OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Stereochemistry of Linoleic Acid Esters of Hydroxy Linoleic Acids

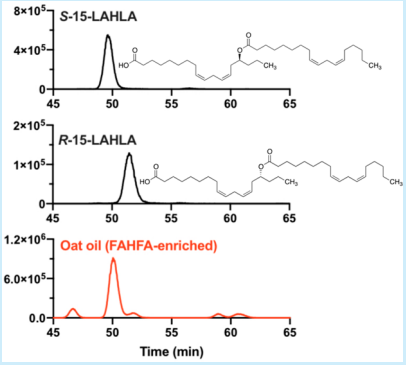
Huijing Wang,[†] Matthew J. Kolar,[‡] Tina Chang,[‡] José Rizo,[†] Srihari Konduri,[†] Clare McNerlin,[†] Alan Saghatelian,[‡] and Dionicio Siegel*[,†]

[†]Skaggs School of Pharmacy and Pharmaceutical Sciences, UC San Diego, 9500 Gilman Drive, La Jolla, California 92093-0934, United States

[‡]Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037-1002, United States

Supporting Information

ABSTRACT: The syntheses of linoleic acid esters of hydroxy linoleic acids (LAHLAs) present in oat oil and human serum have been achieved, providing access to material for testing and the determination of the stereochemistry of the natural compounds. While 9- and 13-LAHLAs were found to be a mixture of enantiomers 15-LAHLA is generated in a single optical form in oat oil. The stereochemistry of 15-LAHLA in oat oil was found to be opposite to that reported for digalactosyldiacylglycerol that possesses an embedded 15-LAHLA.



Fatty acid esters of hydroxy fatty acids (FAHFAs) are oxidized and functionalized fatty acids that represent a new and growing class of signaling lipids. Following from the first discovery of FAHFAs in 2014,[1] these lipids have been found in organisms ranging from plants to humans.[1,2] In their structurally simplest form, FAHFAs possess a saturated, monooxygenated fatty acid bound through an ester linkage to a saturated fatty acid. The most studied of the FAHFAs to date has been the palmitic acid ester of 9-hydroxy stearic acid (9-PAHSA) which has shown promising anti-inflammatory activity, particularly in colitis and diabetic models of disease[1,2] (Figure 1). In addition to 9-PAHSA, related structures have been found with a remarkable diversity in the positioning of the ester linkage, the lengths of the hydroxy fatty acid (HFA), and composition of the fatty acid (FA), providing a structurally diverse set of endogenous compounds that have yet to be explored. Proceeding from the saturated FAHFAs, there is increasing interest in unsaturated FAHFAs with both the HFA and FA bearing unsaturation as the compounds reported to date have been characterized as having improved anti-inflammatory activities relative to saturated FAHFAs. Docosahexaenoic acid ester of 13-hydroxy linoleic acid (13-DHAHLA) (Figure 1) has been shown to possess anti-inflammatory and pro-resolving properties with greater potency than 9-PAHSA.[2b] Similarly, linoleic acid ester of 13-hydroxy linoleic acid (13-LAHLA) characterized from oat oil, the predominant LAHLA isomer in human serum after oat oil ingestion, and an endogenous lipid in mouse and human adipose tissue were found to have enhanced anti-inflammatory effects relative to 9-PAHSA.[3] Comparison of the anti-inflammatory effect of 13-LAHLA and 9-PAHSA on suppression of LPS-stimulated cytokine expression in RAW 264.7 macrophages revealed that 13-LAHLA had a much greater effect. Additionally, mRNA levels of iNOS and COX-2 in RAW 264.7 cells were also suppressed by 13-LAHLA when cells were first stimulated with lipopolysaccharide (LPS).[3]

FAHFAs that originate from unsaturated fatty acids, particularly in the HFA portion, have been studied to a lesser extent than the saturated FAHFAs as a result of difficulties in accessing material for testing through laboratory syntheses. The synthesis of saturated FAHFAs has proven successful using different strategies,[1,2g,4] and enantioselective syntheses[4c] have been achieved. The synthetic routes to saturated derivatives benefit from less functional group incompatibility

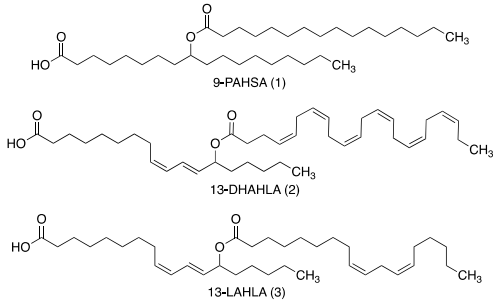


Figure 1. Structures of 9-PAHSA, 13-DHAHLA, and 13-LAHLA.

