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Chemoenzymatic Synthesis of Carbasugars (+)-Pericosines A−C from Diverse Aromatic *cis*-Dihydrodiol Precursors

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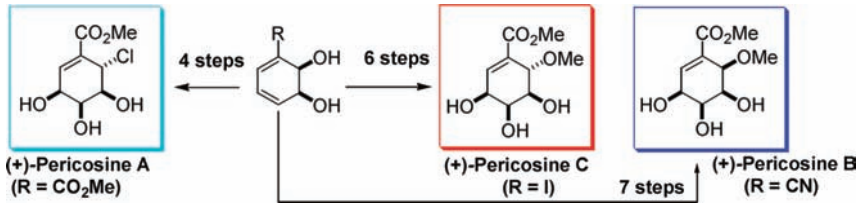
ABSTRACT



***cis*-Dihydrocatechols, derived from biological *cis*-dihydroxylation of methyl benzoate, iodobenzene and benzonitrile, using the microorganism *Pseudomonas putida* UV4, were converted into pericosines A, C, and B, respectively. This approach constitutes the shortest syntheses, to date, of these important natural products with densely packed functionalities.**

The naturally occurring pericosines A, B, and C, Figure 1, were originally isolated as metabolites from the fungus *Periconia byssoides* found in the gastrointestinal tract of the sea hare *Aplysia kurodai*.[1] There has been considerable interest in the synthesis of pericosines, due to their cytotoxicity against P388 lymphocytic leukemia cells, antitumor activity against murine P388 cells, and selective growth inhibition against human cancer cell lines HBC-5 and SNB-75.[2a,b] The first synthesis of pericosine B was accomplished by Donohoe[3] over ten years ago and recently there has been an upsurge of interest in these molecules. This has culminated in syntheses leading to a structural reassignment of pericosine A,[4] the synthesis of pericosine A plus a diastereoisomer,[5] pericosine B,[6] an epimer thereof,[7] pericosine C,[8] and pericosine D.[9] Unusually, for a natural product, pericosine C was found to exist as a mixture of enantiomers with a low preference for the (−)-isomer (14% ee).[2] This observation may be linked to the pseudosymmetry present within the pericosine structures, in which allylic rearrangement provides a potential mechanism for partial racemization. The structural similarities between pericosines (polyhydroxylated cyclohexenes) and the pseudosugars (polyhydroxylated cyclohexanes) are obvious and both may be classified as carbasugars.[10]

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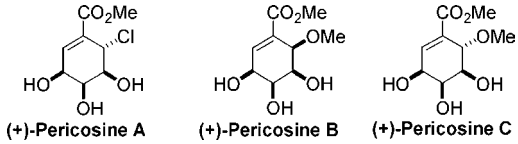


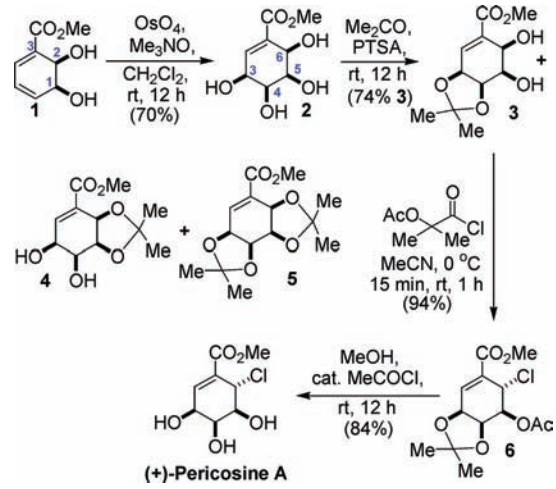
Figure 1. Structures of pericosines A−C.

