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Synthesis of α,β-unsaturated Epoxy Ketones Utilizing a Bifunctional Sulfonium/Phosphonium Ylide

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Roozbeh Eskandari,[a] Jeremy P. Hess[a] and Gregory P. Tochtrop*[a]

Herein, a new protocol for rapid synthesis of α,β-unsaturated epoxy ketones utilizing a bifunctional sulfonium/phosphonium ylide is described. This approach comprises two sequential chemoselective reactions between sulfonium and phosphonium ylides and two distinct aldehydes, which allows for the rapid construction of a variety of unsymmetric α,β-unsaturated epoxy ketones. This methodology allows the rapid construction of the core reactive functionality of a family of lipid peroxidation products, the epoxyketooctadecenoic acids, but can be further broadly utilized as a useful synthon for the synthesis of natural products, particularly those derived from oxidized fatty acids. Accordingly, a protocol utilizing this approach to synthesize the epoxyketooctadecenoic acid family of molecules is described.

The ability to quickly and efficiently link molecules through carbon-carbon bonds is essential for the synthesis of large molecules. Ylide-based coupling reactions such as the Wittig olefination[1] and the Johnson-Corey-Chaykovski epoxidation[2] have become cornerstones of synthetic strategy. While bifunctional ylides have been utilized to produce symmetric molecules[3], chemoselective routes generating unsymmetrical products remains largely unexplored chemistry. The first demonstration of asymmetric products with bifunctional ylides took advantage of differences in reactivity between phosphorous ylides in the context of cyclobutane.[4] More recently, Nagorny *et al.* published a route to access asymmetric polyenes utilizing more diverse forms of bifunctional ylides.[5]

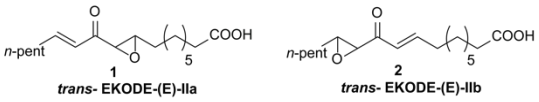


Fig.1 Type-II EKODE molecules

Our primary interest in bifunctional ylides stems from our desire to design more tractable synthetic routes to the epoxyketooctadecenoic acids (EKODEs) in order to probe their biological relevance. The methods described herein are capable of generating type-II EKODEs (**Fig. 1**) and their derivatives, further enabling the production of derivatives not possible with existing methodology.[6]

To understand the relevance of the α,β-unsaturated epoxy ketone and the methodology presented, one must begin by understanding the biosynthetic context of the EKODEs. Polyunsaturated fatty acids (PUFAs) are primarily structural components of membranes. In recent years, their significance has increased as studies have demonstrated the ability of PUFAs to function as signaling molecules.[7] A characteristic trait of almost all naturally occurring PUFAs is an alternating series of *cis* double bonds generating doubly allylic positions that define the reactivity of these molecules. During periods of oxidative stress, the concentration of reactive oxygen and nitrogen species (ROS/RNS) overwhelms the body's antioxidant systems. The non-enzymatic ROS/RNS can subsequently perform radical hydrogen abstraction at the doubly allylic carbon, leaving a stabilized radical (**Fig. 2**) that can further propagate to form lipid peroxidation (LPO) products.[8]

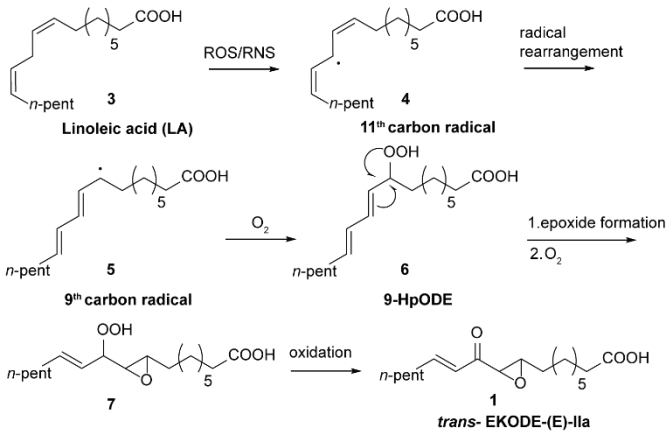


Fig.2 Non-enzymatic formation of *trans*-EKODE-(*E*)-IIa from linoleic acid (**3**)

[a] *Department of Chemistry, Case Western Reserve University, Cleveland, Ohio, USA. E-mail: gpt6@case.edu*

