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Synthetic Methods

Total Syntheses and In Vivo Quantitation of Novel Neurofuran and Dihomo-isofuran Derived from Docosahexaenoic Acid and Adrenic Acid

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Abstract: Neurofurans (NeuroFs) and dihomo-isofurans (dihomo-IsoFs) are produced in vivo by non-enzymatic free-radical pathways from docosahexaenoic and adrenic acids, respectively. As these metabolites are produced in minute amounts, their analyses in biological samples remain challenging. Syntheses of neurofuran and dihomo-isofurans described are based on a pivotal strategy, thanks to an enantiomerically enriched intermediate, which allowed, for the first time, access to both families: the alkenyl and enediol. Owing to this formation, quantitation of specific NeuroF and dihomo-IsoFs in biological samples was attainable.

Introduction

Isofurans are arachidonic acid (AA C20:4 n-6) oxygenated metabolites from human origin, produced under oxidative stress by free radicals by an enzyme-free pathway.[1] Isofurans consist of a furanic core and two lateral oxygenated and unsaturated chains. Their biosynthesis follows a pathway closely related to isoprostanes (IsoPs),[2] and therefore they are termed isofurans (IsoFs).[3] Interestingly, the formation of IsoFs increases under oxygen tension while IsoPs formation remains constant above 21% of oxygen.[1] IsoPs are commonly used in clinical trials as reliable oxidative-stress biomarkers in many diseases and pathologies,[4] and more than biomarkers, they are also biologically active.[5] In the grey matter of the brain, docosahexaenoic acid (DHA, C22:6 n-3) is the most abundant polyunsaturated fatty acid (PUFA).[6] Under oxidative stress, neurofurans (NeuroFs) are formed following the same non-enzymatic free-radical pathway as IsoFs.[7] Therefore, great potential is embedded into NeuroFs as complementary biomarkers of neuronal oxidative stress, especially in oxygen-tension associated pathologies. In the white matter of the brain, adrenic acid (AdA, C22:4 n-6) is most abundant, and leads to the formation of dihomo-isofuran (dihomo-IsoF) metabolites. We previously highlighted that dihomo-isoprostanes were early biomarkers in Rett syndrome disorder,[8] and that one type of dihomo-IsoFs was indeed highly elevated in preterm pig brain.[9] Besides being potential biomarkers, such metabolites could provide pharmacological properties yet to be discovered. The biosynthesis of IsoFs allowed two coexisting pathways that lead to two families of IsoFs: the alkenyl-IsoFs and the enediol-IsoFs (Scheme 1). We therefore envisioned a divergent synthetic strategy to access all furanic metabolites (IsoFs, NeuroFs, dihomo-IsoFs) from both alkenyl and enediol families. Six syntheses of furanic oxy-

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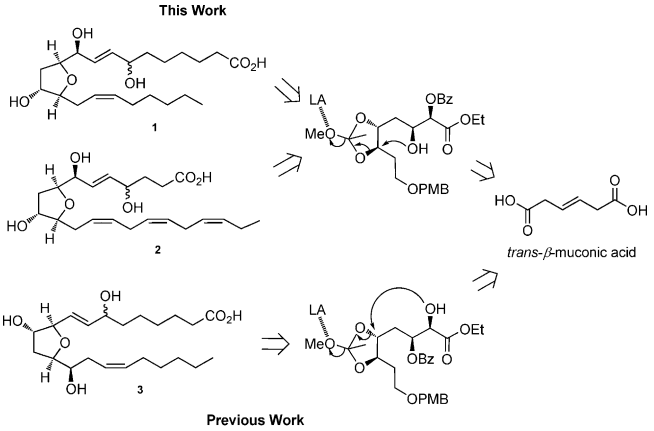


