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Total synthesis of *cis*-reticulatacin-10-ones A and B: absolute stereochemical assignment†

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***cis*-Reticulatacin-10-ones A and B were synthesised as a predefined mixture of diastereoisomers (dr ~ 1 : 9) in nine steps from the acid chloride 8, and without the use of hydroxyl protecting groups. Comparison of the chiral HPLC chromatogram of the synthetic sample with that of the natural product isolated from the roots of the tropical fruit tree *Annona muricata* L. showed the natural product to be a mixture of A and B diastereoisomers (dr ~ 1 : 1).**

Acetogenins isolated from *Annonaceae* (custard apple family) exhibit a wide range of significant bioactivities including pesticidal, antiparasitic, and potent *in vitro* cytotoxic antitumour activities.[1] Investigation of the roots of the tropical fruit tree *Annona muricata* L. (soursop) led Cavé and co-workers to isolate seven mono-THF acetogenins including the previously known *trans*-mono-THF solamin.[2] Among the six new mono-THF compounds, possessing the less common *threo*/*cis*/*threo* configuration in their 2,5-bis-hydroxyalkyl THF (THF-diol) cores, were *cis*-solamin (**1**), *cis*-uvariamicin I (**2**), *cis*-reticulatacin (**3**), and *cis*-reticulatacin-10-one (**4**). On the basis of the physical data available for the natural products or their derivatives, it was not possible to identify the absolute stereochemistry within the *cis*-THF-diol region. For example the structure of *cis*-solamin was thought to be either (15*R*,16*R*,19*S*,20*S*,34*S*)-*cis*-solamin (**1A**) or (15*S*,16*S*,19*R*,20*R*,34*S*)-*cis*-solamin (**1B**).[3] For convenience, these diastereoisomers will be referred to as *cis*-solamin A and *cis*-solamin B, respectively.

Subsequently, we discovered that the THF containing compounds *cis*-solamin, *cis*-uvariamicin I and *cis*-reticulatacin isolated from *Annona muricata* L. are all present as mixtures of *threo*/*cis*/*threo* diastereoisomers A and B in approximately equal amounts (Fig. 1).[4] The specific rotations, proton and carbon NMR spectra of these pairs of diastereoisomers are "substantially identical" due to the local "*meso*" symmetry of the THF-diol core,[5] which extends out by ten methylene units on either side. However, the A and B diastereoisomers **1A/B–3A/B** could be distinguished using chiral HPLC or chiral HPLC-MS.[3f,4]

cis-Reticulatacin-10-one differs most obviously from the other *cis* mono-THFs isolated from *Annona muricata* L. in that it possesses a ketone functionality at C10 of its carbon backbone. It also has localised symmetry in the THF-diol core, but only extending out through six methylene groups. We suspected that *cis*-reticulatacin-10-one, isolated from the same plant source, was also a mixture of A and B diastereoisomers. Therefore, we set out to establish this proposal by total synthesis of a predefined mixture of *cis*-reticulatacin-10-one A/B (**4A/B**), and comparison by chiral HPLC with the natural isolate.[6,7]

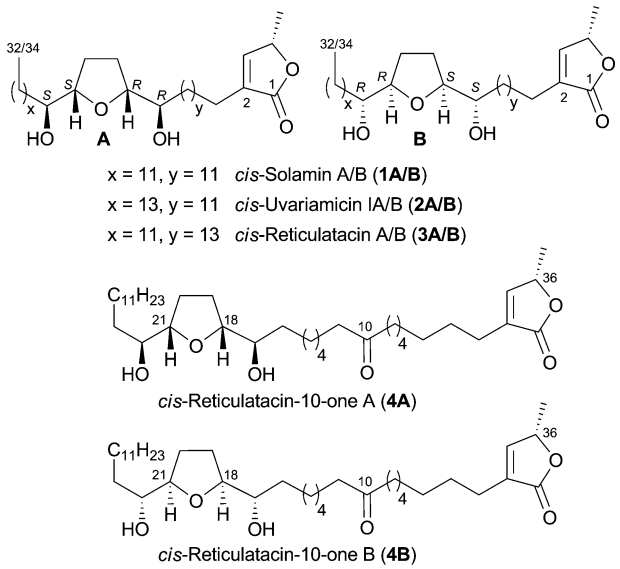

Fig. 1 Structures of *threo*/*cis*/*threo* configured mono-THF acetogenins isolated from *Annona muricata* L.

