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Design and Synthesis of Novel Prostaglandin E_2 Ethanolamide and Glycerol Ester Probes for the Putative Prostamide Receptor(s)

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ABSTRACT

Novel prostaglandin-ethanolamide (PGE_2-EA) and glycerol ester (2-PGE_2-G) analogs were designed and synthesized to aid in the characterization of a putative prostamide receptor. Our design incorporates the electrophilic isothiocyanato and the photoactivatable azido groups at the terminal tail position of the prototype. Stereoselective Wittig and Horner-Wadsworth-Emmons reactions install the head and the tail moieties of the PGE_2 skeleton. The synthesis is completed using Mitsunobu azidation and peptide coupling as the key steps. A chemoenzymatic synthesis for the 2-PGE_2-G is described for first time.

Keywords: Endocannabinoids, Prostamides, Prostaglandin glycerol ester, Lipids

Introduction

Prostamides are a class of endogenous eicosanoids resulting from the cyclooxygenase-2 (COX-2) metabolism of the endocannabinoid anandamide (AEA).[1,2] The biosynthesis of prostamides is similar to that of the prostaglandins and involves stimulus-induced phospholipase release of anandamide, oxygenation by COX-2 to a hydroxyl-endoperoxide, and finally enzymatic conversion by one of the prostaglandin synthases.[1] While basal levels of the precursor AEA are not sufficient to produce significant concentrations of prostamides, it is likely that physiological conditions exist, as in inflammatory or infectious conditions, where anandamide release coincides with COX-2 induction.[2,3] The involvement of prostamides in inflammatory settings suggests that they constitute a novel class of lipid mediators, modulation of which could lead to new anti-inflammatory approaches.[4,5]

Since their discovery in 1997,[6] the effects of prostamides have been studied on various systems known to recognize endocannabinoid and prostaglandin classes of compounds. Prostamide E_2 (PGE_2-EA) has shown little to no affinity for cannabinoid receptors CB_1 and CB_2 and little to no activity at the endocannabinoid metabolizing enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL).[7,8] While the prostamides have been shown to possess the ability to activate the human prostaglandin receptors (hEP), it is with 100-1,000-fold lower affinity than the respective prostaglandins, making prostaglandin receptors an unlikely target for the prostamides.[9] Additionally, in *ex vivo* functional assays on isolated tissue preparations from guinea pig known to contain prostaglandin EP_2 and EP_3 receptors, PGE_2-EA activity was found to be approximately 10-fold higher than those determined by the purified hEP_2 and hEP_3 receptor radioligand binding assay and argues for the existence of putative selective receptors within these tissues.[9] Moreover, the lack of affinity of prostamides at prostaglandin, cannabinoid receptors and the endocannabinoid enzymes FAAH and MGL suggests that there may be more substantial interactions with other biological targets. A more detailed

understanding of the physiological roles of these novel compounds can be greatly enhanced by the availability of unique pharmacological reagents and is the motivating factor for the work presented here. The current study presents a multiple step synthesis of PGE_2-EA analogs that allows for convergent functionalization of both the head and/or tail groups and provides potentially useful probes for the characterization of the prostamide biochemical system.[10] Because PGE_2-EA is the major product of prostamide biosynthesis, analogs of the E_2 configuration were selected for synthesis.[6] The initial set of compounds incorporates azido and isothiocyanato functionalities at the terminal tail position as affinity probes for covalent binding to the putative prostamide receptor (Figure 1). Upon photoirradiation to a nitrene intermediate, the azido moiety can attach to reactive residues in the vicinity of the binding site.[11-13] Similarly, the electrophilic isothiocyanato group is capable of reacting with nucleophilic amino acid residues including thiol, imidazole, or amino groups that are unprotonated under physiological conditions.[14-16] These covalent probes allow for the future isolation and characterization of putative protein targets involved in prostamide function. In earlier work we have shown that introducing steric hindrance and/or chirality adjacent to the amide nitrogen atom in endocannabinoids leads to analogs with enhanced stability towards hydrolyzing enzymes without any reduction in bioactivity.[17] Thus, in our rational design of PGE_2-EAs we have included the *R*- and *S*-2-methyl ethanolamide and cyclopropylamide moieties as head group variations (Figure 1).

