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Enzyme assisted syntheses of chiral building blocks for isosters of diglycerides, phospholipids and PAF

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Abstract—Lipase catalyzed desymmetrizations of suitably substituted, achiral 1,3-diols lead to the corresponding chiral building blocks of high enantiomeric purities, starting materials for the synthesis of isosteric carba-analogues of 1,2-*sn*-diglycerides and phospholipids with interesting biological activities. Lipase catalyzed resolutions of the corresponding ether derivatives lead to the corresponding building blocks for carba-analogues of PAF.

1. Introduction

Molecules with a glyceride substructure are among the most important and at the same time ubiquitous biologically active compounds in living organisms. While certain phospholipids are essential constituents of cell membranes,[1] others are involved in highly important processes of cell regulation and signal transduction, resulting—due to specifically acting phospholipases—in the formation of important second messengers such as arachidonic acid, 1,2-*sn*-diglycerides and inositol phosphates.[2] Platelet activating factor (PAF), an ether lipid displays a wide variety of biological (physiological) properties and is, among others, an important mediator of platelet aggregation, inflammation and anaphylaxis.[3,4]

In view of our continuing interest in molecules of the inositolphospholipid pathway,[5,6] indications in the literature that carba-analogues of phospholipids could be interesting substrates and—possibly—effective inhibitors of phospholipase A_2,[7,8] prompted us to synthesize a series of such molecules in which the sp^3—oxygens of the 2-positions are replaced by sp^3—carbons (Fig. 1).

These changes result in isosteric mimics of the natural molecules with minimal deviations regarding bond angles and distances. Moreover, it can be expected that carba-analogous 1,2-*sn*-diglycerides would display considerably higher stability and lifetime as compared to the native second messengers. Furthermore, certain derivatives of PAF, e.g. Ilmofosine (BM 41.440)[9] or (ET-18-OCH3)[10]—Edelfosine are claimed to be promising anti-tumoractive compounds and anti-proliferation active derivatives.[11–13]

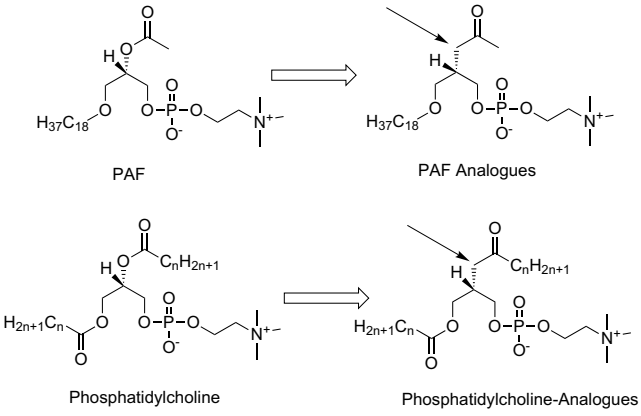

Figure 1. Isosters of phospholipids and PAF.

While a number of such molecules and related derivatives have been described in the past[7,14] in only few cases they have been prepared as single enantiomers.

The frequently observed close relationship between absolute configurations and biological activities—together with their proven or potential properties—provided sufficient motivation to develop a general

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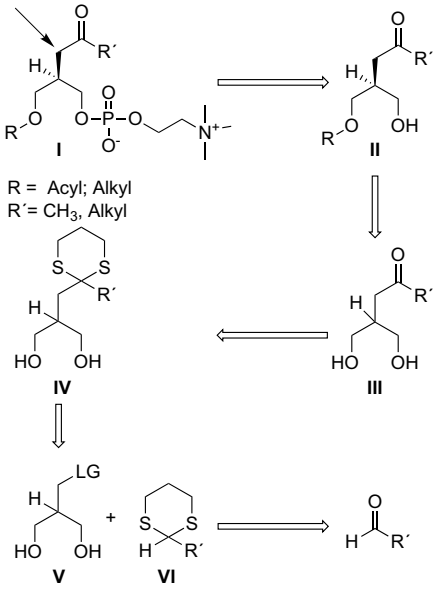
synthetic strategy towards the preparation of the title compounds in enantiomerically pure form. In order to compare biological activities, both enantiomeric series had to be made available for every target structure.

2. Retrosynthesis

Retrosynthetic analysis (Scheme 1) of an enantiomerically pure 2-*sn*-carba-analogous phospholipid **I** leads—via formal removal of the phosphocholine head group—to the corresponding carba-analogues of 1,2-*sn*-diglycerides **II**, which in turn, can be correlated to the corresponding diols **III**, which are clearly equivalent to the thioketals **IV**. It can easily be envisaged that both **III** and **IV** could possibly be desymmetrized via lipase catalyzed asymmetric hydrolyses or acylations.