Received: August 29, 2019

DOI: 10.1021/acs.orglett.9b03054
Org. Lett. XXXX, XXX, XXX−XXX

and more options for starting material selection. The syntheses of 9-, 13-, and 15-LAHLAs were targeted, given the promising effects seen in the previous studies of LAHLAs[3] and the connection of LAHLAs to previously characterized estolides[5] (Figure 2). Both 9- and 13-LAHLA could be produced

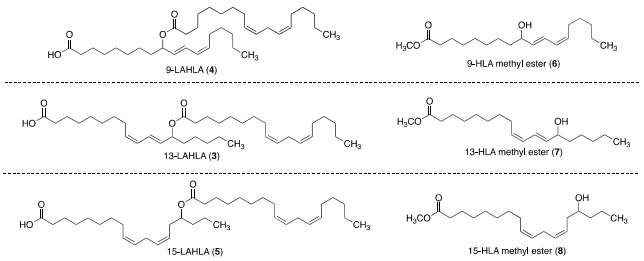


Figure 2. Structures of 9-, 13-, and 15-LAHLAs and the methyl esters of the corresponding HLAs.

through an enzymatic process delivering a single enantiomer or could be envisioned to arise through auto-oxidation of linoleic acid. The isomer 15-LAHLA would likely require enzyme-catalyzed oxidation to replace the homoallylic hydrogen with oxygen.

Previously, the structure of a galactolipid digalactosyldiacylglycerol (DGDG) found in oat oil possessed 15-LAHLA embedded within the full structure.[6] In addition to characterizing the atomic connectivity, olefins as all *cis*, and the positioning of the ester linkage at C-15 of linoleic acid, the stereochemistry of the ester linkage of the 15-LAHLA was determined to be *R*- through degradation studies and comparison to *N*-(propionoxyacy)-L-phenylalanine methyl ester derivatives of 3(*R*)- and 3(*R*,*S*)-hydroxy-hexanoic acid.[7] Following from this, additional DGDGs were characterized with multiple linked 15-HLAs (Figure 3).[5b] Alternatively, both

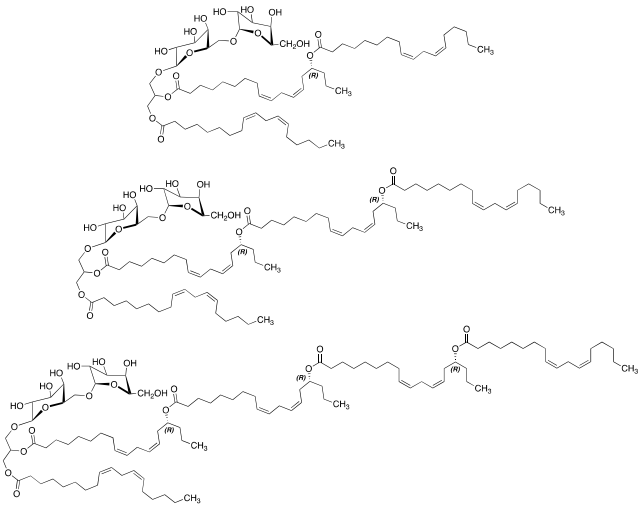


Figure 3. Structures of digalactosyldiacylglycerol (DGDG) found in oat oil that possess embedded 15-LAHLA.

9-LAHLA and 13-LAHLA could be produced through enzymatic processes or potentially auto-oxidation given the previously characterized 9-HLA and 13-HLA also referred to as 9- and 13-HODE.[8] With this as a starting point, racemic syntheses were first developed to generate authentic standards for comparison to isolated LAHLAs.