† Electronic Supplementary Information (ESI) available: reagents and procedures for new compounds with their ^{1}HNMR and ^{13}CNMR. See DOI: 10.1039/x0xx00000x

The postulated non-enzymatic formation of type-II EKODEs from the initial stabilized radical is summarized in **Fig. 2.** The conversion of linoleic acid (**3**) to either 9- or 13-hydroperoxy (HpODE) followed by rearrangement to an epoxy functionality leads to a second site for oxygenation or a new hydroperoxide at the C-11 position (**7**). This position is eventually converted to a ketone with further oxidation to afford the final α,β-unsaturated epoxy ketone**.**

The accumulation of LPO products have been known to track with the progression of a number of diseases involving oxidative stress. It is currently unknown whether LPO products have a causative effect in disease progression or simply increase in concentration as a result of the disease.[9] Past work in our laboratory on 4-hydroxy-2(*E*)-nonenal, a prevalent LPO product, has identified a novel signaling role[10] and an evolved catabolic pathway[11, 12] of particular interest in the type-II EKODE series is the electrophilic reactivity of the α,β-unsaturated epoxy ketone that predisposes these molecules to a unique reactivity profile among LPO products. Specifically, it is predicted that the EKODEs could potentially crosslink proteins due to their multiple electrophilic sites. Additionally, the regiochemistry of the unsaturated carbonyl relative to the epoxide is expected to facilitate the generation of stable LPO adducts via a reaction cascade involving a Michael reaction followed by an epoxide opening rearrangement. Because of this and the stable LPO adducts that would result, these molecules would be predicted to be superior in terms of monitoring oxidative stress damage via immunohistochemical methods. Further, in recent years, EKODEs have displayed novel signaling roles in disease states,[13], and hormone production.[14] The only reported synthesis for the EKODE-II molecules involves the generation of the reactive core of the molecules via an aldol, epoxidation, and elimination sequence.[6] A fundamental drawback of this route is the multiple manipulation steps required after the reactive core is constructed. A critical tool to move this field forward is the development of better synthetic methods to increase efficiency and allow access to novel derivatives not currently accessible.

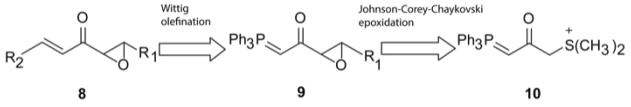
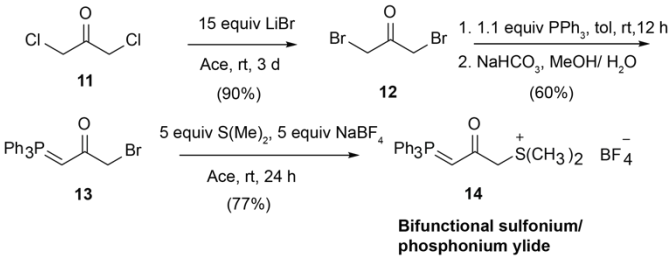


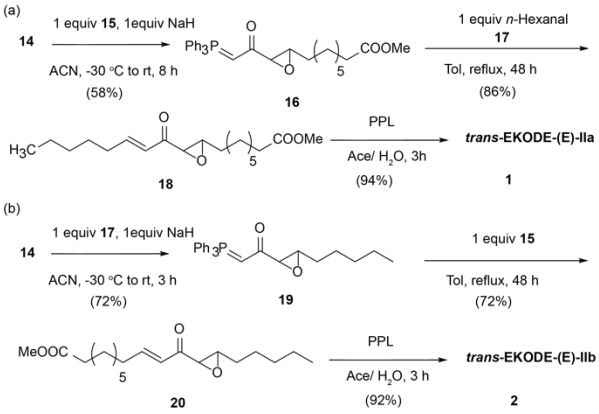
Fig.3 Retrosynthetic analysis of α,β-unsaturated epoxy ketones

A retrosynthetic analysis (**Fig. 3**) targeting the core of α,ß-unsaturated epoxy ketones revealed that this functionality could be assembled in two steps from a bifunctional sulfonium/phosphonium ylide. In the case of the phosphonium ylide, the carboaninon is stabilized by the adjacent heteroatom rather than the corresponding sulfonium derivative. This allows chemoselective reactivity of the sulfonium ylide with electrophiles such as aldehydes under basic conditions.[15, 16] This is followed by the addition of a second aldehyde to initiate a Wittig reaction with selectivity of sulfonium versus phosphonium ylides.[17] While selectivity in ylide chemistry has been observed previously, this work represents the first example of a bifunctional ylide that can undergo asymmetric sequential reactions with aldehydes to form α,β-unsaturated epoxy ketones.



