Remote induction of asymmetry in [13]-macro-dilactone topology by a single stereogenic center†

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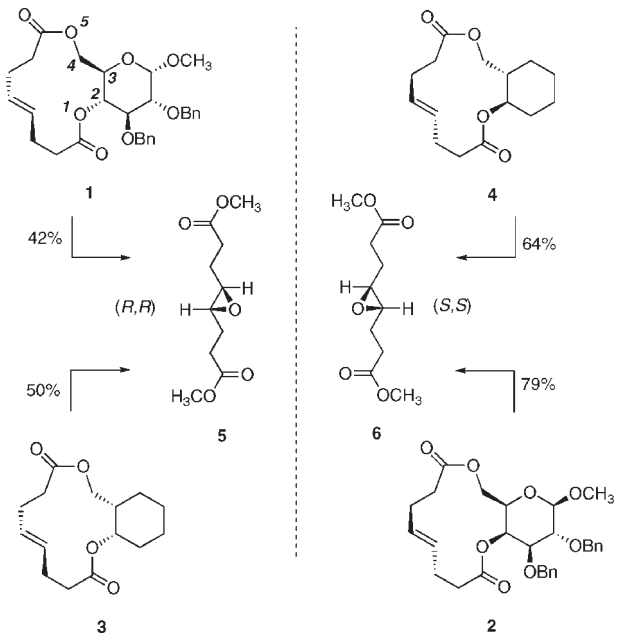
Analysis of a series of unsaturated [13]-macro-dilactones showed that the configuration of a single carbon dictates the planar chirality of a macrocycle backbone and in turn remotely switches the facial display of an embedded alkene unit.

Medium rings containing an embedded (*E*)-alkene are known to take up left- or right-handed helical topologies whose absolute configurations are defined by a planar chirality.[1,2] Individual factors influencing the configuration of the macrocycle include size,[3,4] points of articulation,[5,6] and substituents that adorn the ring.[7] Interplay between these features governs the energetics of transannular interactions and ultimately the low energy conformation of a given structure.

Reported here is a novel example where a single stereogenic center dictates the planar chirality of a [13]-macro-dilactone prepared by a ring closing metathesis (RCM) reaction. Inverting the stereochemistry at the key stereocenter was found to invert the handedness of the macrocyclic backbone. Control of planar chirality in a macrocycle based on this effect has consequences on the facial selectivity in reactions of the ring alkene and also on the molecule's ability to interact with biological targets.

We recently reported on the epoxidation of carbohydrate-fused [13]-macro-dilactones.[8] In the dimethyldioxirane (DMDO) mediated epoxidation of **1** and **2** (Scheme 1) opposite alkene faces reacted to give, after transesterification, enantiomeric epoxy-octanedioates **5** and **6** with high selectivity. The switch in stereoselectivity was dramatic considering the only difference was the configuration[9,10] at the C2 atom. Structural information from X-ray crystallographic data on **2** and the epoxide derived from it showed that **2** presented the pro-*S*,*S* face of the ring alkene for reaction with electrophiles. Further comparison of the X-ray structures of the alkene- and epoxide-containing macro-dilactones showed that, aside from the epoxide oxygen, they had the same macrocyclic conformation. In the present work we endeavoured to define the minimum structural requirement that could recapitulate the observed conformational switch. To that end, we first approximated the pyranose skeleton of **1** and **2** with a functionalized cyclohexane as in **3** and **4**.



Scheme 1 Products of DMDO-mediated epoxidation followed by Zemplén transesterification ($NaOCH_3$–MeOH) of bicycles (**1–4**) including (two step) yields of the appropriate dimethyl 4,5-epoxy-octanedioates.

Based on our rationale, **3** and **4** represented readily accessible "pseudo" enantiomers of **1** and **2**. The syntheses of **3** and **4** started from the diols (1*S*,2*S*)-2-(hydroxymethyl)cyclohexanol and (1*R*,2*S*)-2-(hydroxymethyl)cyclohexanol, respectively.[11] Similar to our earlier strategy, the diols were acylated with 4-pentenoic acid then cyclized by RCM.[12] Epoxidation and transesterification provided a functional read-out on the configuration of the new macro-dilactones. In accordance with the "pseudo" enantiomer model, *cis*-fused macro-dilactone **3** provided the (4*R*,5*R*)-epoxy-octanedioate **5** and the *trans*-fused **4** gave the (4*S*,5*S*)-enantiomer. The results supported our prediction that the alkene topology of **4** was enantiomeric to **1** whereas that of **3** was enantiomeric to **2**. Evidence in support of this argument came from comparison of the crystal structures corresponding to the epoxide derived from **2** and the epoxide derived from **3**.[13] Fig. 1 depicts the enantiomeric relationship of the macrocyclic backbone in these two structures where **3[epox]**‡ contains a right-handed helical twist and **2[epox]** a left-handed one. Stereogenic centers elsewhere on the pyranose apparently did not influence the backbone

