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The Synthesis of (+)-Pericosine B

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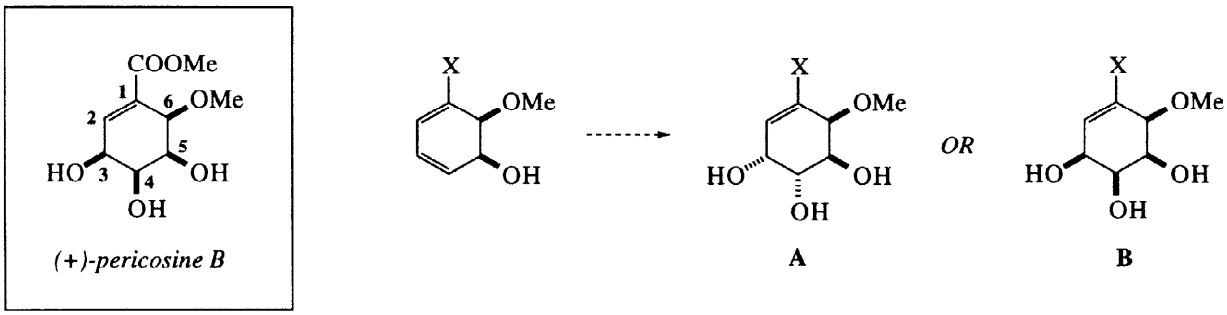
Abstract: The first synthesis of (+)-pericosine B is described: this takes seven steps and proceeds in 10% overall yield. The key step in our work is a hydrogen-bonding controlled contra-steric dihydroxylation reaction using osmium tetroxide and an amine promoter. The absolute stereochemistry of the natural product was deduced from the known absolute stereochemistry of our starting material and moreover, the relative and absolute stereochemistry of our synthetic material was determined unambiguously from an X-ray crystal structure of an advanced intermediate.

We were drawn to a recent report of the isolation of pericosine B (**Scheme 1**) from a micro-organism (a strain of *Periconia byssoides*) drawn from the gastrointestinal tract of the sea hare *Aplysia kurodai*.[1] The relative stereochemistry of pericosine B was deduced from NMR data and its absolute configuration assigned without definitive proof.[1] We considered pericosine B to be a worthwhile target as it exhibited significant activity (ED_{50} = 4 μg/ml) in the P388 lymphocytic leukaemia test system and, as it had not been the subject of a successful synthesis, our work would also aim to confirm unambiguously the stereochemistry of the natural product.



Scheme 1

The disconnection that we chose to simplify the target involved the introduction of the hydroxyl groups at C-3,4 *via* a dihydroxylation reaction. One would normally expect this reaction to give a diol with the wrong stereochemistry (**A, Scheme 1**): several years ago, Kishi demonstrated that chiral allylic alcohols (both cyclic and acyclic) were oxidised with osmium tetroxide and that they formed the *syn, anti* triol selectively.[2] However, we have recently described methodology for performing the (hydrogen-bonding) directed dihydroxylation of cyclic allylic alcohols using osmium tetroxide with either a mono-[3] or bidentate[4] ligand. As this methodology should give access to the *syn, syn* triol (**B, Scheme 1**), we proposed to use it in our synthesis.