LAHLAs are comprised of an ester-bound linoleic acid connected to an HLA (Figure 2). Disconnection to reveal the HLA components provided the subtarget for synthesis as the combination of the unsaturated HLAs with the LA, and selective ester hydrolysis of a terminal methyl ester over the internal ester joining the HLA and LA was supported by previous syntheses of saturated FAHFAs.[4c,f] These racemic syntheses of the HLAs were achieved first, along with synthesis of nonracemic LAHLA pending identification of enzymatically formed, chiral LAHLAs. Two routes were developed for the three HLA methyl esters **6**, **7**, and **8**. For 9- and 13-LAHLA, the HLAs **6** and **7** could be accessed in racemic form together by selenium dioxide oxidation of the methyl ester of linoleic acid **9** (Scheme 1).[9] The synthesis of 15-HLA proved more challenging and required eight steps and utilized Sonogashira cross-coupling reaction and partial hydrogenation. While this route was first achieved generating racemic material, the translation to an enantioselective synthesis could be readily achived.[10]

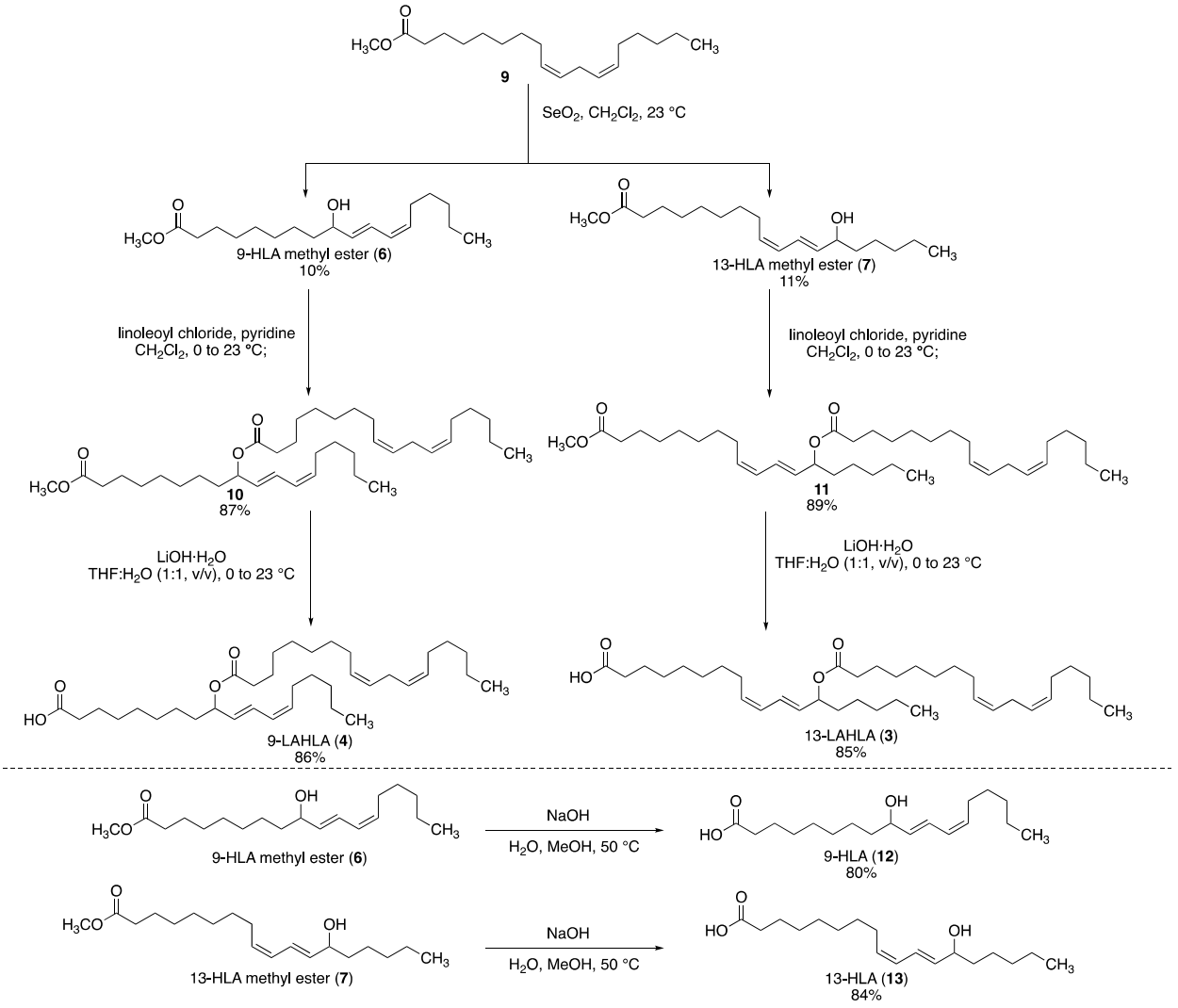
For our purposes, determining the stereochemistry of natural LAHLAs and generating material for testing our syntheses of 9-LAHLA and 13-LAHLA required the preparation of large quantities of the intermediate methyl esters of 9-HLA and 13-HLA. Synthetic efforts to prepare 9- and 13-HLA (also known as 9- and 13-HODE)[8] have been reported. The concise approach employing a selenium dioxide-mediated oxidation of the methyl ester of linoleic acid (Scheme 1)[9] was ideal as it proceeded in one step and generated both methyl esters of 9-HLA and 13-HLA in a single reaction. Key to the success of this reaction was our ability to purify the products by silica gel column chromatography using a stepwise gradient of mobile phases consisting of hexanes/ethyl acetate to get the pure isomers **6** and **7**, removing the undesired *E*/*E*-isomers.[9] Both of these compounds were hydrolyzed to generate 9-HLA and 13-HLA and are used for controls in testing anti-inflammatory effects.[3] Steglich esterification of the methyl esters of 9-HLA and 13-HLA (**6** and **7**) with LA generated the methyl esters of 9- and 13-LAHLA (**10** and **11**). Selective hydrolysis of the methyl ester using LiOH·H_2O in turn generated 9-LAHLA (**4**) and 13-LAHLA (**3**) in racemic form.

