A general approach to cyclopentenone neuroprostanes: total synthesis of 14-A$_4$-NeuroP

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Dedicated to the Morrow’s group in occasion of the first anniversary of a fruitful collaboration.

Neuroprostanes are generated both in vitro and in vivo by the free radical promoted oxidation of docosahexaenoic acid (DHA). The phenomenon, commonly referred to as lipid peroxidation, has long been associated with neurodegenerative diseases, such as Alzheimer and Parkinson. In order to set diagnostic tests for these pathologies, we embarked in the synthesis of cyclopentenone neuroprostanes, to be used as biomarkers in vivo. The synthesis of 14-A$_4$-NeuroP (1) was realized through an original approach based on a highly stereoselective Julia olefination and, due to its versatility, can be considered a general approach to cyclopentenone neuroprostanes.

1 Introduction

Neurodegenerative diseases, such as Alzheimer, mild cognitive impairment, dementia with Lewy bodies and Parkinson, affect millions of people, greatly reducing their quality of life and, in many cases, causing death. Therefore, great efforts have been made to get a deeper knowledge of the pathogenesis and to develop non-invasive diagnostic tests. Since the lipid peroxidation induced by oxidative stress has been implicated in the pathogenesis of various central nervous system diseases, it has been proposed to use the radical mediated peroxidation products of docosahexaenoic acid (C22:6ω3, DHA), named neuroprostanes (NeuroPs), as specific and practical biomarkers for assessing oxidative stress and neuronal damage, as well as for evaluating the effects of therapies [1]. Motivated by these aspects, by the lack of precedent syntheses, and by the challenging structural features, we embarked in the total synthesis of 14-A$_4$-NeuroP (1) as a racemic mixture of diastereomers.

2 Retrosynthetic analysis

Since NeuroPs are formed in vivo as racemic mixture of diastereomers through a non-enzymatic pathway from DHA [2], we embarked in the synthesis of the mixture of 14-A$_4$-NeuroPs. The main synthetic challenge is the –cis relative stereochemistry of the two lateral chains on the five membered ring, which proved to be less stable than the –trans stereochemistry commonly found in prostanoids. From a retrosynthetic point of view we envisioned a first fundamental disconnection, in analogy with the well-known prostaglandin chemistry, based on a retro-Wittig olefination [3]. This approach identified lactol 2 as the electrophilic partner of the reaction. The installation of the lower chain, on the other hand, was based on an original approach, namely a retro-Julia olefination, identifying aryl-sulfone 3 and aldehyde 4 as the partners of the reaction. While the former could be synthesized from compound 5, a key intermediate already prepared in our laboratories [4], the latter could be obtained from alcohol 7 via a Kiliani-Fischer approach. Disconnection of C4-C5 bond in alcohol 7 finally identified 1-butynol and 1-bromo-2-pentyne as the precursor for a Stephen-Castro coupling [5]. 

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Fig. 1: The formation of NeuroPs from DHA by reaction of Reactive Oxigen Species (ROS).

Fig. 2: Retrosynthetic analysis of 14-A₄-NeuroP.

### 3 Synthesis

The synthesis of 14-A₄-NeuroP as a racemic mixture of diastereomers thus commenced with the coupling between 1-butynol and 1-bromo-2-pentyne, yielding the unstable 1,4-diyne 9 as the only product. Compound 9 was then stereoselectively reduced to 1,4-diene 7 by using H₂ and Lindlar catalyst in 70% yield. Reduction with NiP₂ resulted in comparable yield but lower stereoselectivity. Oxidation of 7 was performed with DMP, and after partial purification of the resulting unstable aldehyde [6], KCN, 18-c-6 and TBSCN were added to give a prompt one-pot addition and protection to obtain cyanohydrine 6 in 80% yield. Reduction of the nitrile to aldehyde with DIBAI-H at -78 °C failed, and the use of the complex n-BuLi·DIBAI-H [7] formed in situ at 0 °C was required to get racemic aldehyde 4, which was obtained in 55% yield over the five steps.