Dioxygenase-catalyzed oxidation of arene substrates provides a direct route to a wide range of enantiopure mono- and poly-hydroxylated bioproducts. Earlier studies of aromatic substrates in these and other laboratories, using mutant strains (e.g. UV4, 39D) of the soil bacterium *Pseudomonas putida* and *Escherichia coli* recombinant strains, each containing toluene dioxygenase, have provided access to an extensive range of over 400 metabolites.[11a−i]

To date, only a very small number of benzene *cis*-dihydrodiols have been used as "chiral pool" intermediates and these have recently resulted in a diverse range of syntheses.[12a−d] The majority of synthetic studies using *cis*-dihydrodiols as precursors have focused on those derived from bromobenzene, chlorobenzene, and toluene. The remarkable synthetic versatility of the *cis*-diol derived from iodobenzene has been utilized extensively in our laboratories,[13a−i] and others,[14a,b] and is a key precursor in the synthesis of a range of carbasugars.[14b,15]

In contrast, *cis*-dihydrodiol metabolites derived from cyanobenzene[16a−d,17a,b] and methyl benzoate[12b,18] have, to date, seen limited application in synthesis. Use of these *cis*-dihydrodiols is growing in popularity and both have been used as precursors to carbasugars.[12b,16b,18] These metabolites seemed ideal precursors for pericosine syntheses, as all the carbon atoms were in place and only regio- and stereoselective functional group manipulations were required. We now report that enantiopure *cis*-diol metabolites derived from methyl benzoate,[12d,16d,18] iodobenzene,[13d] and cyanobenzene[13d,16a,d,17] can be converted to the carbasugar pericosines A, C, and B, respectively (Schemes 1−3).

Scheme 1. Synthesis of Pericosine A



Dihydroxylation of *cis*-dihydrodiol **1**, using the Donohoe protocol,[19] gave a 4:1 mixture of two *cis*,*cis*-tetraol diastereoisomers, resulting from oxidative attack on the same face at the 5,6 and 3,4 double bonds, respectively, from which the desired regioisomer **2** could be isolated in 70% yield after chromatography.[18] As expected, and in line with other dihydroxylations, the existing *cis*-hydroxyl groups dictated the stereochemical outcome of this reaction—the new diol being created on the same alkene face as the existing hydroxyl groups. Since the hydroxyl group at the C-6

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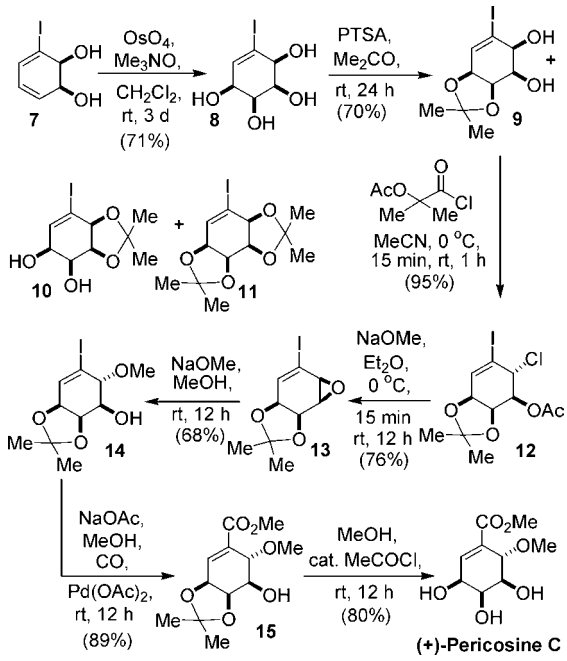
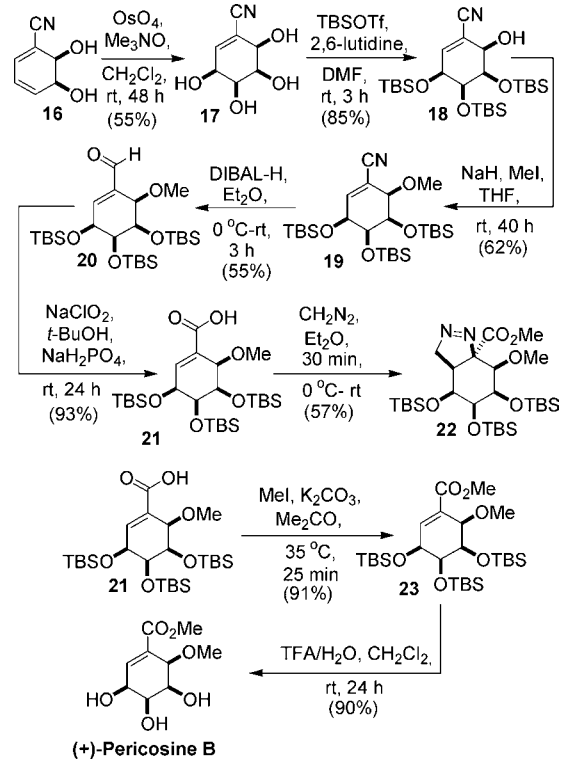
Scheme 2. Synthesis of Pericosine C