As shown in Scheme 2, the synthesis of 15-LAHLA proceeded from alcohol **16**, obtained by the regioselective opening of epoxide **14** with THP-protected propargyl alcohol **15**.[10] Removal of the THP group of **16** with TsOH·H_2O generated diol **17**. Selective conversion of the propargylic alcohol to a bromine, in the presence of the secondary homopropargylic alcohol, was achieved with triphenylphosphine and carbon tetrabromide, yielding bromine **18**.[11] The Sonogashira coupling[12] of bromine **18** and the known alkyne **19**[13] in the presence of CuI, NaI, and Cs_2CO_3 in DMF yielded the skipped diyne **20**. Partial hydrogenation of **20** with Brown's P-2 Ni catalyst in the presence of ethylene diamine[14] afforded the key intermediate, corresponding to the all-(*Z*)-diene of the methyl ester of 15-HLA (**8**) in 85% yield. The reduction was highly selective, and no over-reduced products or olefinic isomers were observed. Subsequently, esterification of the methyl ester of 15-HLA (**8**) with linoleic acid using a Steglich esterification yielded the methyl ester of 15-LAHLA. Selective hydrolysis of the methyl ester done over the LA ester generated 15-LAHLA (**5**).

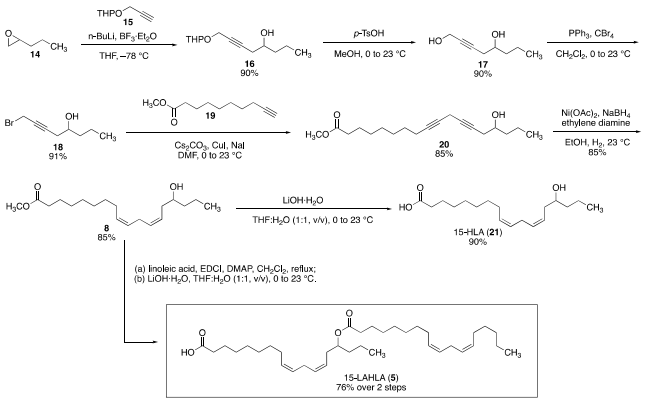
We have previously developed an LC-MS chiral separation method for analyzing PAHSAs.[4c] Using a modified version of

DOI: 10.1021/acs.orglett.9b03054
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of 9-HLA, 13-HLA, and 9- and 13-LAHLAs from Methyl Linoleate



Scheme 2. Synthesis of 15-HLA and 15-LAHLA



this method, we were able to achieve resolution of the 9-, 13-, and 15-LAHLA stereoisomers (Figure 4). Specifically, LAHLA resolution was achieved over 80 min using a Lux Cellulose-3 chiral column (3 μm, 250 × 4.5 mm, Phenomenex) with an isocratic flow rate of 0.15 mL/min of 97:3 MeOH:H2O + 0.1% formic acid solution at 35 °C. Mass spectrometry settings were as previously established.[4c] LAHLAs were analyzed using multiple reaction monitoring in positive ionization mode, monitoring the following precursor-to-product ion transitions, m/z 557.5 → 279.2 and m/z 557.5 → 295.2, which correspond to the parent LAHLA to linoleic acid and hydroxy linoleic acid, respectively. Analyzing the 15-LAHLA stereoisomers revealed that the *S*-enantiomer elutes earlier than the *R*-enantiomer (Supporting Information S1). This trend is consistent with our previous studies analyzing PAHSA stereoisomers with the same column[4c] and most likely holds true, with the earlier peaks of rac-13- and rac-9-LAHLA being the *S*-enantiomer. Of note, the smaller area under the curve of the *R*-15-LAHLA compared to *S*-15-LAHLA is due to the addition of less of the *R*-15-LAHLA stereoisomer.