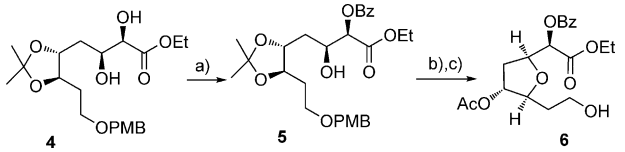
Scheme 1. Retrosynthetic analysis of enediol and alkenyl dihomo-IsoFs **1** and **3** and enediol-NeuroF **2**.

genated metabolites of PUFAs have been described to date. The first syntheses realized by Taber et al. allowed the access to arachidonic acid derived alkenyl- and enediol-type IsoFs (Δ^{13}-9-IsoFs, *ent*-SC-Δ^{13}-8-IsoF and *epi-ent*-SC-Δ^{13}-8-IsoF), whereas the furan core was obtained by diol epoxide benzenesulfonate cyclization.[10–12] More recently, Zanoni and co-workers used Trost asymmetric allylic alkylation for the synthesis of an alkenyl-NeuroF.[13] In 2007, the group of Falck described the synthesis of enzymatic epoxygenase eicosanoids.[14] The furan ring was obtained from D(+)-glucose by hydroalkoxylation.[15] It should be mentioned that the latter ones are enzymatically formed and are structurally different from IsoFs as they only possess one hydroxyl function on the lateral chains. We recently validated the total synthesis of alkenyl 17(*RS*)-10-*epi*-SC-Δ^{15}-11-dihomo-IsoF **3** by 5-*exo*-tet Borhan's orthoester-directed cyclization[16] (Scheme 1).[9] To unify this strategy a 5-*endo* cyclization mode would lead to enediol isofuran **1** and neurofuran **2**.

Herein, we describe the total syntheses of enediol 7(*RS*)-ST-Δ^{8}-11-dihomo-IsoF **1** and 4(*RS*)-ST-Δ^{5}-8-NeuroF **2**.

Results and Discussion

Starting from previously synthesized enantiomerically pure intermediate diol **4**,[9] the synthesis of cyclic compound **6** proceeded as follows. Diol **4** was selectively protected in α-position to the ethyl ester using classical conditions of benzoyl chloride and Et_3N at $-78\,^{\circ}C$ (Scheme 2)

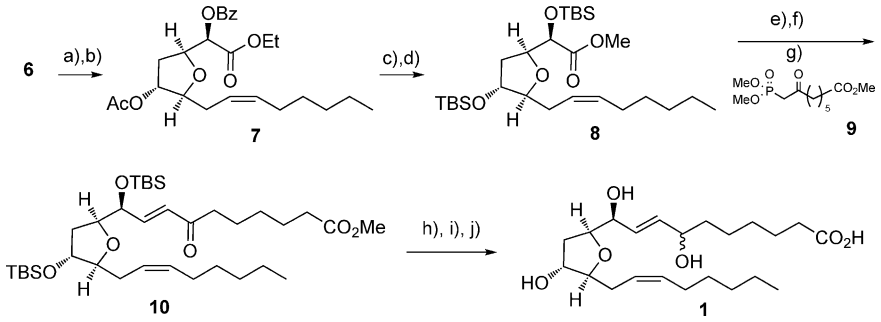


Scheme 2. a) BzCl, Et_3N, DMAP, CH_2Cl_2, $-78\,^{\circ}C$, 75%; b) PTSA, MeOH/H_2O (9:1), RT, then $NaHCO_3$ (s), 94%; c) $MeC(OMe)_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, $0\,^{\circ}C$ to RT, then DDQ, $0\,^{\circ}C$, 53%; Bz = Benzoyl, DMAP = 4-dimethylaminopyridine, PTSA = *para*-toluenesulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

to obtain compound **5** in 75% yield. The acetonide moiety was removed using PTSA in 94% yield prior to the cyclization step. The latter was initiated by the 1,2-orthoester formation using $MeC(OMe)_3/BF_3{\cdot}Et_2O$, followed by subsequent intramolecular attack of the free hydroxyl moiety onto orthoester intermediate to give furanic compound **6**. As previously observed,[9] the acidic conditions of the cyclization led to partial deprotection of PMB group (after initial cyclization process) with a 7/3 ratio of free alcohol/PMB protected along with moderate yield. Unfortunately, conditions to avoid deprotection could not be found; therefore, complete PMB cleavage with DDQ was performed in one pot after cyclization process to give free alcohol **6** in 53% yield.