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† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data for all intermediates in the preparation of **3**, **4** and **7**; full data on the determination of facial selectivity of **3** and **4**; crystallographic reports for **3[epox]**, **4[epox]** and **7**. CCDC reference numbers 686765–686767. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b807562j

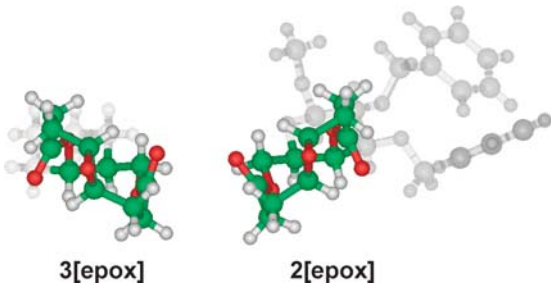

Fig. 1 Crystal structures, centered on the epoxide ring oxygen, of the [13]-macro-dilactone epoxides derived from **2** and **3**. The enantiomeric macrocycle topology is emphasized by coloring atoms that are part of the macrocycle while shading those that are not.

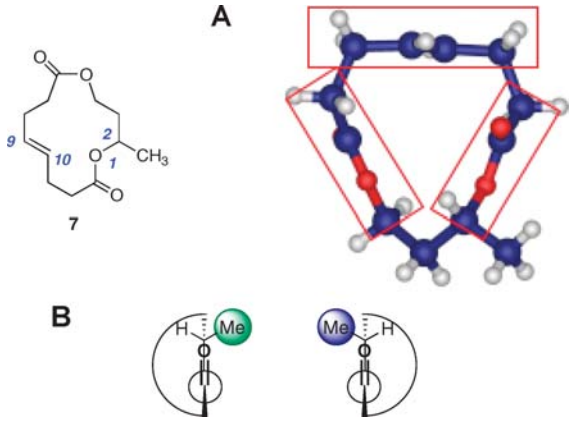

Fig. 2 Structural features of [13]-macro-dilactone **7**. (A) Top view of (*R*)-**7** with red boxes defining the three planar units in the macrocycle. (B) Newman projection of *S* (left) and *R* (right) configurations depicting the eclipsing relationship of C2 with its C=O oxygen. The methyl group is positioned on the outside of the macrocycle.

conformation of the macro-dilactone. In fact, careful inspection of the macro-dilactone structures in Scheme 1 suggested that the key factor governing the shape of these molecules is the absolute configuration at C2 of the macrocycle. Note that macro-dilactones **1** and **3** with the *S* configuration at C2 gave **5** whereas those with the *R* configuration (**2** and **4**) gave **6**. We hypothesized that the configuration of the other stereocenter (C3) in **3** and **4** was of little or no consequence for determining the planar chirality of the corresponding macro-dilactones.

In order to gauge the importance of the stereochemistry at the C2 position and to determine how important the fused ring feature was for maintaining the macrocyclic topology, we prepared macro-dilactone **7**. For **7**, there is only one stereogenic center with the sole substituent on the macrocyclic backbone being a methyl group in place of the erstwhile pyranose/cyclohexane moiety. Macrocycle **7** was prepared from racemic 1,3-butanediol following the acylation/RCM route. Surprisingly, the new macro-dilactones appeared to be of one atropisomer for each enantiomeric configuration.[14] It seemed that **7** was a racemic mixture of only two enantiomeric [13]-macro-dilactones. One (*E*)-alkene configuration was being formed for each of the *R* and *S* configured molecules. This observation proved to be consistent with the structure of **7** (*vide infra*) and the thermodynamic conditions[15] of the RCM reaction. We reasoned that the backbone of the macro-dilactone fell into one of two low energy sinks exhibiting the classic helical chirality akin to that known for (+)- and (−)-(*E*)-cyclooctene.[16] Overall, the results showed that the magnitude of the effect arising from the stereochemistry at C2 was greater than anticipated.

Racemic **7** formed a crystalline solid that was analyzed by X-ray crystallography.§ The unit cell from the crystal structure contained both enantiomers of **7** related by a center of symmetry. From the data was developed a model describing the effects of the sole stereocenter on the conformation of the macrocycle. We speculated that the effects observed in this minimal [13]-macro-dilactone (**7**) would translate to the fused bicyclic macro-dilactones.

The major architectural features that govern macrocycle topology are the three planar units in the macrocycle[5,6] and the stereogenic carbon at C2 (Fig. 2). The first planar unit in **7** is the alkene unit itself—including the two allylic carbons adjacent to it (C8–C9–C10–C12 dihedral = 174.8°). Similarly, both esters in **7** adopt the archetypal s-*trans* conformation (C4–O5–C6–C7 = 175.1°, C12–C13–O1–C2 = 178.5°).[17] Together these three units comprise 12 of the 13 atoms in the macrocycle and likely make a significant contribution to its rigidity.[18] The only atom not in a planar motif is C3. It is expected that a [13]-macro-dilactone similar to those reported here, but having substitution at C3 rather than C2 would give macro-dilactones of both planar chiralities for each C3 configuration.[14] This is because the symmetry contained in the diene starting material would render the C3 substituents homotopic. There would be no energetic preference for one (*E*)-alkene geometry over another. By virtue of the s-*trans* conformation of the ester, C2 is eclipsed with its carbonyl oxygen and positions its substituents either into the macrocycle or away from it (Fig. 2). Along with the other ester carbon (C4), C2 is unique in disposing its substituents in this way. The other sp^3 carbons (C3, C7, C8, C11, C12) dispose their substituents in either a pseudo-axial or pseudo-equatorial manner. This preference to put the most sterically demanding substituent on the outside of the ring determines the handedness of the helix backbone twist. The descent into either the right- or left-handed helical twist driven by the methyl group is facilitated by the loss of rotational freedom imparted by the planar units. As a result, this stereogenic center governs the overall molecular topology based on these features (Fig. 3).