Oat oil contains 9-, 13-, and 15-LAHLA.[3] Although 13-LAHLA is the predominant isomer in human serum after ingestion, 15-LAHLA was shown to be the most abundant isomer in pure oat oil. In analyzing FAHFA-enriched oat oil (Figure 4, bottom panel), we clearly see five peaks which correspond to both enantiomers of 9- and 13-LAHLA and a single *S*-15-LAHLA stereoisomer (for enantioselective synthesis vida infra). Interestingly, this is opposite to that reported for DGDGs from oat oil (Figure 3).

While 9- and 13-LAHLA were racemic in oat oil, 15-LAHLA was a single optical form; therefore, a synthesis of enantiopure *S*-15-LAHLA (**5**-*S*) and *R*-15-LAHLA (**5**-*R*) was developed.

DOI: 10.1021/acs.orglett.9b03054
Org. Lett. XXXX, XXX, XXX−XXX

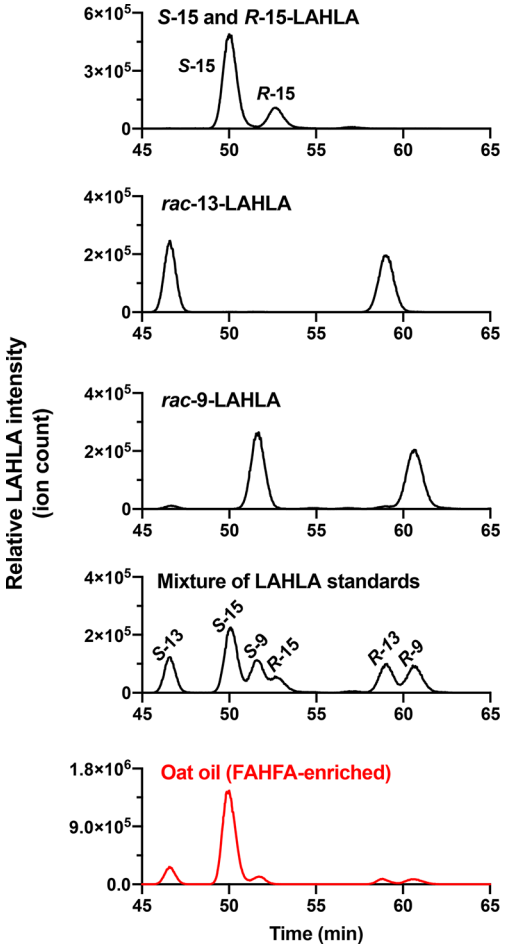
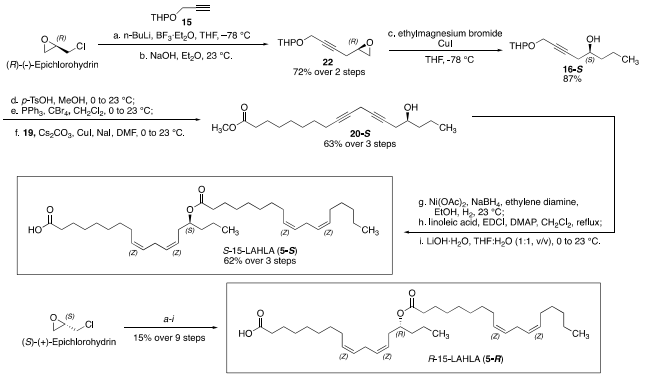


Figure 4. LC-MS chromatograms showing the retention times of *S*-15-LAHLA and *R*-15-LAHLA (top panel), *rac*-13-LAHLA, *rac*-9-LAHLA, a mixture of LAHLA standards, and LAHLAs in FAHFA-enriched oat oil. Stereopure *S*-15-LAHLA and *R*-15-LAHLA were combined (top panel).