With intermediate **6** in hand, the synthesis of 7(*RS*)-ST-Δ^{8}-11-dihomo-IsoF **1** was completed in a few steps.

Dess–Martin oxidation of the primary alcohol was followed by the introduction of the first lateral chain using a Wittig reaction between the resulting aldehyde and commercially available hexyl triphenylphosphonium bromide in the presence of NaHMDS. Compound **7** was obtained in a moderate yield of 46% (57% based on recovered aldehyde) and this step was not optimized (Scheme 3). For the introduction of the second lateral chain, the acetyl and benzoyl moieties were replaced by *tert*-butyldimethylsilyl ethers. A methanolysis/TBS protection

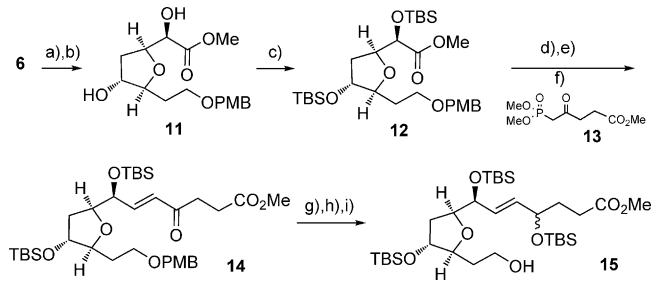


Scheme 3. a) DMP, CH_2Cl_2, RT; b) $BrPh_3P(CH_2)_5CH_3$, NaHMDS, THF, $-78\,^{\circ}C$ to RT, 46%; c) K_2CO_3, MeOH, RT, 86%; d) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 90%; e) DIBAl-H, CH_2Cl_2, $-78\,^{\circ}C$; f) DMP, CH_2Cl_2, RT; g) **9**, NaHMDS, THF, $-78\,^{\circ}C$, 55% over 3 steps; h) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, $0\,^{\circ}C$; i) TBAF, THF, RT; j) LiOH, THF/H_2O (1:1), RT, 63% over 3 steps. DMP = Dess–Martin periodinane, NaHMDS = Sodium *bis*(trimethylsilyl)amide, TBS = *tert*-butyl-dimethylsilyl, DIBAl-H = diisobutylaluminium hydride, TBAF = tetrabutyl ammonium fluoride.

sequence using K_2CO_3 in MeOH was initiated prior to TBSCl protection in the presence of imidazole and DMAP (77% over two steps), and as anticipated methyl ester **8** was recovered. $LiBH_4$ reduction of **8** led to 66% of unwanted TBS 1,2-migration while DIBAl-H reagent at $-78\,^{\circ}C$ afforded a mixture of aldehyde and alcohol derivatives with no TBS-migration. From this mixture, Dess–Martin periodinane reagent provided the required aldehyde to perform Horner–Wadsworth–Emmons reaction with β-keto-phosphonate **9**[17] in the presence of NaHMDS to give enone **10** in 55% yield after three steps. Quantitative reduction of enone **10** into allylic alcohol was performed under Luche conditions prior to TBS group deprotection and methyl ester saponification to finally access enediol 7(*RS*)-SC-Δ^{8}-11-dihomo-IsoF (**1**).

Accordingly, the first total synthesis of 7(*RS*)-ST-Δ^{8}-11-dihomo-IsoF **1** was completed after 13 linear steps and 4.6% yield starting from common intermediate **4**, without considering the preparation of β-ketophosphonate **9**.

