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Total Synthesis of Peroxyacarnoates A and D: Metal-Mediated Couplings as a Convergent Approach to Polyunsaturated Peroxides

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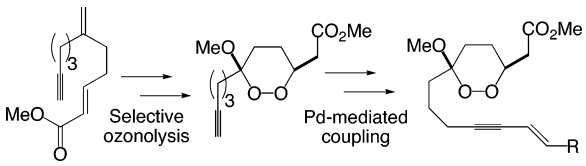
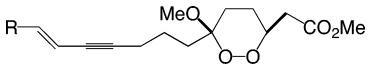
ABSTRACT



The first syntheses of peroxyacarnoates A and D, members of a family of enyne-containing alkoxydioxanes, have been achieved on the basis of chemoselective ozonolysis within a polyunsaturated framework and Pd-mediated cross-couplings of a functionalized 1,2-dioxane.

The peroxyacarnoates are a family of sponge-derived natural products containing polyunsaturated side chains affixed to an alkoxydioxine acetic acid core and displaying activity against fungal and/or cancer cell lines (Table 1).[1,2] No syntheses of either the peroxyacarnoates or the related peroxyplakorates[3] have been reported. We now report the total synthesis of peroxyacarnoates A (**1**) and D (**2**) by a route applicable to any member of the family.

Table 1. Peroxyacarnoates



R	this work	peroxyacarnoate
8-nonenyl	(**1**)	A (ref 1)
nonanyl	(**2**)	D (ref 2)
8-nonynyl		B (ref 1)
8-oxononanyl		C (ref 2)

Several 3-alkoxy-1,2-dioxine acetic acid natural products have been prepared in racemic form through a route involving photooxidation of an enone and photomediated cyclization of the resulting γ-hydroperoxy α,β-unsaturated ketone.[4] More recently, asymmetric syntheses of alkoxydioxine natural products have been reported on the basis of photomediated cyclization of enantiomerically enriched hydroperoxyenones.[5] However, the application of these approaches to synthesis of the peroxyacarnoates or peroxyplakorates is constrained by the challenge of removing the endocyclic alkene in the presence of side chain unsaturation. Similarly, while simplified 3-alkoxy-1,2-dioxane acetates have been prepared through intramolecular conjugate addition of hydroperoxy-2,3-enoates,[6] any approach to the peroxyacarnoates proper must simultaneously accommodate instal-

(1) Yosief, T.; Rudi, A.; Wolde-ab, Y.; Kashman, Y. *J. Nat. Prod.* **1998**, *61*, 491 (peroxyacarnoates A and B).

(2) Fontana, A.; d'Ippolito, G.; D'Souza, L.; Mollo, E.; Parameswaram, P. S.; Cimino, G. *J. Nat. Prod.* **2001**, *64*, 131 (peroxyacarnoic acids A, C, and D).

(3) Kobayashi, M.; Kondo, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 1324.

(4) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1992**, *114*, 1790.

(5) Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem.* **1999**, *64*, 1789.

(6) (a) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2001**, *12*, 69. (b) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281.

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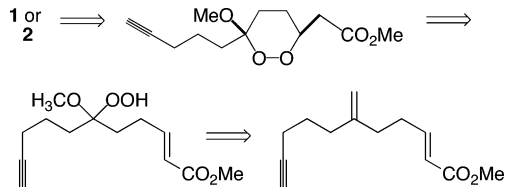
lation of both a reduction-sensitive 1,2-dioxane and an oxidation-sensitive enyne. A possible solution arose from our previous research into carbon−carbon bond constructions compatible with protected hydroperoxides.[7] The successful application of Pd-mediated couplings to a functionalized alkoxydioxane would allow us to employ an oxidation-stable synthon in place of the enyne while also providing a convergent entry approach for the synthesis of any desired peroxyacarnoate. Our synthetic strategy, illustrated in Scheme 1, introduces the enyne side chain via a Pd-mediated sp/sp^2