This used the same strategy as the racemic synthesis starting instead from nonracemic epichlorohydrin, proceeding through either **16**-*S* or **16**-*R* (Scheme 3). The synthesis of *S*-15-LAHLA (**5**-*S*) started with the regioselective ring opening of (*R*)-(−)-epichlorohydrin with THP-protected propargyl alcohol followed by epoxide formation to yield epoxide **22**, which then underwent a second epoxide opening reaction at the less substituted position, using ethylmagnesium bromide in the presence of cuprous iodide to afford secondary alcohol **16**-*S*.[10] The relay of enantiopurity was determined by derivatization of **16**-*S* as the Mosher ester[15] with the diastereomeric ratio found to be 99:1 (Supporting Information, SI). Starting from secondary alcohol **16**-*S*, enantiopure *S*-15-LAHLA (**5**-*S*) was synthesized in an analogous manner with the racemic 15-LAHLA (**5**). Similarly, *R*-15-LAHLA (**5**-*R*) was obtained through the same ten-step sequence, substituting (*S*)-(+)-epichlorohydrin as the starting material.

Scheme 3. Synthesis of *R*/*S*-15-LAHLA



Recent studies have shown that naturally occurring 13-LAHLA serves as a beneficial lipid with the ability to abrogate inflammation by reducing interleukin 6 (IL-6) secretion upon lipopolysaccharide (LPS) treatment.[3] To assess the relative anti-inflammatory potentials of the LAHLAs and enantiopure *R*-15-LAHLA and *S*-15-LAHLA, the same *in vitro* assay was used (Figure 5). LPS-stimulated RAW 264.7 cells were treated with either DMSO or select LAHLAs. Subsequent quantitation of IL-6 following treatment determined the effectiveness of these lipids in inhibiting inflammatory signaling. Consistent with previous findings, individual treatments with 9-, 13-, or 15-LAHLA successfully reduced secretion of IL-6, further supporting the anti-inflammatory characteristics of LAHLAs (Figure 5). Among the natural lipids tested, 15-LAHLA was the most potent lipid, potentiating more than 50% inhibition of IL-6 secretion. Such differences in cytokine reduction highlight that a structure−activity relationship in the LAHLA lipid family exists and that the positioning of the ester linkage is important. The stereochemistry of 15-LAHLA could also affect the activity, and we observed that *S*-15-LAHLA inhibits IL-6 secretion more effectively than either *R*-15-LAHLA or the racemic 15-LAHLA mixture alone. To ensure that the reductions in IL-6 levels were not attributed to loss of cell viability due to cytotoxicity, we measured the percentage of viable cells post-treatment and found that cells remained viable throughout the treatment (SI Figure S2).

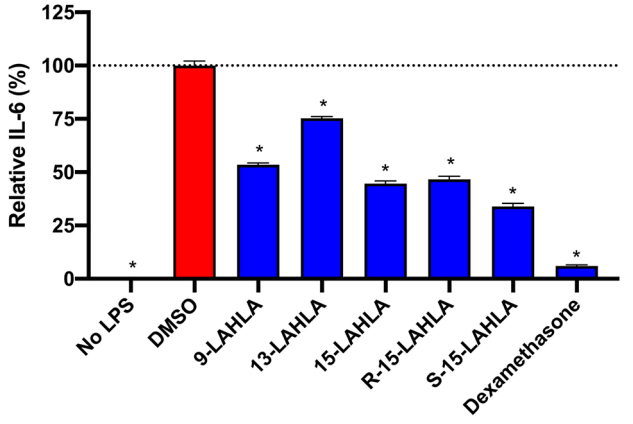


Figure 5. Testing LAHLAs for anti-inflammatory activities. Quantitation of IL-6 following a 20 h treatment of natural LAHLAs and synthetic *R*-15-LAHLA and *S*-15-LAHLA in LPS-stimulated RAW 264.7 cells. Dexamethasone was included as a positive control. Data are means ± SEM with $n = 3$ per treatment at 25 μM. *$p <$ 0.0001 versus DMSO by one-way ANOVA.

