ABSTRACT

Neuroprostanes are cyclic oxygenated metabolites formed *in vivo* from docosahexaenoic acid, the main polyunsaturated fatty acid of the human brain. The non-enzymatic auto-oxidative biosynthesis provides neuroprostanes non-selectively as mixtures of regio- and diastereoisomers, making their isolation and identification difficult without primary standards. Thus, synthetic material is necessary to investigate the biological properties of individual molecules as well as the potential of neuroprostanes as biomarkers of oxidative stress in medical diagnostics. Two different synthetic approaches targeting the most abundant regioisomeric series of neuroprostanes are reported.

First, an enantioselective strategy toward an asymmetric core of cyclopentenone neuroprostanes relying on an organocatalyzed Michael addition was developed. A complementary racemic synthesis involving diastereoselective vicinal difunctionalization is also described. The assembly of the full carbon framework of the target natural product was accomplished via a double olefin metathesis and Wittig olefination.

In the second part, a unified approach to lipid metabolites bearing a 3-hydroxypentenyl side chain is reported. The key steps involved a multiple alkynylation of a central functionalized precursor, constructed by an oxidative dianion radical cyclization, and a stereoselective semihydrogenation. The strategy provides access to a wide range of neuroprostanes thanks to an orthogonal protection of the key intermediate and was applied to the total synthesis of a closely related F_{3t}-isoprostane derived from eicosapentaenoic acid.