Communications to the Editor

Singlet Oxygenation/Radical Rearrangement as an Approach to 1,4-Dioxygenated Peroxides: Asymmetric Total Syntheses of Plakorin and *enantio*-Chondrillin

Patrick H. Dussault* and Kevin R. Woller

Department of Chemistry
University of Nebraska−Lincoln
Lincoln, Nebraska 68588-0304

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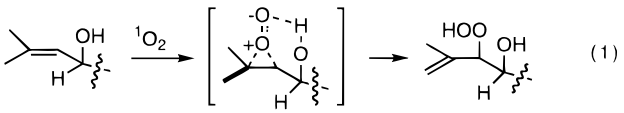
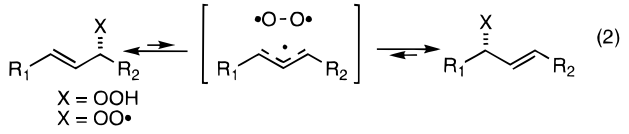
There exists no general methodology for the asymmetric synthesis of 1,4-dioxygenated peroxides, despite the common presence of this subunit in peroxide natural products and their synthetic precursors.[1] While previous reports from these labs have described a chemoenzymatic approach to 4-peroxy 2-enals and related 1,4-dioxygenated peroxides,[2] general application is limited by the intolerance of soybean lipoxygenase for many unnatural 1,4-dienes. We now report an asymmetric route to 1,4-dioxygenated peroxides via sequential hydroxyl-directed singlet oxygenation and [2,3]-peroxyl radical rearrangement (Figure 1). The methodology is applied to the first asymmetric total synthesis of the marine natural product plakorin (**1**) and its C_6-epimer, *ent*-chondrillin (**2**). On the basis of our synthesis, we propose a revised stereochemical assignment for the natural product chondrillin.

The addition of singlet oxygen ($^1O_2$) to chiral (*Z*)-allylic alcohols selectively furnishes *syn*-2-peroxy-3-alkenols through a transition state involving hydrogen-bonding to either $^1O_2$ or the developing perepoxide (eq 1).[3] This potentially powerful methodology remains relatively unexplored outside of simple allylic alcohols and related species. Similarly, the rearrangement of allylic hydroperoxides, although the focus of numerous mechanistic studies,[4,5] has not been widely exploited as a synthetic method. Abstraction of hydroperoxide hydrogen produces a peroxyl radical which undergoes nearly stereospecific isomerization through a tight radical cage (eq 2). Abstraction of hydrogen from another hydroperoxide propagates the reaction and produces rearranged product.



(1)



(2)

Chondrillin and plakorin, members of a larger family of alkoxydioxins derived from marine organisms reportedly differing only in the stereochemistry or substitution at the C_6 position, are obvious targets for the new strategy.[6,7] While several members of the family, including chondrillin, have demonstrated activity against cancer cell lines,[1,6,8] only a single racemic approach to this class of natural products has been reported.[9]

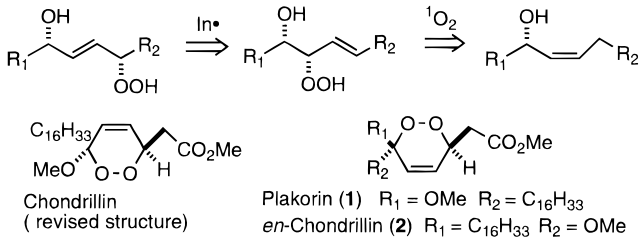
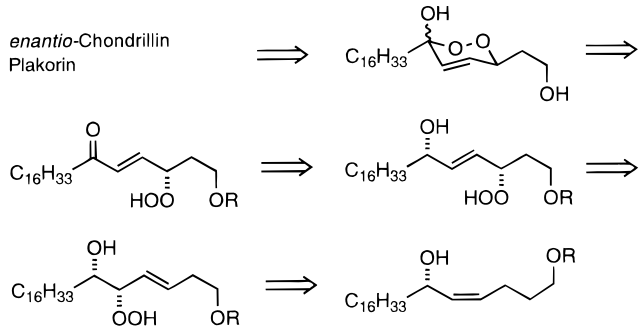


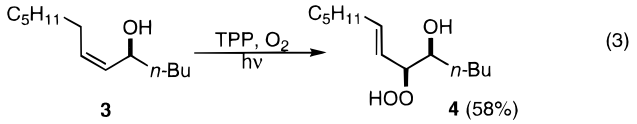
Figure 1.