In summary, linoleic acid esters of hydroxy linoleic acids (LAHLAs), a family of unsaturated FAHFAs, present in oat oil and human serum, are anti-inflammatory lipids in which their ability to mitigate proinflammatory signaling is dependent on their chemical structures. Relative to saturated FAHFAs such

DOI: 10.1021/acs.orglett.9b03054
Org. Lett. XXXX, XXX, XXX−XXX

as 9-PAHSA,[3] 13-LAHLA dose treatments demonstrated an improved IC_{50} in IL-6 reduction, suggesting that unsaturated FAHFAs may be more superior in suppressing acute inflammation (SI Figures S3 and S4). The role of structural chemistry and stereochemistry in LAHLA and how this shapes the lipids' ability to mediate acute inflammation were made possible through synthesis. Three members of LAHLAs, 9-LAHLA, 13-LAHLA, and15-LAHLA have been synthesized to provide material for testing and analysis. In analyzing FAHFA-enriched oat oil, 9- and 13-LAHLA are found to be naturally racemic mixtures, while 15-LAHLA is generated as a single optical form, *S*-15-LAHLA. Interestingly, the stereochemistry of 15-LAHLA was found to be the opposite of that reported for digalactosyldiacylglycerol that possessed embedded 15-LAHLA. In addition, 15-LAHLA, specifically *S*-15-LAHLA, demonstrated potent anti-inflammatory activities and warrants further study of the new method of laboratory access through synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03054.

Experimental details and characterization of new compounds (^1H and ^{13}C spectra) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: drsiegel@ucsd.edu (Dionicio Siegel).

ORCID

Alan Saghatelian: 0000-0002-0427-563X

Dionicio Siegel: 0000-0003-4674-9554

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank the Dr. Brendan Duggan for NMR experiment assistance and analysis. NMR spectra were collected at the UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences NMR Facility.

■ REFERENCES

(1) Yore, M. M.; Syed, I.; Moraes-Vieira, P. M.; Zhang, T.; Herman, M. A.; Homan, E. A.; Patel, R. T.; Lee, J.; Chen, S.; Peroni, O. D.; Dhaneshwar, A. S.; Hammarstedt, A.; Smith, U.; McGraw, T. E.; Saghatelian, A.; Kahn, B. B. *Cell* **2014**, *159* (2), 318−32.

(2) (a) Lee, J.; Moraes-Vieira, P. M.; Castoldi, A.; Aryal, P.; Yee, E. U.; Vickers, C.; Parnas, O.; Donaldson, C. J.; Saghatelian, A.; Kahn, B. B. *J. Biol. Chem.* **2016**, *291* (42), 22207−22217. (b) Kuda, O.; Brezinova, M.; Rombaldova, M.; Slavikova, B.; Posta, M.; Beier, P.; Janovska, P.; Veleba, J.; Kopecky, J.; Kudova, E.; Pelikanova, T.; Kopecky, J. *Diabetes* **2016**, *65* (9), 2580−2590. (c) Zhang, T.; Chen, S.; Syed, I.; Stahlman, M.; Kolar, M. J.; Homan, E. A.; Chu, Q.; Smith, U.; Boren, J.; Kahn, B. B.; Saghatelian, A. *Nat. Protoc.* **2016**, *11* (4), 747−63. (d) Vijayakumar, A.; Aryal, P.; Wen, J.; Syed, I.; Vazirani, R. P.; Moraes-Vieira, P. M.; Camporez, J. P.; Gallop, M. R.; Perry, R. J.; Peroni, O. D.; Shulman, G. I.; Saghatelian, A.; McGraw, T. E.; Kahn, B. B. *Cell Rep.* **2017**, *21* (4), 1021−1035. (e) Brezinova, M.; Kuda, O.; Hansikova, J.; Rombaldova, M.; Balas, L.; Bardova, K.; Durand, T.; Rossmeisl, M.; Cerna, M.; Stranak, Z. *Biochim. Biophys. Acta, Mol. Cell Biol. Lipids* **2018**, *1863* (2), 126−131. (f) Zhu, Q. F.; Yan, J. W.; Zhang, T. Y.; Xiao, H. M.; Feng, Y. Q. *Anal. Chem.* **2018**, *90* (16), 10056−10063. (g) Pflimlin, E.; Bielohuby, M.; Korn, M.; Breitschopf, K.; Lohn, M.; Wohlfart, P.; Konkar, A.; Podeschwa, M.; Barenz, F.; Pfenninger, A.; Schwahn, U.; Opatz, T.; Reimann, M.; Petry, S.; Tennagels, N. *Cell Metab.* **2018**, *28* (2), 217−227. (h) Syed, I.; Lee, J.; Moraes-Vieira, P. M.; Donaldson, C. J.; Sontheimer, A.; Aryal, P.; Wellenstein, K.; Kolar, M. J.; Nelson, A. T.; Siegel, D.; Mokrosinski, J.; Farooqi, I. S.; Zhao, J. J.; Yore, M. M.; Peroni, O. D.; Saghatelian, A.; Kahn, B. B. *Cell Metab.* **2018**, *27* (2), 419−427. (i) Syed, I.; Lee, J.; Peroni, O. D.; Yore, M. M.; Moraes-Vieira, P. M.; Santoro, A.; Wellenstein, K.; Smith, U.; McGraw, T. E.; Saghatelian, A.; Kahn, B. B. *Cell Metab.* **2018**, *28* (4), 543−546.