2-Glycerol ester and 15*R* isomers were also incorporated in this set of compounds to explore their effects on metabolic stability and bioactivity. 2-Arachidonoylglycerol (2-AG) is an additional key representative of another class of endocannabinoids and was found to be subject to the same biosynthetic pathway via COX-2 to the prostaglandin glycerol esters.[18] For this reason the respective 2-PGE_2-G analog was included in this series of targeted analogs. Also, while the 15*S* isomer is the native prostanoid configuration, the 15*R* isomer mimics the stereochemistry of the aspirin-triggered lipoxins

(ATL), shown to have a leading role in mediating inflammation resolution.[19] This COX-2 mediated metabolite of AA not only exhibits anti-inflammatory and pro-resolving properties, but in its 15*R* configuration also increases potency and metabolic stability over that of the native 15*S* compounds.[20] Thus, representative analogs with the 15*R* configuration were included in the targeted set of compounds synthesized in this study.

Results and discussion

Our overall synthetic strategy incorporates Corey's prostaglandin synthesis[21] along with an additional protecting group at the tail terminal carbon. It is essential that the protective scheme allow for complete selectivity in removal of the terminal protecting group to avail further functionalization at this site. In the initial synthesis, triisopropylsilyl (TIPS) groups at the 11 and 15 secondary alcohol positions and a *tert*-butyldimethylsilyl (TBS) group at the primary terminal position were chosen for this purpose.

The synthesis begins with the commercial starting material, benzoyl protected Corey's lactone aldehyde **1** (Scheme 1), undergoing a Horner-Wadsworth-Emmons reaction to give the E-enone **3** exclusively as confirmed by ^{1}H NMR analysis ($^3J_{CH=CH}$ = 15.8 Hz) and in near quantitative yield. The phosphonate reagent **2** used here is prepared by reaction of *n*-butyllithium with dimethyl methyl phosphonate followed by ring opening of ε-caprolactone and protection of the terminal hydroxyl with TBS chloride (details are given under Supporting information).[22] Asymmetric reduction of **3** to enol **4** using Corey's oxazaborolidine catalyst[23] was attempted, however enantiomeric excess never exceeded 30%. Alternatively, we elected to perform a non-stereoselective Luche reduction,[24,25] isolate both 15*S* and 15*R* isomers (86% overall yield), and carry on the remainder of the synthesis in parallel. It should be noted that determination of the exact stereochemistry at C15 in the two isomers 15*S* (less polar, R_f = 0.55, 60% AcOEt in hexanes) and 15*R* (more polar, R_f = 0.45, 60% AcOEt in hexanes) was based on the synthesis

of the respective Mosher esters (see supporting information for details) followed by comparative analysis of their ^{1}H NMR spectral data.[26,27] Our ^{1}H NMR configurational correlations are in agreement with previous assignments done on prostaglandin intermediates with a straight chain where the less polar compound was determined to be the 15*S* secondary alcohol and the more polar compound was found to be the 15*R*.[28] Hydrolysis of the benzoyl group (89-91% yields) followed by TIPS protection of the secondary free hydroxyls (90-93% yields) establishes the last of our strategic protecting groups for intermediate **6**. Reduction of the lactone to the lactol using DIBAL-H (93% yield) is followed by a Wittig reaction to introduce the head carboxylic acid chain with the desired Z-stereochemistry at the newly formed double bond (73-78% yields). Key intermediate **8** avails the choice of establishing either the head or tail moieties first. In our case, we decided to first incorporate the tail moiety and were thus able to synthesize several head group analogs.

Modifications at the tail aimed at incorporating azido and isothiocyanato functionalities are shown in Schemes 2 and 3. Upon exposure to $TMSCHN_2$ in MeOH, the acid **8** is converted to its methyl ester **9** (92-93% yields) and the 9*S*-hydroxy on the ring is oxidized to the ketone **10** (96% yield) with Dess-Martin periodinane buffered with pyridine to avoid potential elimination of the 11-hydroxy substituent to form the α,β-unsaturated ketone. The terminal hydroxy is then selectively deprotected using AcOH:THF:H_2O (3:1:1) to give **11** in high yields (91-93%). At this point we have established a path to synthesize the key primary alcohol **11** which allows the further functionalization of the terminal tail carbon. In the current study we focused on putative affinity probes incorporating azido and isothiocyanato groups. A modified Mitsunobu reaction provides the subsequent conversion to azide **12** in 91% yield (IR: s, 2093 cm^{-1}). Throughout the synthesis certain conditions, specifically those encountered during the amide coupling, led to the formation of the undesirable α,β-unsaturated ketone by dehydration of the 11-hydroxyl group. To prevent this, we reduced the 9-keto back to its hydroxyl