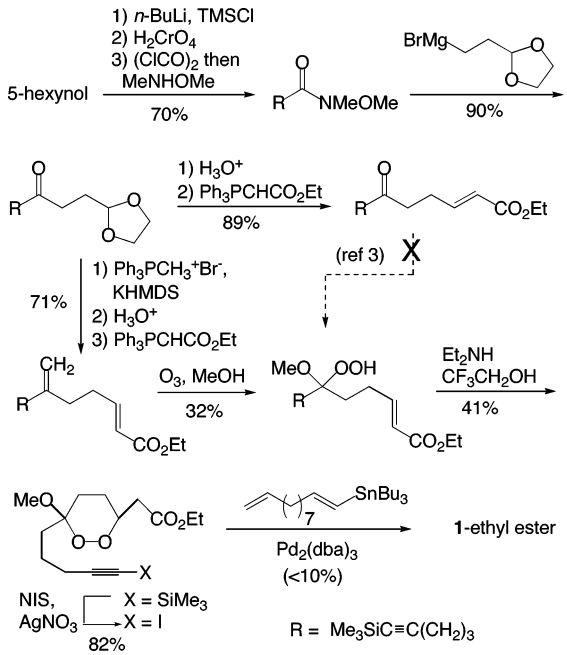
Scheme 1. Retrosynthetic Approach



coupling[8] of an alkynyl-substituted alkoxydioxane, in turn derived from base-promoted conjugate addition of a 6-hydroperoxyenoate. The precursor hydroperoxyacetal will arise through selective ozonolysis of a dienyne.

Enyne introduction could be conceivably accomplished from an alkynyl nucleophile (stannane, silane, or free alkyne) or electrophile (alkynyl iodide). Our model investigations, shown in Scheme 2, were based upon coupling of an alkenyl

Scheme 2. Model Approach to Alkoxydioxanes

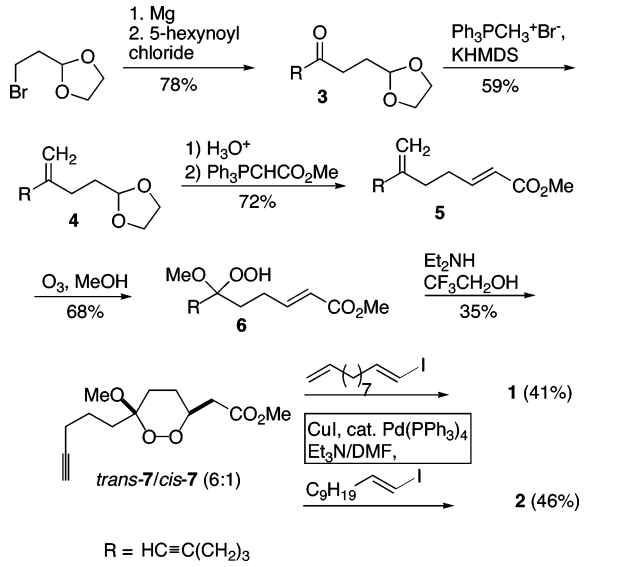


nucleophile with an iodoalkyne. The route began with the conversion of 5-hexyn-1-ol to the Weinreb amide of 6-trimethylsilylhexynoic acid. Acylation of the Grignard reagent derived from 2-bromoethyl-1,3-dioxolane furnished a stable ketoacetal. The keto aldehyde derived from acidic deprotection was subjected to Horner−Emmons homologation to furnish a 6-keto-2-enoate. However, attempts to install the hydroperoxyketal via a reported Sc(OTf)$_3$-promoted hemiketalization produced only traces of the desired product.[6]

We therefore chose to introduce the hydroperoxyacetal via methanolic trapping of a carbonyl oxide. Wittig methylenation of the ketone, followed by ozonolysis in methanol/methylene chloride, furnished the desired 6-hydroperoxy-6-methoxy-2-enoate, accompanied by byproducts derived from cleavage of the enoate. Base-promoted cyclization of the hydroperoxyenoate in trifluoroethanol[6] provided the 1,2-dioxane acetate as a 82:18 mixture of stereoisomers favoring the *trans*-3,6-dialkyl isomer. For the purposes of the model synthesis, the two isomers were carried on as a mixture. Silver-promoted iodination of the trimethylsilylalkyne, followed by Pd-mediated coupling of the resulting iodide with 1-tributylstannyl-1,10-undecadiene, produced enyne-containing product with ^{1}H and ^{13}C spectra corresponding to peroxyacarnoate A.[1] However, the yield for this reaction was consistently less than 10%.