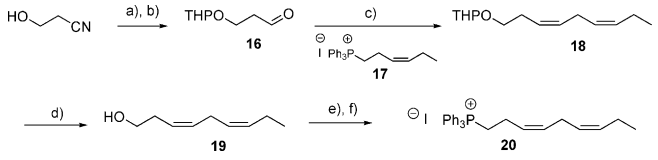
Although we confirmed the flexibility of our synthetic design to access both alkenyl and enediol structures via intermediate **4**, the DHA-derived metabolite presents one additional challenge to be dealt with; that is, the introduction of the more complex lateral chain (possessing multiple skipped-diene units) at the end of the synthesis. This means that for target **2** the sequence order described above needs to be modified to accommodate that necessity.



Scheme 4. a) PMBTCA, $La(OTf)_3$, RT, 87%; b) K_2CO_3, MeOH, RT, 79%; c) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, quant.; d) DIBAl-H, CH_2Cl_2, −78 °C; e) DMP, CH_2Cl_2, RT; f) **13**, NaHMDS, THF, −78 °C, 62% over 3 steps; g) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 °C, 95%; h) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 82%; i) DDQ, 0 °C, 86%. PMBTCA = *para*-methoxybenzyl trichloroacetimidate, Tf = trifluoromethanesulfonyl.

Thanks to our intermediate **6**, the primary alcohol was first protected using *para*-methoxybenzyl trichloroacetimidate and $La(OTf)_3$ in 87% yield before acetyl and benzoyl methanolysis to give methyl ester **11** in 79% yield (Scheme 4). Quantitative silylation of secondary alcohols with TBSCl, imidazole and a catalytic amount of DMAP afforded **12** in good yield. DIBAl-H reduction of methyl ester followed by oxidation of the resulting aldehyde/alcohol mixture using Dess–Martin periodinane provided the desired aldehyde for Horner–Wadsworth–Emmons olefination using previously described β-keto-phosphonate **13**.[18] The resulting α,β-unsaturated ketone **14** (3 steps, 62% yield) was reduced under Luche conditions and the resulting allylic alcohol was protected into *tert*-butyldimethylsilyl ethers prior to PMB deprotection. Alcohol **15** was then obtained after 3 steps in a 67% yield.

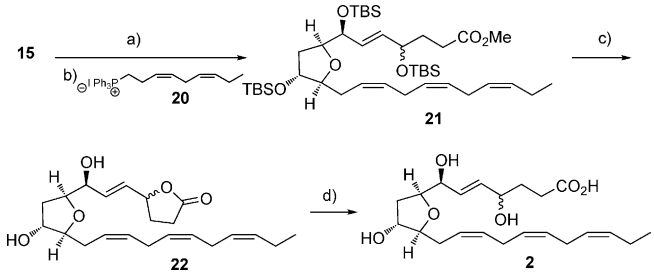
At this stage, the complex omega chain needed to be installed. In 2000, our laboratory performed the synthesis of the 4-F_{4t}-NeuroP methyl ester containing the same omega chain, by Wittig reaction using phosphonium salt **20**.[19] The latter was obtained by a convergent strategy with a total of 8 steps and 51% yield, in collaboration with Viala and Santelli.[20] We decided to improve the synthesis of **20** (Scheme 5), because the previous synthesis was costly and tricky.



Scheme 5. a) DHP, PPTS, CH_2Cl_2, RT, 87%; b) DIBAl-H, Et_2O, −78 °C, 82%; c) **17**, NaHMDS, THF, −78 °C; d) PPTS MeOH, reflux; e) I_2, PPh_3, Imidazole, RT; f) PPh_3, K_2CO_3 (cat), BHT, CH_3CN, 71% (over 4 steps). DHP = dihydropyran, PPTS = pyridinium *para*-toluenesulfonate, BHT = butylated hydroxytoluene.