counterpart and reintroduced it again after the amide coupling step. This strategy is essentially utilized as a protection/deprotection approach during the incorporation of the azido moiety and was found to be advantageous over the use of additional 9-OH protection groups that would require selective deprotection. Thus, Luche reduction of the ring ketone (83-89% yields) is followed by hydrolysis of the methyl ester **13** (NaOH, THF/H_2O) to give the precursor acid **14** in 84-85% yields.

Varying the head moieties begins with the free acid (**14**) coupling to the amine derivatives to give the desired amide analogs (Scheme 3). As we reported earlier for the synthesis of novel anandamide analogs, the carbonyldiimidazole (CDI) activation procedure worked well and provided these compounds in excellent yields (88-92%).[29,30] The Dess-Martin periodinane/pyridine system oxidizes the 9-hydroxy back to the ketone **16** (97-98% yields). The desilylation step leading to azides **17** proved to be challenging because of the enhanced stability of the TIPS group at the 11-hydroxy position. After considerable experimentation we found that the 48% HF/pyridine reagent works effectively and provides the azido analogs **17a**-**17d** in acceptable yields (45-48%) along with unidentified byproducts. Subsequently, the isothiocyanato compounds **18a** and **18b** were isolated after treatment of the respective azido-ethanolamides **17a** and **17b** with carbon disulfide in the presence of triphenylphosphine (94-96% yields, IR: s, 2090 cm^{-1}). For the synthesis of the *n*-pentyl chain tail analogs **23** (Scheme 4) where no selectivity in removal the silyl protecting groups is required, the full synthesis was carried out using TBS protection for both the 11- and 15-hydroxyls. In the final step, removal of all three silyl groups was carried out smoothly with 1% HCl in 95% MeOH and produced the amides **23** in short reaction time (5 min) and high yields (80-83%). The intermediate ketones **22a**-**22c** were synthesized with high chemical efficiency from the precursor acid **20** which was in turn synthesized in three steps from commercially available **19** following previously reported procedures.[31] It should be noted that an earlier synthesis of **23a** (no yields reported) involved exposure of PGE_2 to ethyl chloroformate and treatment of the in situ

generated mixed carbonic anhydride to (*S*)-(+)-amino-2-propanol.[7] Carbonyldiimidazole mediated coupling of acid **20** with readily available 1,3-divaleric glycerol[32] gave the triglyceride **24** in 82% yield (Scheme 5). Dess-Martin oxidation of the free hydroxy on the cyclopentane ring (97% yield) was followed by the deprotection of both silyl protecting groups (79% yield). Finally, the precursor triacylglycerol **26** was conveniently deprotected in ethanol with *Candida rugosa lipase* type VII to give the desired 2-PGE_2-G (**27**) in 46% yield. To the best of our knowledge the chemoenzymatic synthesis of this endogenous substance is reported here for the first time and parallels those we reported earlier for the endocannabinoid lipid 2-AG and its analogs.[33,34] Importantly, our approach provides the 2-PGE_2-G essentially free of 1(3)-acylglycerol rearrangement byproducts as confirmed by ^{1}H NMR data. In a previous study on the metabolism of prostaglandin glycerol esters the 2-PGE_2-G was the minor product which was synthesized as a mixture with the 1(3) regioisomer in a ratio 1: 9.[35]

The involvement of prostaglandins as pro-inflammatory lipid mediators has long been recognized. However, more recent studies have established that certain prostaglandins, specifically PGE_2 and PGD_2, trigger eicosanoid class switching from pro-inflammatory to local acting pro-resolving lipid mediators.[36] However, the role of this new class of prostaglandin related amides and ester is not well understood. In this preliminary study the actions of a representative analog within the series, the 15*S* hydroxy, 20-isothiocyanato compound **18a** was assessed *in vivo* using a widely employed model of inflammation, namely zymosan A-stimulated murine peritonitis.[37] Prostaglandin PGE_2 was also tested for comparison. The results of administration on cell numbers of both polymorphonuclear neutrophils (PMN) and monocytes are illustrated in Figure 2. We observe that while both PGE_2 and **18a** effectively reduce PMN infiltrates in this inflammatory model, **18a** was slightly more efficacious.