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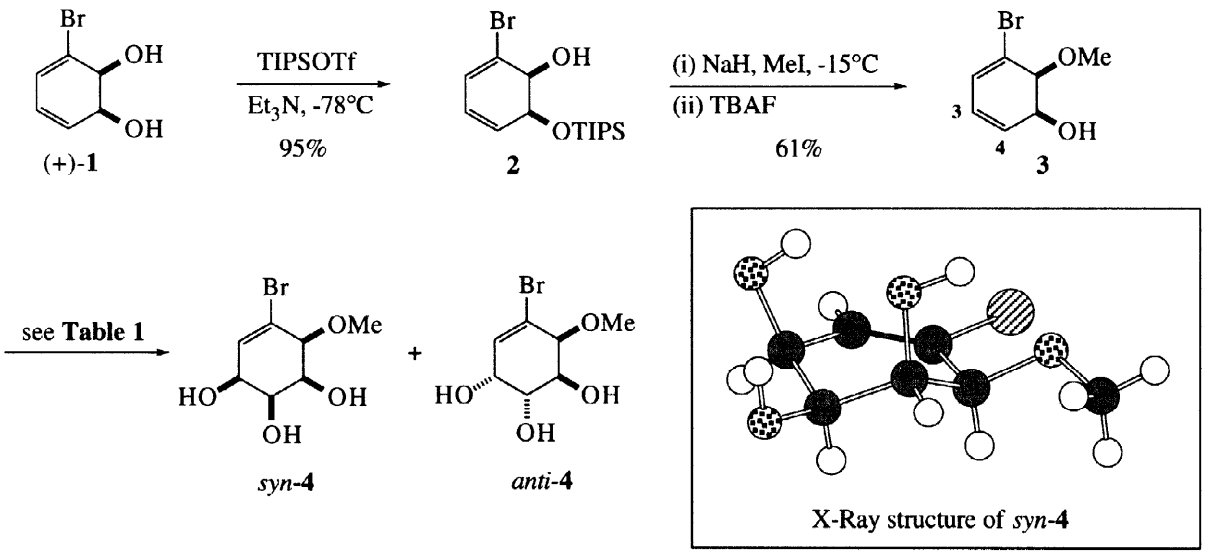
The route began with commercially available bromocyclohexadiene diol (+)-**1** which is obtained in enantiopure form (of known absolute configuration) from natural sources and is also of the correct enantiomeric series for pericosine B (as described in the original paper).[5] We were able to differentiate between the two hydroxyl groups of **1** by reaction with one equivalent of TIPSOTf at -78°C (**Scheme 2**):[6] the regioselectivity of this reaction appears to be complete and rational as silicon is introduced onto the most electron rich and sterically least hindered alcohol group.[7] A methyl group was introduced onto the remaining hydroxyl group under standard conditions and the silyl protecting group subsequently removed with TBAF. This sequence of reactions proceeded in 58% overall yield.

Our next objective was introduction of the two hydroxyl groups on C-3 and C-4 (natural product numbering) of **3** with the correct *syn* stereochemistry. We examined dihydroxylation with osmium tetroxide under a variety of conditions in order to obtain the contra-steric product *syn*-**4** (**Table 1**). Both the relative and absolute stereochemistry (made possible by the presence of a heavy atom) of *syn*-**4** were proven by X-ray crystallography (**Scheme 2**).



Scheme 2

Table 1

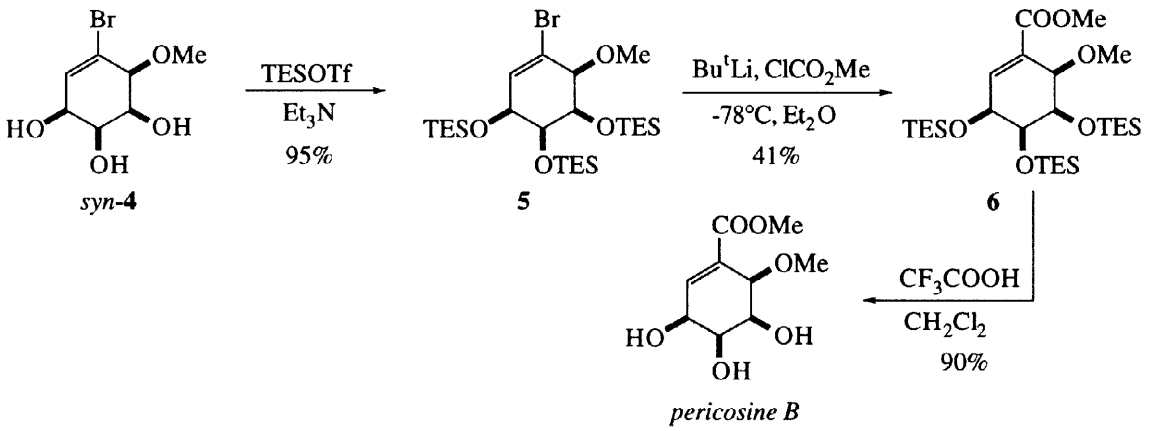
Entry	Conditions	Ratio[a] *syn*-4/*anti*-4	Yield (%)
1	OsO_4 (cat.), NMO, acetone/water	1:3	65
2	OsO_4 (cat.), $Me_3NO.2H_2O$, CH_2Cl_2	2:1	40
3	OsO_4 (1 eq.), TMEDA, CH_2Cl_2, -78°C	≥1:20	84
4	OsO_4 (1 eq.), quinuclidine, CH_2Cl_2, -78°C	2.2:1	71

[a] In each case, the ratio of *syn/anti*-4 was assessed by ^1H NMR spectroscopy.