Starting from 1-hydroxypropanenitrile, aldehyde **16** was obtained in two steps and 71% yield by protecting the alcohol into THP-ether and reducing the nitrile with DIBAl-H reagent. A Wittig reaction between aldehyde **16** and previously described phosphonium salt **17**[17] gave diene **18**. THP deprotection in acidic conditions prior to iodination and nucleophilic substitution using triphenylphosphine gave desired diene phosphonium salt **20** with a 71% yield over the four last steps and a 51% overall yield. Though this new synthesis offers the same overall yield, it remained more convenient on a large scale and less expensive. It is interesting to note that butylated hydroxytoluene (BHT) was added during the preparation and storage of **20** for preservation of the "$-CH_2-$" in *bis*-allylic position. Moreover, although most phosphonium salts are in solid state, **20** remained a sticky oil despite several crystallisation attempts. Therefore phosphonium **20** was dried by three cycles of dissolution in acetonitrile followed by desiccation at 120 °C under vacuum (10^{-1} mbar, for 15 min) before carrying out the Wittig reaction.

From alcohol **15**, the tandem oxidation-Wittig reaction proceeded, in 62% yield, to give the expected 5E,13Z,16Z,19Z-tetraene **21** (Scheme 6). TBAF-deprotection of silylated ethers afforded the five-membered ring lactone **22**, which was saponified using LiOH to achieve the synthesis of 4(*RS*)-SC-Δ^5-8-NeuroF (**2**).



Scheme 6. a) DMP, CH_2Cl_2, RT; b) **20**, NaHMDS, THF, −78 °C, 62% over 2 steps; c) TBAF, THF, RT, 90%; d) LiOH, THF/H_2O (1:1), RT, 87%.

Consequently, the first total synthesis of 4(*RS*)-SC-Δ^5-8-NeuroF (**2**) was completed after 13 steps and 14% yield starting from alcohol **6** and without considering the preparation of β-ketophosphonate **14** and phosphonium salt **20**.

To date, the specific type of NeuroFs, 4(*RS*)-ST-Δ^5-8-NeuroF **2** described in this report has not been identified in biological samples. Furthermore, in our previous report[9] we have shown the measurement of dihomo-IsoF, 17(*RS*)-10-*epi*-SC-Δ^{15}-11-dihomo-IsoF **3** in prefrontal cortex of preterm pig brain and it is unknown if the second type 7(*RS*)-ST-Δ^8-11-dihomo-IsoF **1**, as shown in the strategy herein, is measurable in biological samples. We now report the levels of 4(*RS*)-ST-Δ^5-8-NeuroF **2** and 7(*RS*)-ST-Δ^8-11-dihomo-IsoF **1** in heart and brain samples from adult rats. The levels are compared with IsoFs, 17(*RS*)-10-*epi*-SC-Δ^{15}-11-dihomo-IsoF **3** and total NeuroFs as well as the respective isoprostanoids.

As expected the concentration of the PUFAs AA, AdA, and DHA were higher in the brain tissues than the heart (Figure 1). Interestingly, 4(*RS*)-4-F_{4t}-NeuroP (from DHA) concentration was very high in both heart and brain tissues, and this also coincides with our previous findings,[9] in which it predominates among the isoprostanoids. However, in this evaluation we also found 5-F_{2t}-IsoP from AA to be highly concentrated in both tissues. In comparison between the heart and the brain, the iso-