In summary, a successful synthetic strategy has been established for the construction of a focused family of prostamide analogs containing head and tail modifications to aid in the characterization of a putative

prostamide receptor. This synthesis incorporates the strategic use of silyl protecting groups for selective deprotection and functionalization of the ω terminus. Azide and isothiocyanate functionalities are introduced at this tail position to serve as affinity probes designed to covalently attach to target proteins associated with this prostamide thus aiding in their identification. In a preliminary biological study we found that the isothiocyanato compound **18a** effectively reduces PMN infiltrates in the zymosan A-stimulated murine peritonitis model of inflammation and is more efficacious than PGE_2. A more detailed biochemical characterization of the compounds reported here is currently being explored.

Acknowledgments

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Supplementary data

Experimental procedures, characterization data for compounds and murine peritonitis. These data can be found in the online version.

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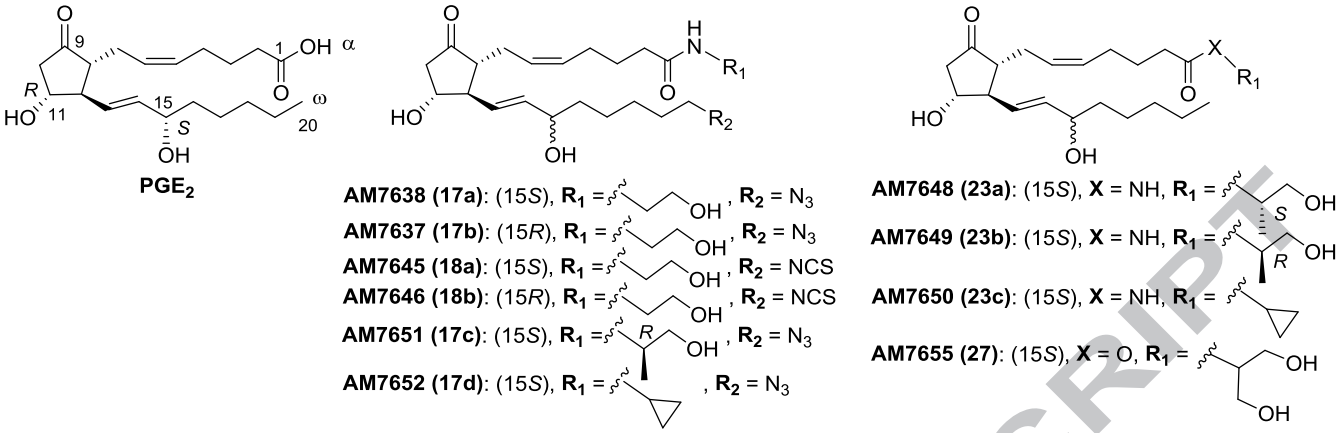


Figure 1: PGE_2-EA and 2-PGE_2-G analogs synthesized.

