# Synthesis of Membranacin

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With best wishes to Professor Clayton Heathcock upon his retirement from U.C. Berkeley

**Abstract:** The synthesis of the *Annonaceous* acetogenin membranacin (**2**) has been achieved, using transition metal-oxo and transition metal-peroxy species in the key steps.

**Key words:** oxidations, asymmetric synthesis, natural products, manganese, total synthesis

*Annonaceous* acetogenins are a large class of natural products isolated from certain plants belonging to the family *Annonaceae*.[1–3] Their structures are characterised by a core region consisting of one or more saturated oxygen heterocycles (THF/THP), usually flanked on both sides by hydroxyalkyl groups (Figure 1). One of these alkyl chains usually carries a butenolide group at its end, and either or both of the chains may possess unsaturation or hydroxylation along their length. Major interest in the acetogenins stems largely from their cytotoxic anti-tumour activity, although insecticidal properties have also received attention.[1]

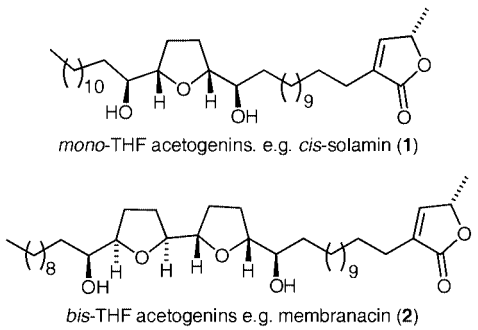
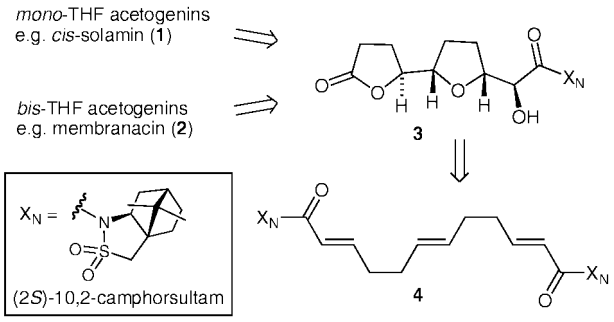



**Figure 1** Examples of *Annonaceous* acetogenin natural products

During our programme to develop routes to acetogenins and related analogues, the lactone **3** was identified as a versatile precursor to both *mono*- and *bis*-THFs (Scheme 1). We had previously shown that racemic lactones related to **3** could be prepared in six steps from ethyl acetoacetate and 1,4-dibromobut-2-ene.[4] Extension of the methodology to the synthesis of acetogenins would rely on the diastereoselective oxidation of **4** to provide **3**, followed by chemoselective reduction of the acylsultam functionality to permit further elaboration. The lactone ring would later facilitate introduction of the left hand alkyl chain or the second THF ring, depending on whether *mono*- or *bis*-THF were to be the target. Here we describe the successful application of this strategy to the synthesis of membranacin (**2**), a cytotoxic anti-tumor acetogenin isolated from the seeds of the fruit tree *Rollinia mucosa*.[5]




**Scheme 1** Synthesis of *mono*- or *bis*-THF acetogenins from lactone **3**

The required triene starting material **4** was prepared using established procedures prior to introduction of the (2*S*)-10,2-camphorsultam auxiliary (Scheme 2).[4] Permanganate oxidation of **4** followed by treatment of the crude reaction mixture with $NaIO_4$–$SiO_2$ proceeded efficiently to afford a single isolated diastereoisomeric lactone **3** in high yield.[4,6–8]

A combination of $BH_3$·DMS and $NaBH_4$ provided the most effective conditions for the selective reduction of the acylsultam functionality present in **3**, returning diol **7** in reasonable yield.[9] Other reductive conditions typically gave mixtures including over reduced compounds. Addition of the C3–C13 chain required chemoselective reaction at C14 with a cuprate reagent, which was achieved after conversion of diol **7** to the corresponding epoxide **8**.