In conclusion, we have demonstrated that a methyl group can chaperone the macrocyclic backbone skeleton of [13]-macro-dilactones into of one of two enantiomeric conformations. The handedness of the macrocycle's helical twist is governed by the configuration of the stereogenic center in the context of one of the planar units of the macro-dilactone. The effect is pronounced enough so that by modifying the configuration of the key backbone carbon (C2/C4) with something as simple as a methyl group, a complete switch in the facial presentation of the reactive alkene five atoms/bonds away occurs. In fact, this effect persists even in the presence of other substituents (as in the case of the cyclohexyl- or pyranosyl-substituted macro-dilactones) on the macrocyclic backbone. Finally, the structural features enumerated here, which enable such consummate conformational stereocontrol, will find

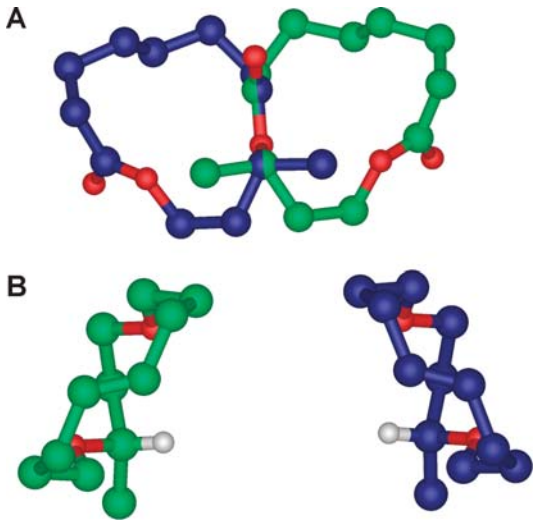

Fig. 3 (A) Overlay of (*R*)- and (*S*)-**7** superimposed along the C12–C13–O1–C2 dihedral angle from the X-ray data. *R* is displayed in blue and *S* in green. The view emphasizes the influence of the chiral center and its pendant methyl group in governing the macrocyclic configuration. (B) Side view of the macrocyclic backbones of (*S*)-**7** (left) and (*R*)-**7** (right).

application in organic synthesis and biological chemistry. Given a facile transesterification reaction, the stereoselective epoxidation reactions of alkenes embedded in the [13]-macrodilactones reported here could be developed into an organocatalytic process using chiral 1,3-diols as auxiliaries. Alternatively, the key structural features governing this system may be integral to understanding the structure/conformation of macrocyclic natural products and to the design of novel natural product like molecules with desired biological activities.

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Notes and references

‡ X-Ray quality crystals of **3[epox]** were obtained by slow evaporation from hexanes. $C_{15}H_{22}O_5$, $M = 282.33$, orthorhombic, $a = 6.4153(13)$, $b = 12.269(3)$, $c = 18.605(4)$ Å, U=1464.4(5) Å^3, $T = 173(2)$ K, space group $P2_12_12_1$, $Z = 4$ 3801 reflections measured, 2021 unique ($R_{int} = 0.0000$, Friedel pairs were not merged.). The final w$R(F_2)$ was 0.1022 (all data). CCDC 686766.

§ X-Ray quality crystals of **7** were obtained by slow evaporation from hexanes. $C_{12}H_{18}O_4$, $M = 226.26$, monoclinic, $a = 7.8101(16)$, $b = 18.266(4)$, $c = 9.2291(18)$ Å, $U = 1218.5(4)$ Å^3, $T = 173(2)$ K, space group $P2_1/n$, $Z = 4$, 5332 reflections measured, 3180 unique ($R_{int} = 0.$ 0.0614). The final w$R(F_2)$ was 0.1376 (all data). CCDC 686767.

¶ X-Ray quality crystals of **4[epox]** were obtained by slow evaporation from hexanes. $C_{15}H_{22}O_5$, $M = 282.33$, monoclinic, $a = 7.0375(14)$, $b = 11.004(2)$, $c = 9.6494(19)$ Å, $U = 728.3(3)$ Å^3, $T = 173(2)$ K, space group $P2_1$, $Z = 2$, 3617 reflections measured, 2167 unique ($R_{int} = 0.0000$, Friedel pairs were not merged). The final w$R(F_2)$ was 0.0956 (all data). CCDC 686765.

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