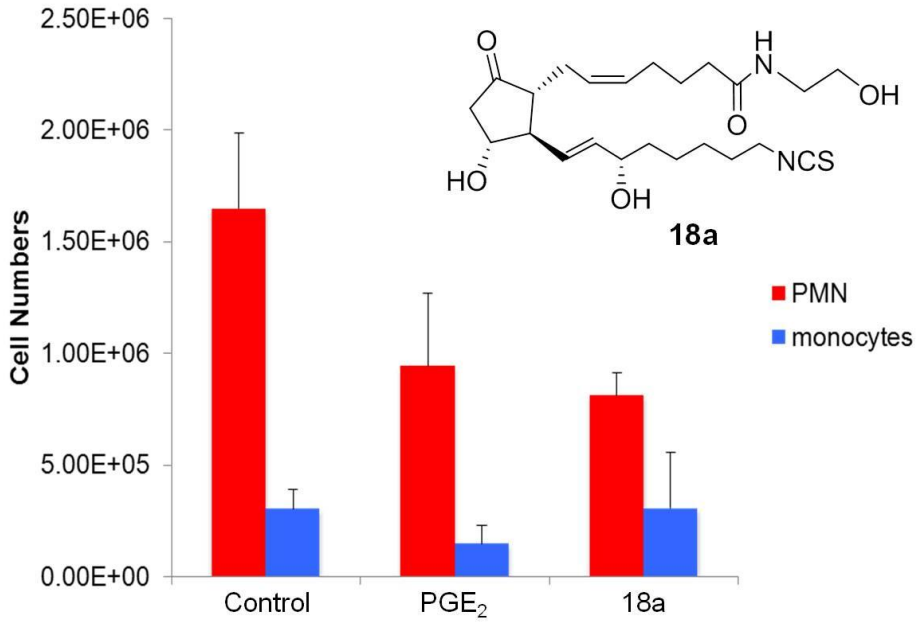
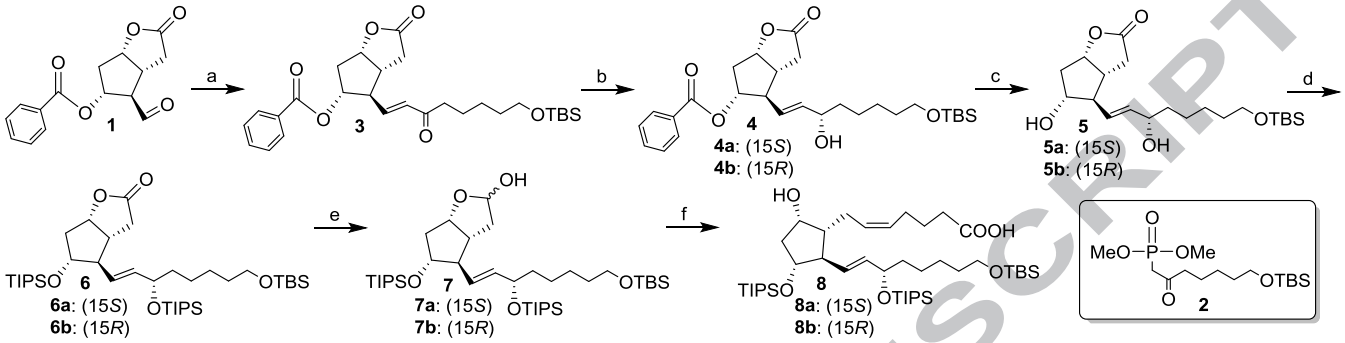


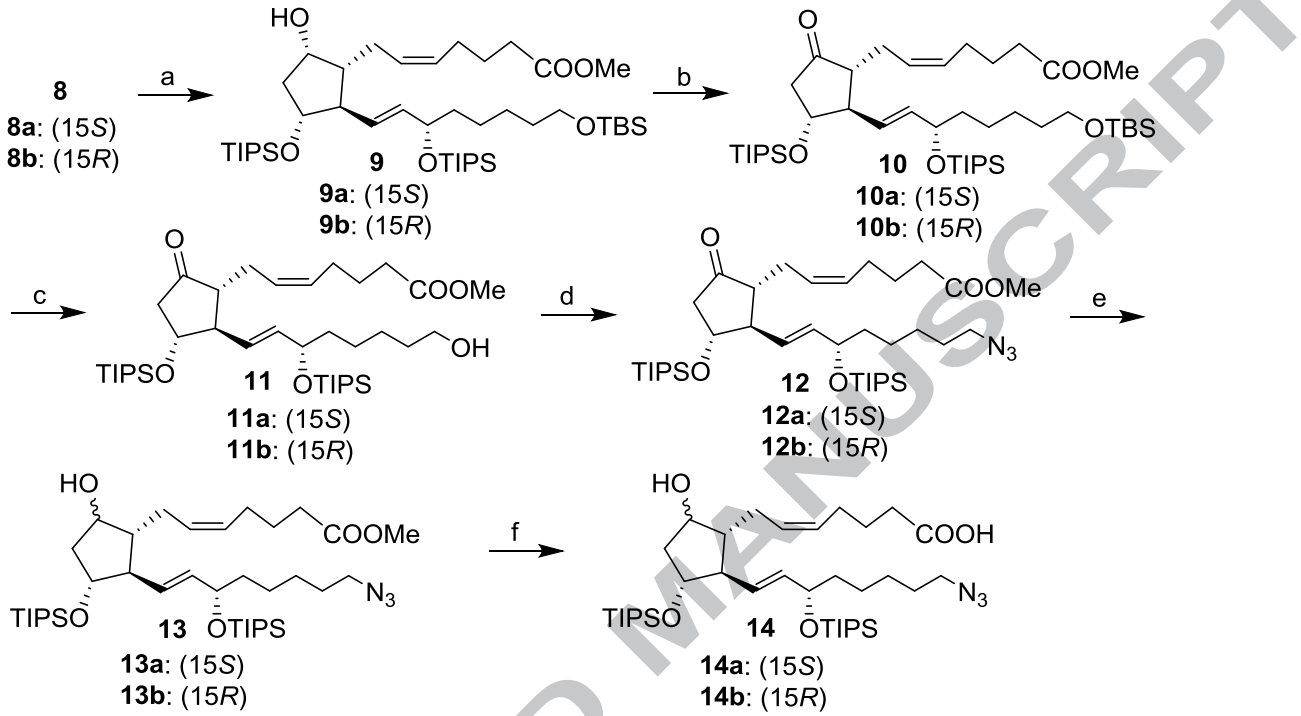
Figure 2: Comparisons for PGE2 and **18a** in reducing leukocytes in murine peritonitis. Polymorphonuclear neutrophils (PMN) and monocytes were enumerated following injection with 1µg/mouse compound i.v., after 5 min initiation of peritonitis with 1mg zymosan A. After 4 hrs, leukocytes were obtained via lavages and leukocytes were identified and enumerated using light microscopy as well as fluorescence-activated cell sorting.