Protection of alcohol **9** as its TBS ether and reduction of the lactone ring gave the corresponding lactol **11**, which underwent *trans*-selective olefination affording α,β-unsaturated ester **12** in excellent yield (Scheme 3). DIBALH reduction of the ester gave the *E*-allylic alcohol substrate **13** for a highly diastereoselective Sharpless asymmetric epoxidation and in situ THF ring closure to provide the *bis*-THF diol core of the natural product.[10] This second oxidative cyclisation process produced a single diastereo-

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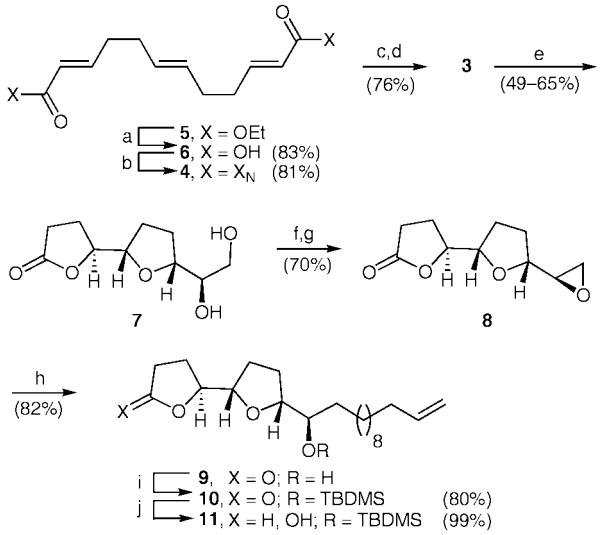
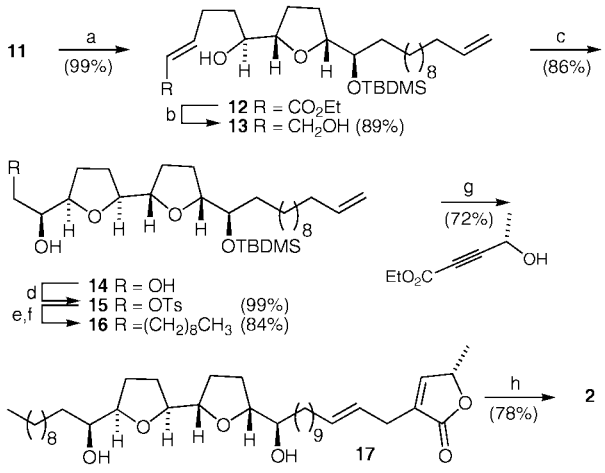



**Scheme 2** *Reagents and conditions*: (a) NaOH, $NaHCO_3$, MeOH, $H_2O$, 80 °C; (b) $(COCl)_2$, DMF, $CH_2Cl_2$, then (2*S*)-10,2-camphorsultam, NaH, THF; (c) $KMnO_4$ (2.6 equiv), adogen 464 (5 mol%), acetone–HOAc (3:2); (d) $NaIO_4$–$SiO_2$, $CH_2Cl_2$; (e) $BH_3$·$SMe_2$, $NaBH_4$, THF then $CH_2Cl_2$–MeOH; (f) $Bu_2SnO$, TsCl, TBAB, PhH; (g) DBU, $CH_2Cl_2$; (h) undec-10-enylmagnesiumbromide, CuI, THF, –50 °C; (i) TBDMS-Cl, imidazole, $CH_2Cl_2$; (j) DIBALH, THF.

meric product, representing an example of 'matched' double asymmetric induction as the enantiomeric oxidation conditions afforded the diastereoisomeric product and **14** in a lower ratio (15:1, NMR). Repeating the sequence of 1° alcohol activation, epoxide formation and cuprate addition completed the C3–C34 region of the natural product. The butenolide portion of membranacin (**2**) was introduced using Trost's ruthenium-catalysed Alder–ene reaction to afford the desired product **17** alongside a




**Scheme 3** *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, PhMe; (b) DIBALH, THF; (c) L-(+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, *t*-BuOOH, 4 Å sieves, $CH_2Cl_2$; (d) $Bu_2SnO$, TsCl, TBAB, PhH; (e) DBU, $CH_2Cl_2$; (f) $CH_3(CH_2)_8MgBr$, CuI, THF; (g) CpRu(cod)Cl, MeOH, reflux; (h) $TsNHNH_2$, NaOAc, THF, $H_2O$, reflux.

smaller amount of the uncyclised regioisomer (isolated dr = 4:1).[3d,11] Selective reduction of the C4–C5 double bond with diimide completed the synthesis, affording a compound giving spectroscopic data consistent with those of membranacin (**2**).[5a]

In conclusion, the total synthesis of membranacin (**2**) has been completed using metal-oxo and metal-peroxy-mediated oxidative cyclisations as the key steps. The lactone intermediate **3** should also prove useful for the synthesis of other acetogenins and acetogenin analogues.

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