Rather than preparing the individual *threo*/*cis*/*threo* diastereoisomers **4A** and **4B**, we elected to prepare *cis*-reticulatacin-10-one as an approximately 1 : 9 mixture of the A and B diastereoisomers, respectively (Fig. 2). This was to be achieved from the enantiomeric epoxides (**5B/A**, er ~ 9 : 1) previously synthesised in our laboratory in eight steps from 2-(but-3-yn-1-yn)-1,3-dioxolane, using a permanganate-mediated oxidative cyclisation of a 1,5-dienoyl sultam.[4a]

The synthesis of the C3–C15 chain began from commercially available acid chloride **8**, which was converted to its Weinreb amide and homologated using heptenyl magnesium bromide affording a mixture of haloketones **9** (Scheme 1). During the first of these transformations, some halogen exchange occurred giving a mixture of primary alkyl halides (Br : Cl ~ 4 : 1 by ^{1}H NMR). Use of this mixture was ultimately of little consequence as both compounds converged on the sulfone **6**, following borohydride reduction and halide displacement. At this point we chose to carry the alcohol through the remaining synthetic steps unprotected. However, for this approach to succeed would later require a selective oxidation of the C10 carbinol in the presence of the

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† Electronic supplementary information (ESI) available: Preparation of all novel compounds and copies of ^{1}H and ^{13}C NMR spectra and chromatograms. See DOI: 10.1039/c0ob00259c

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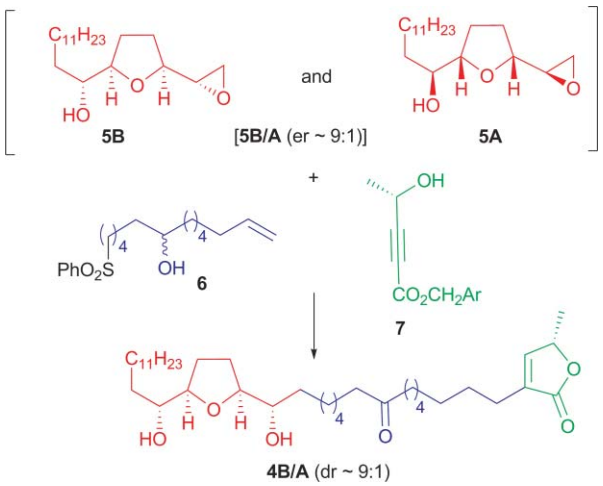
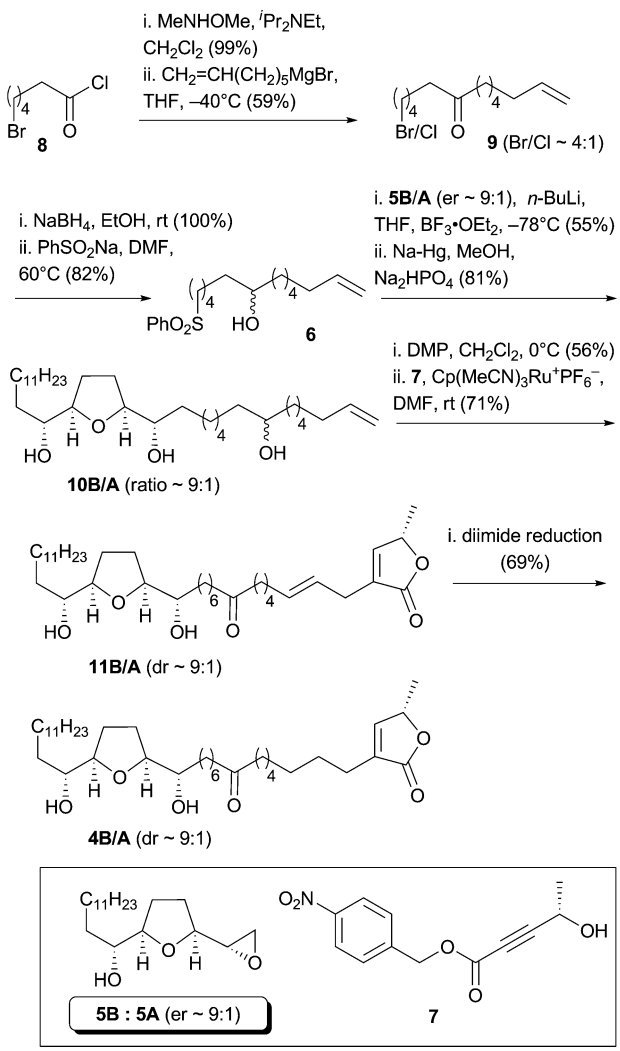