As expected, reaction under Upjohn conditions favoured the formation of *anti*-**4** with a moderate level of stereocontrol (**Table 1**, entry 1).[8] Changing the conditions to those reported by Poli (entry 2) reversed the selectivity and gave *syn*-**4** with reasonable selectivity:[9] we suspected that hydrogen-bonding between the oxidant and the allylic alcohol was encouraged in an aprotic solvent and causes this reversal in stereoselectivity. The low

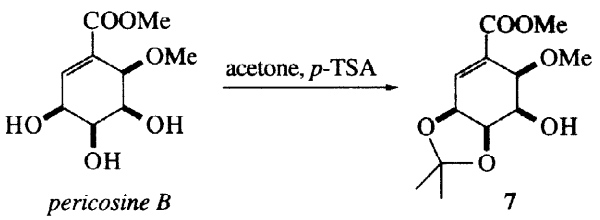
yield reported in this reaction is attributable to the slow rate of dihydroxylation which means that aromatisation of the starting material is competitive with oxidation. Combining osmium tetroxide with TMEDA was expected to lead to even higher levels of *syn* selectivity in the oxidation process.[4] We were, however, disappointed to find that this reagent gave little or none of the desired *syn* triol (entry 3)! At the present time, the reason behind this lack of *syn* selectivity is unclear, but we do suspect that steric and electrostatic repulsion between the oxidant and C-3 methoxy group of **3** may be responsible. This result is particularly surprising when one considers that oxidation of *cis*-1,2-cyclohexadiene diol with osmium tetroxide and TMEDA is a highly *syn* selective reaction, forming conduritol-D in the process.[4] Eventually, we found that the use of stoichiometric osmium tetroxide with one equivalent of quinuclidine (to make the oxidant a moderate hydrogen-bond acceptor[3]) gave a reasonable balance of both *syn* selectivity and high yield (entry 4) and, considering that the two triols could be separated by column chromatography, enabled us to proceed with the synthesis.

Syn-**4** was then protected with three triethylsilyl (TES) groups under standard conditions and the carboxymethyl group was introduced using Bu^{t}Li (to effect halogen-metal exchange) and then methyl chloroformate as an electrophile (**Scheme 3**).[10,11] The use of transition metals to effect a carboxylation in methanol was less successful.[10] The final step of our synthesis required removal of the silyl groups and this was accomplished with trifluoroacetic acid/dichloromethane at room temperature.



Scheme 3

The material that was produced from this sequence had spectroscopic data (^{1}H NMR, ^{13}C NMR, mass spec, IR) which was identical to that reported by Numata *et al.* The original workers reported that pericosine B was an oil whereas the material that we synthesised was a colourless solid (note, this was only when isolated by evaporation from chloroform); in addition our rotation was different from the literature value, $[\alpha]_D^{21}$ +30.6 (*c* 0.8 in EtOH), lit.[1] $[\alpha]_D$ +22.3 (*c* 0.82 in EtOH). However, we regard this discrepancy in rotation to be within the limits of experimental error with a molecule so prone to intra- and inter-molecular hydrogen-bonding.[12] As the rotation of the synthetic material had an identical sign to that of the natural product (and we can be sure of the absolute configuration of our synthetic material), this work confirms the absolute stereochemistry of (+)-pericosine B to be as shown. In order to confirm further the match between our synthetic sample and the natural product, we prepared the C-3,4 acetonide **7** under standard conditions (**Scheme 4**). Its proton and carbon NMR spectra were a very good match with those found by Numata.



pericosine B 7

^{1}H nmr: δ ($CDCl_3$, 300 MHz) 6.82 (1H, dd, J= 3, 1 Hz), 4.66 (1H, dd, J= 5, 3 Hz), 4.50 (1H, dd, J= 6, 3 Hz), 4.29 (1H, d, J= 12 Hz), 3.78-3.86 (1H, m), 3.82 (3H, s), 3.60 (3H, s), 3.16 (1H, d, J= 11 Hz), 1.41 (3H, s), 1.38 (3H, s) ppm
^{13}C nmr: δ ($CDCl_3$, 75 MHz) 166.5, 137.5, 130.2, 111.1, 74.69, 72.96, 72.40, 67.87, 61.23, 52.13, 27.66, 26.17 ppm.

Scheme 4

Conclusions: We have reported the first synthesis of (+)-pericosine B and in so doing proven the relative and absolute stereochemistry of the natural product. The key step in our sequence is the directed dihydroxylation of **3** which proceeded with acceptable levels of stereocontrol. Considering that our route is only seven steps long with an overall yield of 10%, we believe that this chemistry is amenable to the production of useful quantities of the natural product.

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