Scheme 1: Synthesis of the C-8 and C-12 chain appendages.



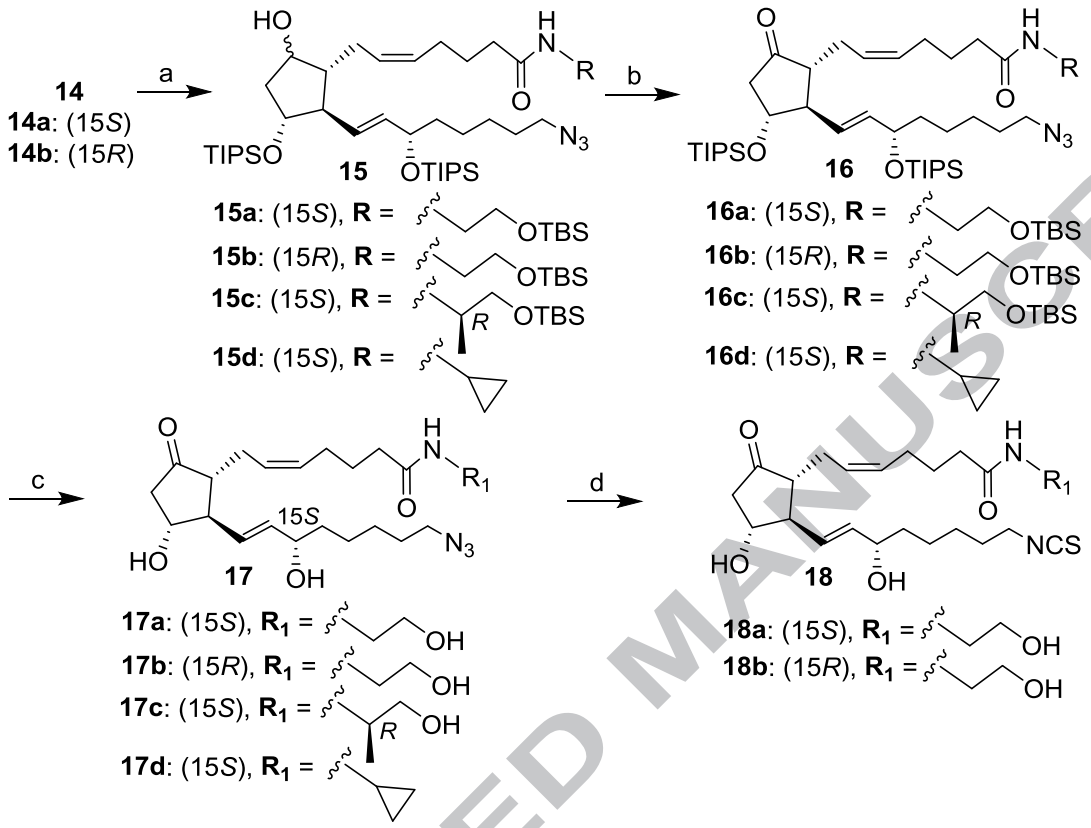
Reagents and conditions: (a) **2**, NaH, THF, 0^{o}C, 1 h, then **1**, 0^{o}C to r t, 2.5 h, 100%; (b) $CeCl_3$, $NaBH_4$, MeOH, 0^{o}C, 30 min, then chromatographic separation of **4a** and **4b**, 86% overall yield; (c) K_2CO_3, THF/MeOH, 50^{o}C, 2.5 h, 91% for **5a** and 89% for **5b**; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0^{o}C, 1h, 90% for **6a** and 93% for **6b**; (e) DIBAL-H, CH_2Cl_2, -78^{o}C, 30 min, 93% for **7a** and **7b**; (f) Br Ph_3P-$(CH_2)_4$-COOH, *t*-BuOK, THF, 0^{o}C, 30 min, then **7a** or **7b**, 1 h, 73% for **8a** and 78% for **8b**.