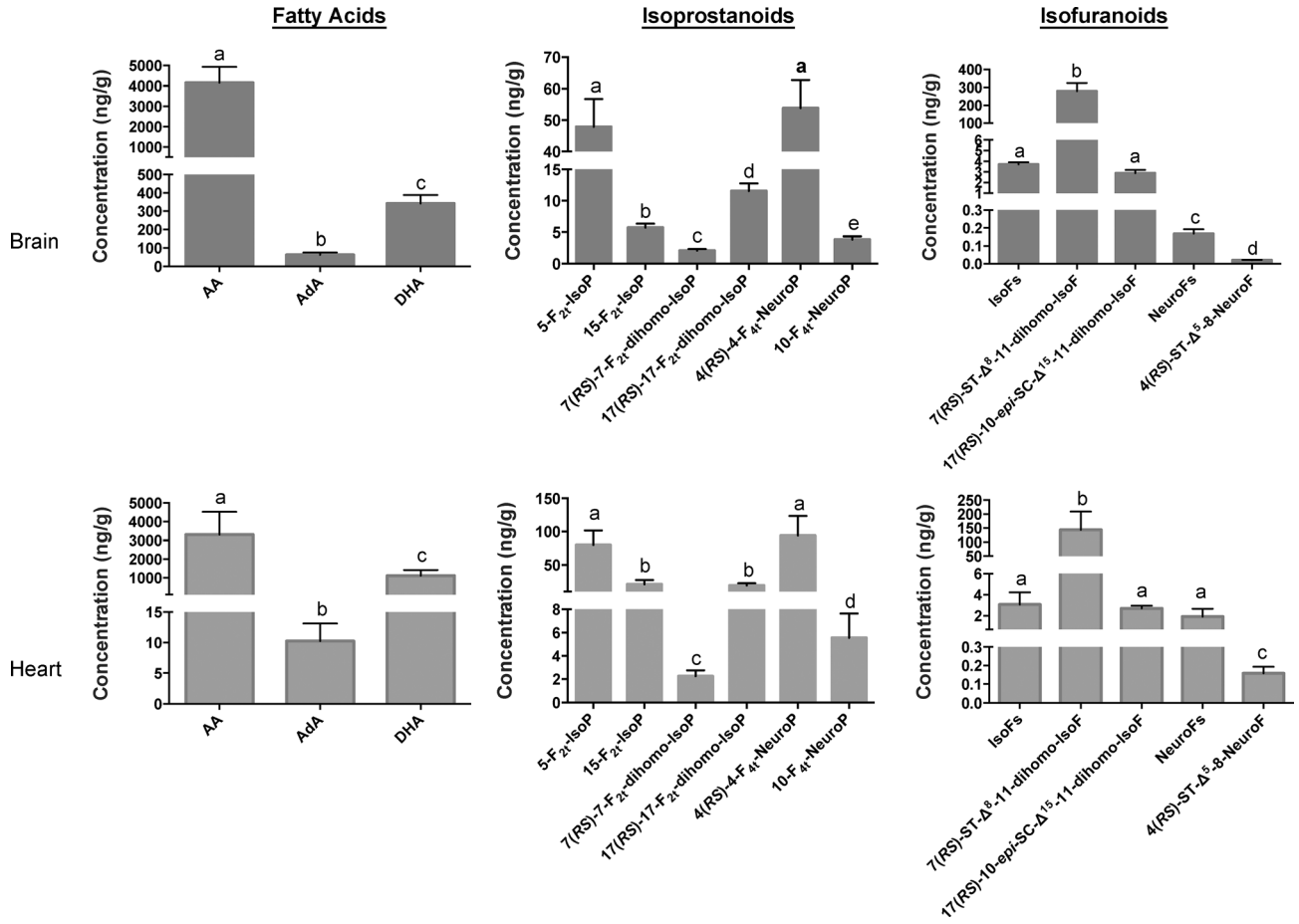


Figure 1. Concentration of isoprostanoids and isofuranoids in rat brain and heart tissues. Values are mean ± SD, $n = 8$. Concentration of each compound is expressed per gram of tissue. Columns sharing different alphabetical superscripts in each graph are significantly different ($p < 0.05$). For references concerning the extraction procedures see refs. [21,22].

prostanoids including 5-F_{2t}-IsoP, 15-F_{2t}-IsoP, 7(*RS*)-7-F_{2t}-dihomo-IsoP, 17(*RS*)-17-F_{2t}-dihomo-IsoP, 4(*RS*)-4-F_{4t}-NeuroP, and 10-F_{4t}-NeuroP were lower in brain than heart (Figure 1).