The results of our model studies guided us to a complementary approach based upon coupling of an alkynyl nucleophile with an sp^2 electrophile (Scheme 3). Acylation

Scheme 3. Total Synthesis of Peroxyacarnoates A and D



of the same Grignard reagent with 5-hexynoyl chloride furnished a ketoalkyne, which underwent methylenation to alkene **4**; a preparative route involving minimal purification of ketone **3** provided **4** in 67% overall yield from 5-hexynoic acid. Deprotection and Wittig homologation were achieved under conditions similar to those used before. The selective ozonolysis, which had proven problematic in the model

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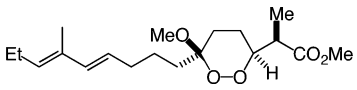
system with regard to undesired oxidation of the enoate, was examined more closely. After some optimization, we found that the best yields of hydroperoxyacetal **6** were obtained by introduction of a dilute solution of O_3/O_2 (reduced generator voltage) into a rapidly stirred and dilute (8 mM) methanolic solution of dienynoate **5**.[9] Diethylamine-catalyzed conjugate addition furnished a 6:1 ratio of *trans*- and *cis*-6-alkoxy-1,2-dioxane-3-acetates, accompanied by a small but variable amount (4−14%) of 6-oxo-2-en-10-undecynoate. Formation of the ketone could be minimized by use of a mixed solvent containing both methanol and trifluoroethanol, by slow introduction of the diethylamine, and by careful monitoring of the reaction to minimize reaction times. The diastereomeric alkoxydioxanes and the ketone, although separable by analytical HPLC, were carried as a mixture through the subsequent coupling. Pd-catalyzed reaction of **7** with (*E*)-1-iodo-1,10-undecadiene, available in approximately 90% geometric purity from Takai homologation of 9-decenal,[10] selectively furnished the (*E*)-enyne. Selective consumption of (*E*)-haloalkenes has been previously observed in Pd-mediated processes.[11] Semipreparative HPLC of the reaction products afforded the *trans*-dioxane peroxyacarnoate A (**1**) and, separately, a mixture of the cis isomer and the ketone byproduct. Attempted acid-catalyzed epimerization ($TsOH{\cdot}H_2O$, MeOH) of the *cis*-alkoxydioxane resulted mainly in decomposition.

The broad utility of the approach is illustrated by the corresponding reaction of alkyne **7** with 1-iodoundecene (2.5:1 *E*/*Z* mixture) to selectively furnish a mixture of the trans and cis diastereomers of **2**. Semipreparative HPLC afforded peroxyacarnoate D (**2**).[12]

In conclusion, we have demonstrated the use of Pd-mediated couplings for the efficient and convergent introduction of sensitive polyunsaturated side chains onto a cyclic peroxide core. Ongoing efforts in our group to extend this approach to peroxyplakorates (eq 1)[3] will be reported in due course.



(1)

Peroxyplakoric acid A_1 methyl ester

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Supporting Information Available: Experimental procedures and spectral characterization for compounds **1**−**7** and comparison of NMR spectra for **2** with previously reported values for **2** and other peroxyacarnoates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Ozonolysis of the corresponding enal proceeded with greater selectivity for attack on the C_6 methylene; however, attempts to prepare the 1,2-dioxane from the resulting 6-hydroperoxy-6-methoxy-2,3-enal furnished only the 2,3-epoxy-6-oxo-alkanal.

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(11) (a) Uenishi, J.; Matsui, K. *Tetrahedron Lett.* **2001**, *42*, 4353. (b) Uenishi, J.; Matsui, K.; Ohmaya, H. *J. Organomet. Chem.* **2002**, *653*, 141.

(12) Chemical shift values reported for aliphatic portions of the side chain of **2** differ significantly from our observations and are also inconsistent with values reported for similar structures (ref 1). See Supporting Information for details.