Scheme 1. Retrosynthesis of Plakorin and "Chondrillin"



Our retrosynthetic approach is illustrated in Scheme 1. Chondrillin and plakorin, reported as epimeric at the C_6-peroxyacetal, would be formed as single enantiomers through photomediated cyclization of an enantiomerically pure hydroperoxyenone followed by ketalization of the intermediate dioxinol, a strategy first reported by Snider in the racemic synthesis of chondrillin and plakorin[9] and more recently modeled in our labs on an enantiomerically pure hydroperoxy enone.[10] In the key series of reactions, the hydroperoxy enone would be introduced through radical isomerization of a 2-hydroperoxy 3-en-1-ol, which would in turn arise through stereoselective dioxygenation of a chiral allylic alcohol.

The lack of examples describing peroxyl radical rearrangements in functionalized systems led us to model the key oxygenation/rearrangement sequence on a (*Z*)-alkenol (**3**) available in 91% ee through Alpine-borane reduction of 5-tridecyn-6-one followed by semihydrogenation of the resulting propargyl alcohol.[11−13] Photooxygenation of **3** (eq 3) slowly furnished a



(3)

90:10 mixture of *syn*- and *anti*-6-hydroperoxy-7-tridecen-5-ol

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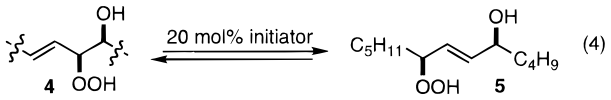
(**4**).[14] A sharp singlet at δ 9.5 ppm in the ^{1}H NMR spectrum indicated the presence of an intramolecular hydrogen bond involving the peroxyl hydrogen.[5]

Equilibration was found to proceed at 60−70 °C in the presence of 0.2 equiv of di-*tert*-butyl hyponitrite (DTBN) to furnish a nearly equal mixture of the 2- and 4-hydroperoxy alkenols **4** and **5** (eq 4), each as single diastereomers.[5] The use of a benzene/water emulsion, an effort to disrupt the intramolecular hydrogen bond, had little effect. Attempts to perform room temperature rearrangement using Et_3B or photochemical initiation of DTBN were unsuccessful.

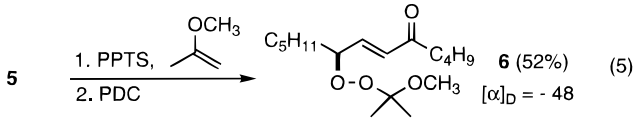


(4)

Conditions	Initiator	T (°C)	Time (h)	Yield (%)	Isolated Yield **4** (%)	Isolated Yield **5** (%)
A	DTBN	60	6.5	40	23	17
B	DTBN	55	7	41	20	21
B	DTBN	68	5	45	23	22
A	Et_3B	RT	6	NR	-	-
A	DTBN/hν	RT	1	decomp.	-	-
C	DTBN	50	7	77	34	30
C	DTBN	41	16	81	29	41

A: 0.01M in C_6H_6 B: 0.01M in C_6H_6/H_2O (9:1)
C: 0.01M in C_6H_6 in presence of 10 equiv. *t*-BuOOH