Scheme 2: Synthesis of the functionalized azido tail.



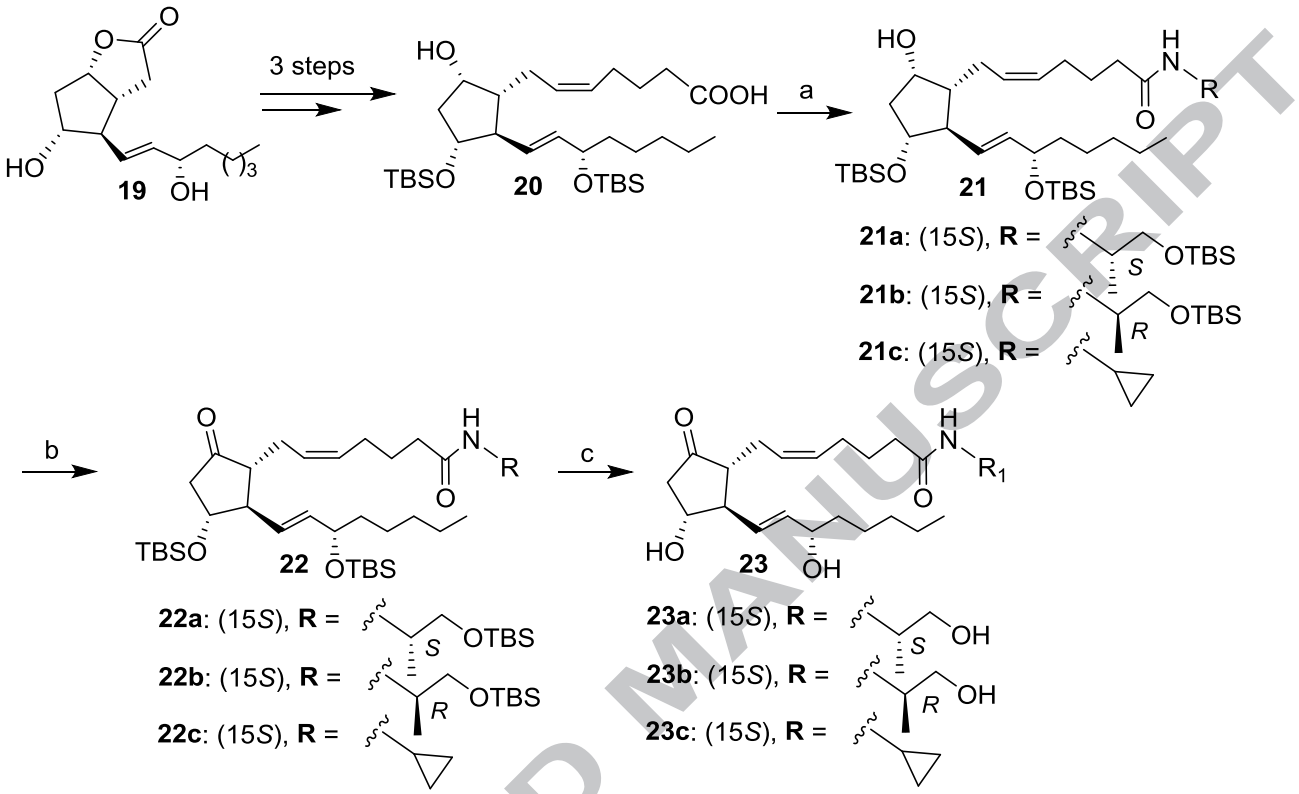
Reagents and conditions: (a) $TMSCHN_2$, Et_2O, MeOH, r t, 15 min, 93% for **9a** and 92% for **9b**; (b) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0^{o}C to r t, 1 h, 96% for **10a** and **10b**; (c) AcOH:THF:H_2O (3:1:1), r t, overnight, 93% for **11a** and 91% for **11b**; (d) $Zn(N_3)_2$-Py, DIAD, PPh_3, toluene, r t, 7 h, 91% for **12a** and **12b**; (e) $CeCl_3$, $NaBH_4$, THF/MeOH, 0^{o}C, 1 h, 83% for **13a** and 89% for **13b**; (f) NaOH, THF/H_2O, r t, 24 h, 85% for **14a** and 84% for **14b**.

