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Facile access to arsenic-containing triacylglycerides

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ABSTRACT

The previously unknown arsenic-containing triacylglycerides (AsTAGs) 3-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,2-diyl dipalmitate **1** and 2-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,3-diyl dipalmitate **2** have been synthesized. They will serve as model compounds in the search for naturally occurring AsTAGs, recently proposed natural constituents of fish oils.

Marine organisms naturally contain high levels of arsenic, an appreciable amount of which is present as lipid-soluble compounds, so-called arsenolipids.[1] Several types of naturally occurring arsenolipids have been identified so far, including arsenic containing derivatives of fatty acids,[2] hydrocarbons,[3,4] fatty alcohols,[4] phosphosugars,[5,6] and phosphatidylcholines[7] and phosphatidylethanolamines.[7] In preliminary toxicological investigations, the arsenic-containing hydrocarbons exhibited significant cytotoxicity[8,9] to human cells and a study with the fruit fly indicated that they are able to cross the blood-brain barrier.[10]

Recently, two separate studies[11,12] have reported the presence of a new type of arsenolipid in fish oil. Taleshi et al.[11] observed that methyl esters of arsenic-fatty acids were formed when a nonpolar lipid extract of oil from the blue whiting fish (*Micromesistius poutassou*) was subjected to silica chromatography with methanol as the eluent. It was reasoned that the methyl esters resulted from transesterification of less polar compounds (Fig. 1), and this hypothesis was supported by the fact that hydrolysis of the less-polar lipid fraction from the blue whiting oil gave arsenic-containing fatty acids (AsFA). The authors suggested that the original compounds in the oil could be arsenic-containing triacylglycerides (AsTAGs); the presence of AsTAGs was also inferred in Peruvian anchoveta (*Engraulis ringens*) in a later study by Pereira et al.[12] It is crucial to have access to a well-characterized AsTAG standard in order to confirm the existence of AsTAGs as marine natural products, and to investigate their biological and toxicological properties.

Herein, we wish to disclose our successful efforts to synthesise the previously unknown AsTAGs 3-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,2-diyl dipalmitate **1** and 2-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,3-diyl dipalmitate **2**. The synthesis towards **1** was achieved in 10 steps starting from ω-pentadecanolide with an overall yield of 4.6% (Scheme 1). We investigated an alternative strategy for the synthesis of **2** using commercially available 1,3-diacylglycerol **11** and **2** was isolated starting from ω-pentadecanolide in an overall yield of 5.6% (longest linear sequence, 8 steps). Both routes are highly flexible and could be exploited for the synthesis of a range of AsTAGs.

On the basis of literature precedence, it was expected that a synthetic route using the thioxo (As = S) analogue of an arsenic fatty acid, namely compound **3**, rather than the corresponding oxo (As = O) analogue would be more practical in terms of workup,[11] and taking into account the basicity[13] of As = O. In addition, a final thioxo-oxo transformation[14] is a straightforward procedure. The synthesis towards **3** is known[2] and was performed similarly. Thus, an acid-catalyzed ω-pentadecanolide opening gave methyl 15-hydroxy- pentadecanoate **4** quantitatively. In order to transform the alcohol functionality into a proper leaving group, an Appel reaction[15] using CBr_4/PPh_3 was performed to give **5** in a yield of 54%. The arsenic moiety $Me_2As(O)$ was then introduced in two steps using Me_2AsI/Na[16–18] followed by treatment with H_2O_2.[16] Saponification and subsequent acidification gave the corresponding oxo-analogue of **3**, which was transformed by treatment with H_2S[14] into the desired thioxo analogue **3**; the combined yield was 32% starting from **5**.

1st Strategy: the synthesis of AsTAG **1** commenced with the introduction of the arsenic-containing fatty acid **3** to