On the other hand aryl sulphone 3 was obtained in two steps in 76% yield from 5 by means of a Mitsunobu thioetherification with PT-SH, DEAD and Ph₃P and a chemoselective oxidation of the S atom with H₂O₂ and (NH₄)₂MoO₄. When aryl sulfone 3 was treated with KHMDS, despite the close values of pKa for the lactone and the sulfone moieties [8], chemoselective deprotonation occurred on the last
one, and the resulting carbanion easily reacted with aldehyde 4 to yield the desired olefine with complete E-stereoselectivity. Reduction of lactone 10 with DIBAL-H in THF finally gave lactol 2 quantitatively.

![Diagram of synthesis](image)

**Fig. 3:** Synthesis of lactol 2: a) NaI 1.2 eq, CuI 1.2 eq, CsCO$_3$ 1.2 eq, DMF, r.t., 3 h; b) Lindlar cat. 77% in w/w, hexane/AcOEt 1:1, r.t., 12 h, 70% (two steps); c) DMP 1.15 eq, DCM, r.t., 1 h, than TBSCN 1.2 eq, 18-c-6 0.1 eq, KCN 0.1 eq, 80% (from 7); d) DIBAL-H 1.7 eq, n-BuLi 1.68 eq, 0°C, 45 min, than 6, 45 min, 94%; e) Ph$_3$P 1.2 eq, PT-SH 1.2 eq, DEAD 1.3 eq, PhMe, 0°C, 3 h, 96%; f) (NH$_4$)$_2$MoO$_4$ 15% w/w, H$_2$O$_2$ 30%, 12 h, 78%; g) KHMDS 1.2 eq, DME, -78°C, 50 min, than 4 1.15 eq, from -78°C to r.t., 12 h, 60%; h) DIBAL-H 1.2 eq, THF, -78°C, 99%.

![Diagram of completion](image)

**Fig. 4:** Completion of the synthesis: i) Me(MeO)NH•HCl, n-BuLi, THF, -78°C, than PPTS, EVE, DCM, 64% overall yield; j) DIBAL-H, THF, -78°C, than KHMDS, 8, PhMe, r.t., followed by aldehyde, -78°C, 70%; k) PPTS, EtOH/DCM (6:1), than Ba(OH)$_2$•8H$_2$O, MeOH, 73%; l) DMP, DCM, than 48% aq HF, MeCN, r.t., 95%.

Wittig reaction on lactol 2 resulted in low selectivity or in the formation of by-products inseparable from the desired olefin, depending on the reaction conditions. Thus lactone 10 was opened as a Weinreb amide. Protection of the resulting hydroxyl as an ethoxyethyl ether (EE) allowed the reduction of the amide with DIBAL-H to yield an unstable aldehyde which was directly used in the next reaction. When the Wittig reaction with phosphonium salt 8 was carried on the newly formed aldehyde under salt free conditions [9], the desired olefine was obtained as a sole Z-stereoisomer in 70% yield. With compound 12 in hand, the synthesis of 14-A$_4$4-NeuroP proceeded smoothly. First the hydroxyl group on C-8 and the carboxylic acid were deprotected by using PPTS in EtOH/DCM and Ba(OH)$_2$•8H$_2$O in MeOH respectively. Subsequently the hydroxyl group was oxidized with DMP, to yield compound 13 in 73% yield over 3 steps. Cleavage of the remaining TBS ether finally yielded 14-A$_4$4-NeuroP as a mixture of diastereomers, but without appreciable epimerization of the C-7 and C-11 stereocenters to the more stable undesired –trans configuration.
4 Conclusions

In conclusion the first total synthesis of a cyclopentenone NeuroP was completed in good total yield. The target molecule was obtained as a mixture of $\alpha/\beta$ diastereomers at C-14, as formed in nature. Since the differences between the compounds belonging to the various series of NeuroPs are represented only by the relative length of the lateral chains, this approach can be considered a general strategy for the synthesis of cyclopentenone NeuroPs.

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