Scheme 3: Final steps to the azido and isothiocyanato substituted prostamide probes.



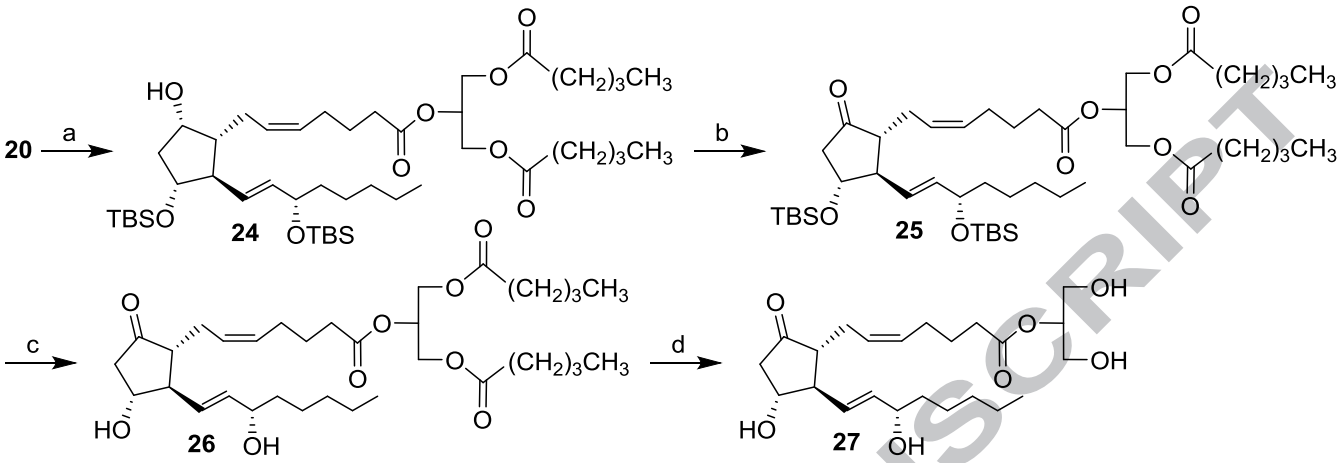
Reagents and conditions: (a) carbonyldiimidazole, CH_2Cl_2, r t, 30 min, then R-NH_2, 3h, 88-92%; (b) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0^{o}C to r t, 1 h, 97-98%; (c) 48% HF, pyridine, THF/MeCN, 0^{o}C to r t, overnight, 45-48%; (d) CS_2, PPh_3, THF, r t, 48 h, 94-96%.

Scheme 4: Synthesis of the *n*-pentyl chain tail analogs.



Reagents and conditions: (a) carbonyldiimidazole, CH_2Cl_2, r t, 30 min, then R-NH_2, 3h, 87-90%; (b) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0^{o}C to r t, 1 h, , 89-91%; (c) 1% HCl, aqueous MeOH, 5 min, 80-83%.

Scheme 5: Chemoenzymatic synthesis of the glycerol ester analog.



Reagents and conditions: (a) HO-CH[CH_2-O-C(O)-$(CH_2)_3CH_3$]$_2$, carbonyldiimidazole, CH_2Cl_2, 0^{o}C to r t, 24 h, 82%; (b) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0^{o}C to r t, 1 h, , 97%; (c) 1% HCl, aqueous MeOH, r t, 5 min, 79%; (d) Candida rugosa lipase, EtOH, 2 h, 46%.

Graphical abstract