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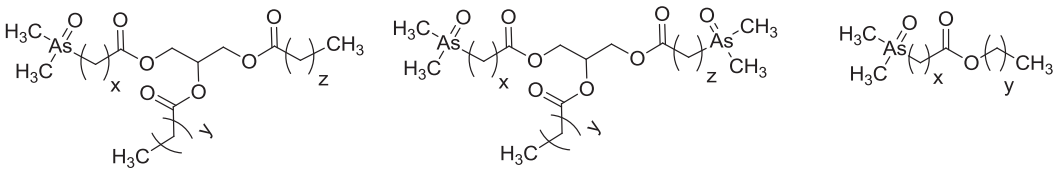
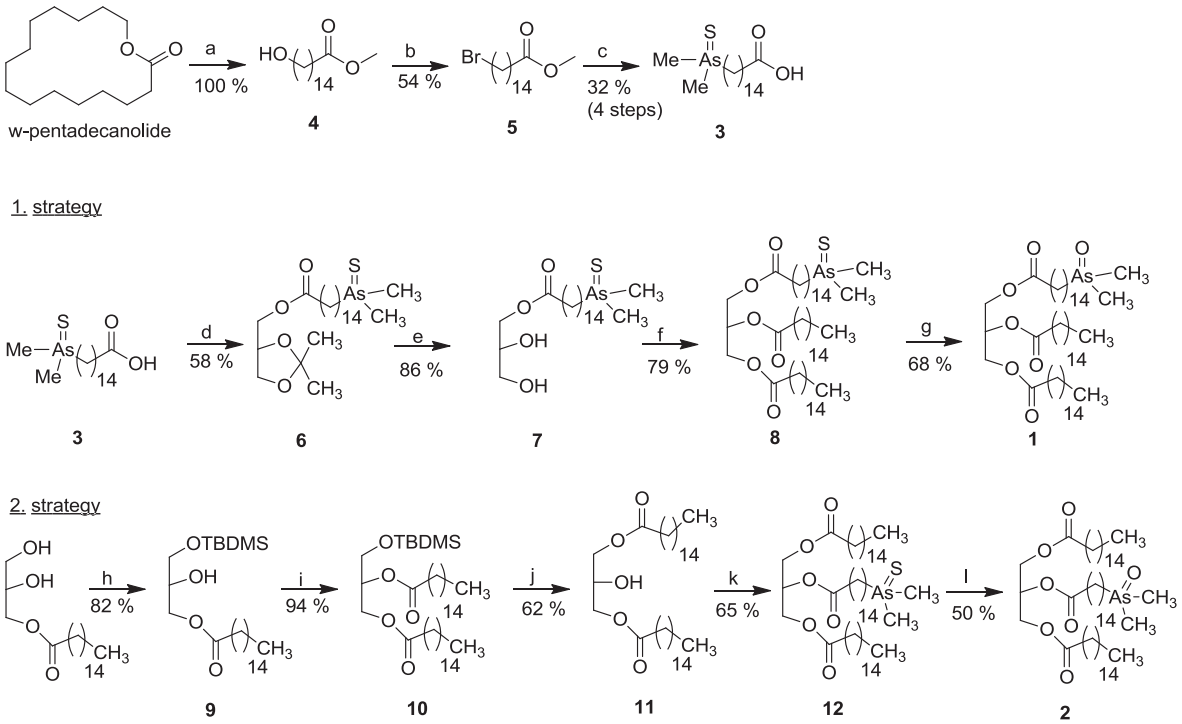


Fig. 1. Postulated structures for less-polar arsenolipids reported in the blue whiting fish[11] and in Peruvian anchoveta.[12]



Scheme 1. Synthesis of the AsTAGs **1** and **2**. Reagents and conditions: (a) cat. H_2SO_4, MeOH, reflux, overnight; (b) 1.1 eq CBr_4, 1.1 eq PPh_3, CH_2Cl_2, 0 °C → rt, 2 h; (c) 5.7 eq Na, 2.9 eq Me_2AsI, THF, −70 °C → rt, overnight then 2.3 eq H_2O_2, THF, 0 °C, 45 min then 2 eq 4 M NaOH, 3 h, rt then HCl then H_2S; (d) 1.2 eq 1,2-isopropylidene-*rac*-glycerol, 1.5 eq DIC, 5 mol% DMAP, CH_2Cl_2, 0 °C → rt, 16 h; (e) ACN/TFA/H_2O (5+4+1 v/v/v), rt, 15 min; (f) 3.0 eq palmitoyl chloride, 40 eq pyridine, CH_2Cl_2, rt, 24 h; (g) 12 eq H_2O_2, 0 °C → rt, 30 min; (h) 1.1 eq TBDMSCl, 1.7 eq imidazole, THF, rt, 16 h, THF; (i) 1.0 eq palmitic acid, 1.3 eq DIC, 0.97 eq DMAP, CH_2Cl_2, 0 °C → rt, 21 h; (j) 1.1 eq TBAF, THF, 0 °C → rt, 24 h; (k) 1.2 eq **11**, 1.0 eq **3**, 1.5 eq DIC, 0.6 eq DMAP, CH_2Cl_2, 0 °C → rt, 19 h; (l) 12 eq H_2O_2, THF, rt, 30 min. TBDMS: *tert*-butyl-dimethylsilyl.