Scheme 1 Synthesis of Bifunctional sulfonium/phosphonium ylide (**14)**

Scheme 1 shows the detailed synthesis of bifunctional sulfonium/phosphonium ylide (**14**). Commercially available 1,3-dichloroacetone (**11**) undergoes halogen exchange to 1,3-dibromoacetone (**12**) when equilibrated in a solution containing excess lithium bromide in 90% yield. A single bromine moiety can be exchanged with triphenylphosphine in 60% yield, and workup in a basic solution provides the phosphonium ylide (**13**) in high yield. The final step is to equilibrate with an excess of dimethyl sulfide and sodium tetrafluoroborate to form the salt of the sulfonium ylide (**14**) in 77% yield. The overall yield for formation of the bifunctional ylide was 42%.



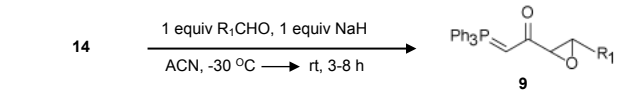
Scheme 2 Synthesis of *trans*-EKODE-(*E*)-IIa and -IIb

We initially examined bifunctional ylide (**14**) for its ability to synthesize the *trans*-EKODE-II family of molecules. Aldehydes were either purchased from commercial sources (*n*-hexanal) or made through known procedures, methyl 9-oxononanoate (**15**) was prepared from ozonolysis of methyl oleate.[18] The bifunctional ylide (**14**) was reacted with either *n*-hexanal (**17**) or methyl 9-oxononanoate (**15**). This first equivalent of aldehyde is reacted at low temperature to ensure only the Johnson-Corey-Chaykovski reaction occurs to form the α-epoxy-phosphonium ylide intermediates (**19, 16**). Formation of the epoxide with *n*-hexanal occurs much faster at lower temperature (0 °C for 3 h). However, methyl 9-oxanonoate needs to be warmed to room temperature and requires extended time to complete the reaction (rt for 8 h). The yields for these reactions were 72 and 58 percent respectively. An equivalent of the

remaining aldehyde at higher temperature undergoes an olefination to yield the methyl ester of the desired EKODEs (**18, 20**) with 86 and 72 percent yield. The

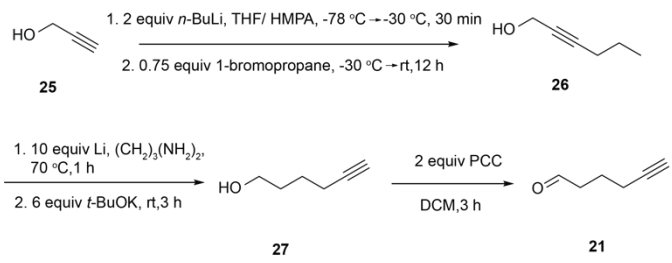
olefination reaction gave the primary *trans* stereoisomer. These molecules were hydrolyzed by porcine pancreas lipase (PPL) to afford *trans*-EKODE-IIa (**1**) and *trans*-EKODE-IIb (**2**) in quantitative yields (experimental section). The selectivity of lipase provided a means of esters hydrolysis without effecting of α,β-unsaturated epoxy ketones.

Table 1 Aldehydes utilized in Johnson-Corey-Chaykovski reaction and their corresponding α-epoxy-phosphonium ylides



entry	aldehyde (R_1CHO)	product	yield(%)
1	15	16	58
2	17	19	72
3	21	22	67
4	23	24	70

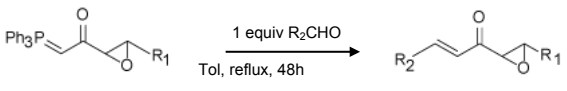
Due to our interest in studying the physiology of the EKODE-II family, we designed a number of derivatives that could be useful as probes in our studies. Isotopic labeling of the terminal methyl can serve as a probe for metabolic tracing studies. This derivative can be synthesized by exchanging hexanal with its deuterated form ($^2H_{11}$-hexanal) (**23**) (electronic supplementary information (ESI)). A terminal alkyne tag possesses the strategic ability to be utilized in a variety of tagging experiments. For example, this molecule can be utilized in alkyne-tagged Raman spectroscopy to track uptake and localization of lipids.[19] In addition, alkynated lipids can be used as click-MS reporters to study their metabolism[20] or in target identification studies.[21]