Scheme 3. Synthesis of Pericosine B



position of compound **2** was hydrogen bonded to the adjacent carbomethoxy group, it was expected to be less reactive in the subsequent acetal reaction. Treatment of tetraol **2**, at room temperature, with acetone under acidic conditions gave a (7:4:9) mixture of acetonides **3**, **4**, and **5**, as indicated by the ^{1}H NMR spectrum of the crude product. No acetal formation was observed between the hydroxyl groups at C-4 and C-5. It was previously reported that in cyclohex-1-ene-*cis*-3,4,5-triols under thermodynamic control, acetal formation favored positions 3 and 4.[20] Separation of the mono- and bis-acetonides, followed by repeated recyling of the unwanted acetals **4** and **5** by hydrolysis and reacetalization of the recovered tetraol **2**, gave the required acetonide **3** in 74% overall yield. Interestingly, on selective hydrolysis of the bis-acetal **5**, the monoacetal **4** formed first allowing ready access to both monoacetonide-protected diols **3** and **4**.

In previous syntheses of pericosine A, introduction of the sensitive allylic chloride, from the allylic alcohol adjacent to the electron deficient alkene, proved troublesome, as there was a strong tendency for an allylic rearrangement coupled with low yields.[4a,b] By using Mattocks' procedure,[21] diol **3** was regio- and stereo-selectively converted to the *trans*-chloroacetate **6**, by reaction with chlorocarbonyl-1-methylethyl acetate. This reaction proceeded cleanly, with inversion at C-6, no allylic rearrangement side products were observed, and it was not necessary to prior protect the hydroxyl group on C-5. Finally, a one-pot acid-catalyzed deprotection of both acetate and acetonide protecting groups, under mild acidic conditions,[22] gave (+)-pericosine A (Scheme 1). This four-step synthetic sequence, achieved in an overall yield of 41% from diol **1**, constitutes the shortest efficient synthesis of (+)-pericosine A, the most biologically active of the pericosines.[2a]

(+)-Pericosine C, in principle, should be available from (+)-perocosine A, by conversion of the *trans*-chloroacetate **6** to the corresponding epoxide, followed by a regioselective ring-opening reaction with sodium methoxide at the allylic position. However, suitable reaction conditions could not be found for epoxide formation; only intractable material was recovered under basic reaction conditions. It was reasoned that the carbomethoxy group, attached to the alkene, was destabilizing the desired allylic epoxide by facilitating nucleophilic addition reactions to the alkene with epoxide ring-opening, under the basic conditions required for its formation. To get around this difficulty, for the synthesis of (+)-pericosine C, the carbomethoxy group was introduced after epoxide formation.