(3) Kolar, M. J.; Konduri, S.; Chang, T.; Wang, H.; McNerlin, C.; Ohlsson, L.; Harrod, M.; Siegel, D.; Saghatelian, A. *J. Biol. Chem.* **2019**, *294* (27), 10698−10707.

(4) (a) Khan, B. B.; Herman, M. A.; Saghatelian, A. P. US2015/0133551 A1 patent, 2015. (b) Balas, L.; Bertrand-Michel, J.; Viars, F.; Faugere, J.; Lefort, C.; Caspar-Bauguil, S.; Langin, D.; Durand, T. *Org. Biomol. Chem.* **2016**, *14* (38), 9012−9020. (c) Nelson, A. T.; Kolar, M. J.; Chu, Q.; Syed, I.; Kahn, B. B.; Saghatelian, A.; Siegel, D. *J. Am. Chem. Soc.* **2017**, *139* (13), 4943−4947. (d) Balas, L.; Feillet-Coudray, C.; Durand, T. *Chem. - Eur. J.* **2018**, *24* (38), 9463−9476. (e) Hancock, S. E.; Ailuri, R.; Marshall, D. L.; Brown, S. H. J.; Saville, J. T.; Narreddula, V. R.; Boase, N. R.; Poad, B. L. J.; Trevitt, A. J.; Willcox, M. D. P.; Kelso, M. J.; Mitchell, T.; Blanksby, S. J. *J. Lipid Res.* **2018**, *59* (8), 1510−1518. (f) Wang, H.; Chang, T.; Konduri, S.; Huang, J.; Saghatelian, A.; Siegel, D. *J. Antibiot.* **2019**, *72* (6), 498−506.

(5) (a) Hamberg, M.; Liepinsh, E.; Otting, G.; Griffiths, W. *Lipids* **1998**, *33* (4), 355−363. (b) Moreau, R. A.; Doehlert, D. C.; Welti, R.; Isaac, G.; Roth, M.; Tamura, P.; Nunez, A. *Lipids* **2008**, *43* (6), 533−48.

(6) Moreau, R. A.; Doehlert, D. C.; Welti, R.; Isaac, G.; Roth, M.; Tamura, P.; Nunez, A. *Lipids* **2008**, *43*, 533−548.

(7) Hamberg, M.; Hamberg, G. *Phytochemistry* **1996**, *42* (3), 729−732.

(8) (a) Chan, C.; Cox, P. B.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1988**, *14*, 971−972. (b) Rao, A. R.; Reddy, S. P.; Reddy, E. R. *J. Org. Chem.* **1986**, *51* (22), 4158−4159. (c) Rao, A. R.; Reddy, E. R.; Sharma, G. V. M.; Yadagiri, P.; Yadav, J. S. *Tetrahedron Lett.* **1985**, *26* (4), 465−468.

(9) Li, Z.; Tran, V. H.; Duke, R. K.; Ng, M. C.; Yang, D.; Duke, C. C. *Chem. Phys. Lipids* **2009**, *158* (1), 39−45.

(10) Ramesh, P.; Chennakesava Reddy, B.; Meshram, H.M. *Tetrahedron Lett.* **2012**, *53* (29), 3735−3738.

(11) Miao, W. S.; Lu, W. S.; Chan, T. H. *J. Am. Chem. Soc.* **2003**, *125* (9), 2412−2413.

(12) Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59* (39), 7787−7790.

(13) Gung, B. W.; Dickson, H. *Org. Lett.* **2002**, *4* (15), 2517−2519.

(14) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, *15*, 553−554.

(15) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127* (22), 8044−8049.

DOI: 10.1021/acs.orglett.9b03054
Org. Lett. XXXX, XXX, XXX−XXX