at C2 presents the 9,10 pro-*R*,*R*-11,12 pro-*R*,*R* face of the diene to the exterior environs. Analogous to race-mic macrocycles we had studied previously, we expected that the [15]-macrodilactones **3** and **4** each would be composed of two enantiomeric planar chiralities directed by the point chiralities of their respective C2 centers. The HPLC profiles of macrodilactones **4** and (–)-**4** (see supporting information) support this conjecture.

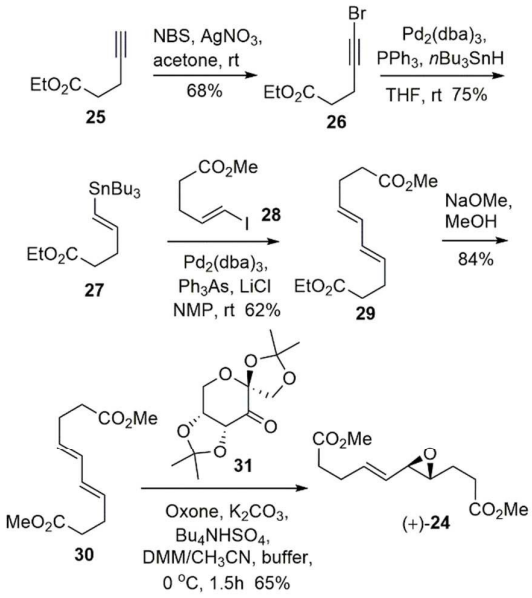
A DMDO epoxidation reaction was conducted to investigate the diastereofacial selectivity of reactions involving the diene of the macrocycle.[7] Racemic macrodilactones **3** and **4** afforded inseparable mixtures of regioisomeric vinyl epoxides **22a** / **22b** and (±)-**23a** / (±)-**23b**, respectively, from DMDO-mediated epoxidation (Scheme 2). Here, each regioisomeric epoxide was expected to be a racemic



Scheme 2. Evaluating the macrocyclic diastereocontrol in [15]-macrodilactones

mixture. [15]-Macrodilactone (–)-**4**, when treated with in situ generated DMDO, also gave an inseparable mixture of regioisomeric vinyl epoxides **23a** and **23b**. NMR data supported the formation the regioisomeric epoxides in 1:1 ratio. Moreover, longer reaction times and addition of excess reagents did not change the distribution of products from these reactions. From the point of view of electronics, the likelihood of forming the bis-epoxide was low because the initial product of epoxidation, a vinyl epoxide, is deactivated to further oxidation.[17] It is important to note that, at this point, we suspected that each regioisomeric vinyl epoxide **23a** and **23b** was a single stereoisomer, and in both the cases, the epoxidation took place from the same pro-*R*,*R* face of the diene. Our next objective was to prove the absolute configuration of **23a** and **23b**.

Determination of the absolute configuration of macrocyclic epoxides was carried out following an approach similar to the one we originally employed for [13]-macrodilactones.[7b] Accordingly, diene diester **30** was synthesized utilizing a strategy based on an intermolecular Stille coupling (Scheme 3). One of the partners of the coupling, vinylstannane **27**, was synthesized from ethyl 4-pentynoate **25** in two steps: first bromination then Pd(0)-mediated hydrostannation. The Stille coupling[18] between vinylstannane **27** and (*E*)-methyl 5-iodo-4-pentenoate[13c] **28** provided the diene ester **29** as a single isomer (62% yield). ^{1}H and ^{13}C NMR confirmed the formation of the expected *E*,*E*-diene diester **29** as the mixed methyl-ethyl ester. Methanolysis of **29** resulted in formation of **30** (84% yield). Under Shi epoxidation[17a] conditions, diester **30** was converted to 5*R*,6*R*-epoxyester (+)-**24** (65% yield). The *R*,*R*-configuration of the asymmetric centers was assigned based on the mode[17a] proposed by Shi and co-workers for the mono-epoxidation of conjugated dienes.



Scheme 3. Synthesis of epoxyester **32** via Shi epoxidation

The transesterification of each mixtures of macrocyclic vinyl epoxides **22a** / **22b** and (±)-**23a** / (±)-**23b**, under Zemplén conditions provided epoxyester **24** in 70% and 73% yield respectively (Scheme 2). At this juncture, based on the symmetric nature of embedded diene in [15]-macrodilactones we reasoned that the resulting epoxyester **24** would be a racemic mixture. Under similar transesterification conditions the mixture of regioisomeric vinyl epoxides **23a** and **23b** afforded epoxyester (+)-**24** (76% yield). Here, (+)-**24** was anticipated to be a single stereoisomer. The HPLC profiles of epoxyesters **24** and (+)-**24** (see supporting information) validated our speculation. Further, the epoxyesters obtained from Shi epoxidation and transesterification of macrocycles **23a** / **23b** were identical by ^{1}H and ^{13}C NMR, polarimetry and chiral HPLC (see supporting information). Thus, the absolute configurations of epoxides in **23a** and **23b** were unambiguously established as 9*R*, 10*R* and 11*R*, 12*R* respectively.

Conclusions

In conclusion, we have described the design, synthesis and characterization of new [15]-macrodilactones as the expanded version of our original [13]-macrodilactones. The work illustrates the generality of the rules that correlate fundamental parameters with the global structure of macrocyclic molecules. Similar to [13]-macrodilactones, the interplay of planar units, a hinge atom and point chiralities present in the macrocyclic backbone give rise to the planar chirality in [15]-macrodilactones and control their overall molecular topologies. In [15]-macrodilactones the absolute configuration of a key atom at C2 became pivotal in guiding the planar units to arrange themselves to create a structure with a specific planar chirality. These results have direct implication in designing new macrocyclic ligands with defined topologies that would interact with therapeutically relevant protein targets. The syntheses described here show how new macrocycles with designed topologies of specific chirality can be prepared by related, but unique, routes (i.e., the design and

synthesis of (–)-**4** that originated from 1). Further, as epoxyester (+)-**24** was obtained from macrocycle (–)-**4** with good enantioenrichment, the overall process of epoxidation of dienes draws an analogy to chiral auxiliary-based organic transformations and could perhaps be potential to build a new macrocycle-based chiral auxiliary.

Acknowledgement

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