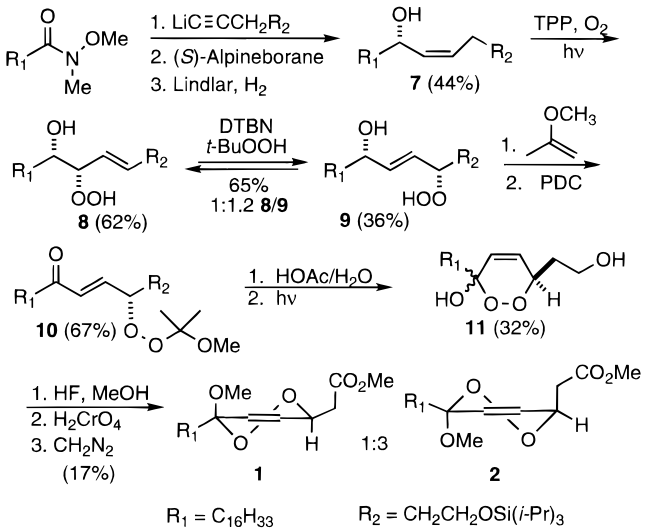
The low overall yield was attributed to a termination reaction, dimerization of peroxyl radicals to unstable tetroxides.[16] Preparative autoxidations, which also proceed via intermediate peroxyl radicals, furnish higher yields in the presence of *tert*-butyl hydroperoxide (TBHP), a radical reservoir which replaces substrate as the chain carrier.[17] As seen in eq 4, equilibration of the 2-peroxy en-1-ol in the presence of 10 equiv of TBHP greatly improved the combined recovery of starting material and product. Protection and oxidation of the separated rearrangement product **5** afforded peroxy enone **6** (eq 5), which was found to be 87% ee on the basis of comparison with material derived from a previously reported chemoenzymatic process.[10]



(5)

We now return to the total synthesis of chondrillin and plakorin (Scheme 2). Addition of a lithiated alkynol ether to the Weinreb amide of heptadecanoic acid furnished a propargyl ketone which underwent reduction with Alpine-Borane to provide a propargyl alcohol in 91% ee.[18] Semihydrogenation

Scheme 2. Total Synthesis of Plakorin and *ent*-Chondrillin



furnished (*Z*)-alkenol **7**, which was subjected to dye-sensitized photooxygenation to afford a 98:2 *syn*/*anti* mixture of 2-peroxy enols **8**. Equilibration in the presence of DTBN and TBHP resulted in a 1:1.25 mixture of recovered **8** and 4-hydroperoxy 1-alcohol **9**, both isolated as single diastereomers. Protection of **9** as the corresponding peroxy ketal was followed by oxidation of the allylic alcohol to form peroxy enone **10**.[10] Deprotection of the hydroperoxide was followed by photocyclization, as per the procedure of Snider, to afford the dioxinol **11**. Treatment with methanolic HF resulted in deprotection of the silyl ether and ketalization to form the methoxydioxin. Oxidation and esterification resulted in a mixture of alkoxydioxins **1** and **2** which were separated with difficulty by normal-phase HPLC.

The spectra of the first (**1**) and second (**2**) eluting isomers exactly matched data previously reported for plakorin and chondrillin, respectively.[6,8,9] The optical rotation obtained for synthetic plakorin (**1**), $[\alpha]_D = +26-29°$, indicated the material to be 85−95% ee.[8] However, the rotation observed for **2**, $[\alpha]_D = -19°$ (c = 0.5, MeOH), is *opposite* in sign to values previously reported for chondrillin.[6,7] We therefore propose 3(*R*),6(*S*) absolute stereochemistry for chondrillin, the enantiomer of the previously reported structure.

In summary, radical rearrangement of the allylic hydroperoxides derived from hydroxyl-directed addition of $^1O_2$ provides a method for the asymmetric synthesis of 1,4-dioxygenated peroxides. The scope and limitations of this methodology, as well as synthetic studies toward chondrillin, are currently under investigation and will be reported in due course.

Acknowledgment. We gratefully acknowledge support from the American Cancer Society (Grant CN-34). NMR spectra were recorded on spectrometers purchased with NIH support (Grant SIG-1-510-RR06307).

Supporting Information Available: ^{1}H spectra for **1** and **2** and experimental procedures for the reactions shown in Scheme 2 (7 pages). See any current masthead page for ordering and Internet access instructions.

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