Scheme 3 Synthesis of terminal alkyne

In order to synthesize this EKODE analogue, we first needed to synthesize 5-hexynal (**Scheme 3**). Propargyl alcohol (**25**) was reacted with *n*-butyllithium and treated with *n*-bromopropane to give (**26**). Next, an alkyne-zipper reaction induced by a *tert*-butoxide afforded the rearranged alkyne as seen in product (**27**). Finally, oxidation with PCC afforded aldehyde (**21**)**.** With precursors in hand, both deuterium-labeled and alkyne-terminal analogues of *trans*-EKODE-IIa and -IIb were synthesized using the general protocol for EKODE synthesis as described above. (**Table 1 and 2**)

Table 2 Aldehydes utilized in Wittig reaction and their corresponding α,ß-unsaturated epoxy ketones



entry	substrate	aldehyde (R_2CHO)	product	yield(%)
1	16	17	18	86
2	16	21	28	81
3	16	23	29	73
4	19	15	20	72
5	22	15	30	65
6	24	15	31	62

In summary, a new method has been developed utilizing a bifunctional sulfonium/phosphonium ylide that is capable of efficient, asymmetric synthesis of α,ß-unsaturated epoxy ketones that avoids conventional, low-yielding aldol reactions. Here, our synthon not only provides gram quantities of these products but in the case of the EKODEs, represents a strategically superior approach to the synthesis of these inherently reactive molecules. Importantly, the methodology outlined here generates the reactive core of the EKODEs as the final step of molecular construction, save ester hydrolysis. This was critical when we were analyzing previous and alternate possible routes using known methodology, and understanding why substrate scope simply could not be expanded beyond known reactions for established routes. While this post-hoc analysis of constructing reactive functional groups during the final steps as a matter of synthetic strategy may seem obvious, it is surprising how often this axiom is not followed in favor of know methods. This method outlined here further provide an affordable synthetic route in which the addition of expensive isotope-labeled moieties occurs at later stages without carrying them through multiple synthetic steps. We utilized this synthon to generate *trans*-EKODE-IIa (**1**), *trans*-EKODE-IIb (**2**), and a

number of derivatives needed to study the physiology of these bioactive lipid metabolites. In addition, this synthon can be used to generate a versatile precursor for other molecules such as epoxy-dehydroparadol and dehydrogingerol, craterellynes, and yashabushiketodiol. Since most oxidized lipids generate palindromic functional groups around double allylic positions, we anticipate this methodology to be more broadly applicable as more of these oxidized lipids are discovered in the years to come.

Methods: Detailed methods are provided in electronic supplementary information (ESI). General methods are below.

General procedure; Johnson–Corey–Chaykovsky reaction: An oven-dried 50- mL, two-necked, round-bottomed flask, containing a magnetic stirring bar was sealed under argon with two rubber septa, one of which contains a needle adapter to an argon-inlet. The solution was cooled in a dry ice-ethanol bath at −30 °C. The flask was charged with 2 mmol of bifunctional Sulfonium/Phosphonium ylide and 2 mmol sodium hydride (80 mg, 60% in mineral oil) and 2 mmol of desired aldehyde and 30 mL acetonitrile. The reaction mixture was continued stirring while warming to room temperatures for 3 hours. The reaction mixture was neutralized with aqueous saturated NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL), and the combined organic phases dried with anhydrous sodium sulfate and concentrated under reduced pressure. Purification by column chromatography afforded desired epoxy products.

General procedure; Wittig reaction: An oven-dried 50- mL round-bottomed flask, containing a magnetic stirring bar charged with 1 mmol of desired epoxy from the previous reaction and 1 mmol of desired aldehyde, and 10 mL toluene. The mixture was heated under reflux overnight, allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure. Purification by column chromatography afforded α,β-unsaturated keto epoxide products.

R.E. Carried out the experiments and wrote the manuscript with support from J.P.H. G.P.T supervised the project and assisted in writing and editing the manuscript.

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Conflicts of interest

There are no conflicts to declare.

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