1,2-isopropylidene-*rac*-glycerol using DIC/DMAP, conditions originally developed by Neises and Steglich[19] to give isopropylidene protected **6**. Acetonide deprotection using ACN/TFA/H_2O (5+4+1 v/v/v) afforded **7**, which was converted to compound **8** via two consecutive acylation reactions using palmitoyl chloride/pyridine in 79% yield. The transformation **7** → **8** was also performed using palmitic acid/DIC/DMAP and gave **8** in a yield of 57% (45 µM scale). A sulfur-oxygen exchange[14] was successful when **8** was treated with H_2O_2 to give desired AsTAG **1**. Both ^{1}H-NMR and ^{13}C-NMR show a clear upfield shift of the methyl groups of $Me_2As(O)$, compared to $Me_2As(S)$, which is in accordance with the literature.[20,21]

2nd Strategy: AsTAG **2** was synthesized starting from 1,3-diacylglycerol **11**. Although **11** is commercially available, we decided to synthesise this compound because the intermediate **9** was expected to be of use for the preparation of alternative AsTAGs, and we could already demonstrate that an esterification of secondary alcohol in **9** using AsFA **3** is straightforward using DIC/DMAP (see Supplementary Data, compound **13**).

Thus, following a literature procedure[22] we started with a selective protection of the primary alcohol in *rac*-1-palmitoylglycerol to give the known silyl ether **9** in a yield of 82%. Introduction of the second palmitoyl chain was achieved using palmitic acid/DIC/DMAP and diacyl glycerol **10** could be obtained in 94% yield. Acyl migration has been reported when standard protocols were used for TBDMS removal in diacyl glycerols.[23] In order to avoid migration, alternative procedures have been applied that omit TBAF.[24–28] Notably, acylation across oxirane- and silyloxy systems has been described as a strategy to the synthesis of enantiomerically pure mono-, di- and triglycerides.[29,30] In a recent report, Fodran et al.[31] achieved the synthesis of enantiopure triacylglycerols in a simple two-step, one-pot procedure starting from glycidyl esters. We exploited acyl migration for the synthesis of **11** by using TBAF for silyl deprotection in **10**, and could isolate **11** in a yield of 62%. Prata et al.[32] synthesized the regioisomer 1,2-di-hexadecanoyl-*rac*-glycerol via a TBAF-mediated desilylation when TBDPS was used as a protecting group rather than TBDMS. The coupling of **11** with arsenic-containing fatty acid **3** was successful and gave late intermediate **12** in a yield of 65%. Theoretically, a transesterification could occur in the transformations **7** → **8** and **11** → **12**, which would not be specifiable by MS or NMR. Transformation of As = S to As = O using H_2O_2 gave **2** in 50% yield. ^{1}H-NMR and ^{13}C-NMR spectra of **1** and **2** are nearly identical, which was expected because of structural similarity.

We were able to synthesise the previously unknown AsTAGs 3-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,2-diyl dipalmitate **1** and 2-((15-(dimethylarsinoyl)pentadecanoyl)oxy)propane-1,3-diyl dipalmitate **2** via two different strategies, which

allows for an expeditious access to various AsTAGs in the future. In the first strategy, AsFA **3** is introduced early in the synthetic route, which adversely affects the overall yield but offers flexibility, as intermediate **7** exhibits two points of diversification. In the second strategy, AsFA **3** is introduced late, which is beneficial to the overall yield. Furthermore, intermediate **9** can be differently decorated providing future facile access to various AsTAGs.

Our study extends the range of synthetically available arsenic-containing organic molecules. Most importantly, AsTAGs **1** and **2** will serve as model compounds with the goal to identify the less-polar arsenolipids observed in marine samples. Investigations of the chemical, biological and toxicological properties of the AsTAGs are currently underway in our laboratory.

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.12.040.

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