Of the isofuranoids, it was surprising to find novel enediol 7(*RS*)-ST-Δ^8-11-dihomo-IsoF **1** and not alkenyl 17(*RS*)-10-*epi*-SC-Δ^{15}-11-dihomo-IsoF **3** to be predominant in both tissues. Concentration of novel 4(*RS*)-ST-Δ^5-8-NeuroF **2** was very low at levels of (0.020 ± 0.005) ng g^{-1} tissue in the brain and (0.157 ± 0.036) ng g^{-1} tissue in the heart. Compared to total IsoFs, 7(*RS*)-ST-Δ^8-11-dihomo-IsoF **1**, 17(*RS*)-10-*epi*-SC-Δ^{15}-11-dihomo-IsoF **3**, and total NeuroFs, the concentration of 4(*RS*)-ST-Δ^5-8-NeuroF **2** is approximately 10- to 100-folds lower in the heart and 10 to 10000-fold lower in the brain. Overall the concentration of isofuranoids in the heart and the brain are similar except for total NeuroFs and 4(*RS*)-ST-Δ^5-8-NeuroF **2**, which are lower in the brain compared to the heart (Figure 1).

Our evaluation showed lipid mediators from AdA, 17(*RS*)-17-F_{2t}-dihomo-IsoP **3** in the heart, and 7(*RS*)-ST-Δ^8-11-dihomo-IsoF **2** in the heart and the brain exceeded the level compared to the PUFA precursor. Similar findings were also made in our previous report in the brain of preterm pigs.[9] The rationale for this is unclear but it could be deduced that the peroxidation rate of AdA to generate these lipid mediators is faster than the elongation rate of converting AA to AdA. Nevertheless, our data obtained in the present evaluation in part is different from our previous report,[9] probably because of the species used, the maturity of the rat, and the region of brain assessed (as mid-sagittal plane was used in the study).

Conclusion

In summary, we report the presence of 4(*RS*)-ST-Δ^5-8-NeuroF and 7(*RS*)-ST-Δ^8-11-dihomo-IsoF in rat brain and heart tissues. It is also the first report to show concentration of known NeuroPs and dihomo-IsoPs in the heart tissue. The concentration difference of 4(*RS*)-ST-Δ^5-8-NeuroF between the heart and the brain indicate that it is a robust indicator for macro- and micro-vascular function, considering disparate in situ oxygen tension of the tissues.

The first total syntheses of two new omega-6 and omega-3 furanic metabolites were achieved as a result of the present strategy. We developed a flexible and convergent strategy allowing the access of both alkenyl- and enediol-type dihomo-IsoFs and enediol NeuroF, and it is therefore suitable for all isofuranoid-containing natural products. The cyclization step using Borhan's method offered ready access to a pivotal inter-

mediate (with or without protecting group) to achieve both syntheses without repeating the whole sequence.

These DHA and AdA metabolites are presently in testing for various pathological models as oxidative stress biomarkers and bioactive compounds.

Experimental Section

Full details of experimental procedures, characterization data, and NMR spectra can be found in the Supporting Information.

Acknowledgements

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Keywords: dihomo-isofurans · fatty acids · neurofurans · oxygenated metabolites · total synthesis

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FULL PAPER

Synthetic Methods

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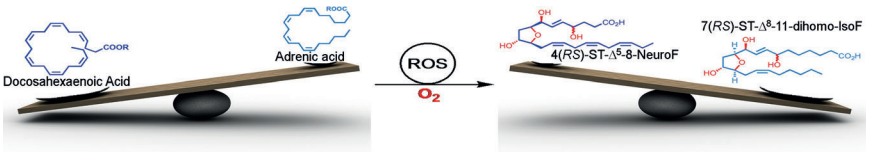
Total Syntheses and In Vivo Quantitation of Novel Neurofuran and Dihomo-isofuran Derived from Docosahexaenoic Acid and Adrenic Acid



Enantioselective syntheses of enediol dihomo-isofuran and neurofuran, metabolites of in vivo adrenic acid and docosahexaenoic acid peroxidation, respectively, are described herein using Borhan conditions through a 5-*endo*-tet process. Mass-spectrometry quantitation in brain and heart showed that dihomo-isofurans, for which parent precursor adrenic acid is less abundant, are formed in higher amounts than other PUFA metabolites.