Fig. 2 Synthetic approach to a predefined mixture of *cis*-reticulatacin-10-one A/B diastereoisomers.



Scheme 1 Synthesis of *cis*-reticulatacin-10-one diastereoisomers **4B/A** (for convenience, only the major B isomeric series is shown).

cis-THF-diol core. We were confident that this could be achieved due to the greater steric demand of the secondary alcohols flanking the *cis*-2,5-disubstituted THF ring.

The dianion of the sulfone fragment **6** was coupled with enantiomerically enriched epoxide (**5B/A**, er ~ 9 : 1), and subsequent reductive desulfonylation of the product gave the triols **10A/B**. Gratifyingly, selective oxidation of the C10 carbinol group of the triols **10A/B**, in the presence of the C17 and C22 carbinol groups, was achieved in 56% yield using Dess–Martin periodinane (33% recovered **10B/A**). The butenolide was then introduced by means of the Trost Alder-ene method in good yield.[8] This reaction provides a robust and chemoselective approach for introduction of the butenolide system with only a small amount of the regioisomeric addition product formed. Finally reduction of the disubstituted alkene using diimide gave the natural product *cis*-reticulatacin-10-one as a mixture of diastereoisomers (**4A/B**, dr ~ 1 : 9).[9]

Comparison of the synthetic sample with the natural isolate using chiral HPLC analysis clearly showed two peaks (Fig. 3),[10] indicating that the natural isolate was also a mixture of the (17*R*,18*R*,22*S*,23*S*,34*S*) and (17*S*,18*S*,22*R*,23*R*,34*S*) *threo*/*cis*/*threo* diastereoisomers **4A** and **4B** in an approximate 1 : 1 ratio.

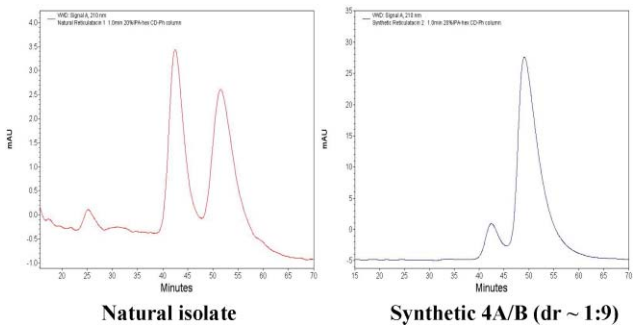


Fig. 3 Chiral HPLC chromatograms for synthetic mixture of **4A/B** and natural *cis*-reticulatacin-10-one.

To conclude, a mixture of *cis*-reticulatacin-10-ones A and B (**4A/B**, dr ~ 1 : 9) was prepared in 5.8% yield over nine steps from acid chloride **8** (or 4.1% yield over thirteen steps from 2-(but-3-yn-1-yn)-1,3-dioxolane) without the requirement for hydroxyl protecting groups. The availability of the synthetic sample allowed us to show that the natural isolate was a mixture of A and B stereoisomers **4A/B** (dr ~ 1 : 1).

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9 The diimide reduction using $TsNHNH_2$ was accompanied with some hydrazone formation (25%). The hydrazone was recycled to **4B**/**A** (dr ~ 9 : 1) by hydrolysis using THF, AcOH, H_2O in 78% yield (not included in the reported yield for the reduction step in Scheme 1).

10 Chiral HPLC separations were performed using a Chiral CD-Ph column (4.6 × 250 mm) eluting with IPA–hexane mixtures (1 : 4), monitored by UV detection at 210 nm.

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