The synthesis of (+)-pericosine C, outlined in Scheme 2, was accomplished by using (1*S*,2*S*)-3-iodocyclohexa-3,5-diene-1,2-ol (**7**) as the starting material. This alternative approach to the base sensitivity problem highlights the advantage of having a range of bioproducts available as chiral pool precursors. Dihydroxylation of *cis*-dihydrodiol **7**, employing the literature procedure (OsO_4, TMNO, DCM),[15] gave a 10:1 mixture of *cis*,*cis*- and *cis*,*trans*-tetraol diastereoisomers from which the required major *cis*,*cis* isomer **8** could be isolated in 71% yield after column chromatography. Again selective acetalization was accomplished under kinetic control, and on repeated recycling of unwanted acetals **10**

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and **11**, the required acetal **9** was obtained in 70% yield. On partial hydrolysis of bis-acetonide **11** the monoacetonide **10** formed first giving access to both mono-protected forms of the tetraol (**9** and **10**). Reaction of diol **9** with 1-chlorocarbonyl-1-methylethyl acetate gave chloroacetate **12**, which on treatment with sodium methoxide in diethyl ether furnished the desired epoxide **13**. Treatment of epoxide **13** with sodium methoxide in a methanol solution resulted in regioselective ring-opening to give the methyl ether **14**. One of the advantages of using vinyl iodides was the ease with which the iodide group could be replaced. Thus, room temperature palladium-catalyzed carbomethoxylation of the vinyl iodide **14** with carbon monoxide in methanol solution gave the methyl ester **15**. Finally, removal of the acetonide group from ester **15**, under acidic conditions in methanol,[22] gave (+)-pericosine C. This is, to date, the shortest synthesis of (+)-pericosine C, six steps from (1*S*,2*S*)-3-iodocyclohexa-3,5-diene-1,2-ol (**7**), in an overall yield of 17%.

It was envisaged that (+)-pericosine B could be easily synthesized from tetraol **2**, after selective protection of the three hydroxyl groups on carbons C-3, C-4, and C-5. The protection of these hydroxyl groups was readily achieved, using the bulky TBS protecting group. However, the remaining hydroxyl group at C-6 proved recalcitrant to methylation under a wide range of conditions.

Our next choice to accomplish the synthesis was to utilize (1*S*,2*R*)-3-cyano-cyclohex-3-ene-1,2-diol (**16**) bearing a CN group, which is less bulky than a CO_2Me group (Scheme 3). Dihydroxylation of diol **16** under conditions similar to those used for *cis*-dihydrodiols **1** and **7** gave (4:1) a mixture of *cis*,*cis*- and *cis*,*trans*-tetraols from which the major *cis*,*cis* isomer **17** was isolated in 54% yield by column chromatography. Reaction of tetraol **17** with 3 mol of *tert*-butyldimethylsilyl triflate gave the tri-TBS derivative **18** as the major product in 85% overall yield, together with small amounts of other unidentified inseparable isomers. The free C-6 hydroxyl group of the crude sample of silyl derivative **18** was methylated, under mild conditions, and a purified sample of methyl ether **19** was readily separated from the product mixture. The nitrile group in compound **19** was converted to the carboxylic acid **21** via partial reduction/hydrolysis to the aldehyde **20** followed by oxidation. Carboxylic acid **21** was reacted with excess diazomethane in an attempt to form the methyl ester **23**. However, the product from this reaction was the crystalline pyrazoline cycloadduct **22**. It is well-known that shikimic acid derivatives react with diazomethane to give pyrazolines,[23] but given the steric crowding around the alkene in compound **21** it is remarkable that the cycloaddition proceeds with such speed and ease. The methyl ester was efficiently introduced by base-mediated methylation of carboxylic acid **21** to give **23**. Finally, acid-catalyzed removal of the TBS protecting groups furnished (+)-pericosine B in seven steps and an overall yield of 12%.

In conclusion, we have demonstrated that *cis*-dihydrodiols derived from methyl benzoate, iodobenzene, and cyanobenzene are versatile complementary intermediates for the rapid synthesis of pericosines A, C, and B, respectively.

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Supporting Information Available: Experimental procedures, product characterization, and copies of ^{1}H NMR and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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