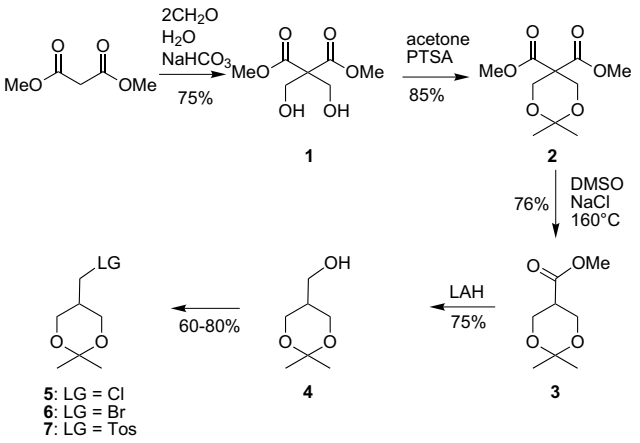


Scheme 1. Retrosynthesis of the title compounds.

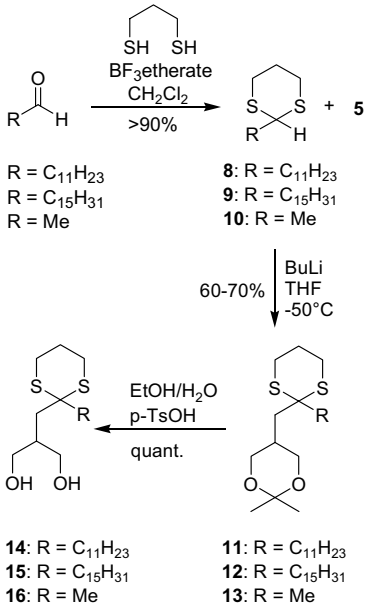
Disconnection of **IV** leads directly to building blocks **V** and **VI**. While **V** can serve as a central building block for the 'glycerol' backbone in all of the title compounds, **VI** can be individually prepared from readily available aldehydes via a simple protection step. Consequently, a series of compounds with the general structure of **IV** were prepared as follows (Schemes 2 and 3).

3. Synthesis of the central building block V

Condensation of formaldehyde with dimethylmalonate leads to the diol **1** which, after protection as acetonide **2** (85%) is submitted to a Krapcho reaction (concomitant hydrolysis and decarboxylation[15]) leading to the protected ester derivate **3** (76%) which, by reduction with $LiAlH_4$ leads to the protected diol **4** in 75% yield. The overall yield, starting from dimethylmalonate is 39%. A successful application of this building block depends, of course on the introduction of a suitable leaving group such as Cl, Br or Tosyl leading to the



Scheme 2. Synthesis of central building blocks **V**.



Scheme 3. Synthesis of building blocks **IV**.

derivatives **5**–**7**, respectively. It turned out that the corresponding chloro-compound **5** is best suited as the electrophile for the following coupling reactions with the 2-alkyl-1,3 dithiane building blocks. Thus **4** was transformed into **5** using CCl_4/PPh_3 in 72% yield. Compound **5** constitutes the central building block for construction of the 'glycerol' backbone.

4. Syntheses of building blocks VI

Using the classical Corey–Seebach methodology[16] aldehydes of wide structural variety can be converted into the corresponding 2-substituted -1,3 dithianes, building blocks **VI**. Thus *n*-dodecanal and *n*-hexadecanal (prepared from *n*-hexadecanol using a Swern-type oxidation[17,18] were converted in the presence of 1,3-propanedithiol/$BF_3 \times Et_2O$ into the corresponding derivatives **8**–**10,** with **10** being **a** potential building block for PAF analogues (Scheme 3).

5. Coupling of building blocks V and VI

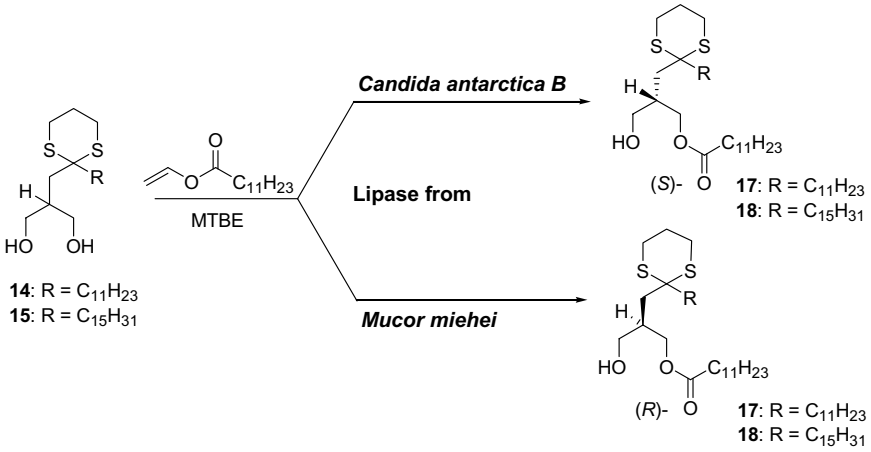
Deprotonation of the 1,3-dithiane moieties in **8**–**10** was achieved with *n*-BuLi (THF, −50 °C) and the resulting anions were reacted with the central building block **5** leading to the protected 1,3-diols **11**–**13**, respectively in yields of 70%. Deprotection **11**–**13** was achieved quantitatively using *p*-TsOH leading to achiral diols **14**–**16**, respectively (Scheme 3).

6. Lipase-catalyzed desymmetrizations of alkyl-1,3 dithiane derivates 14 and 15

It was confirmed with the 1,3-dithiane derivatives that enantioselective acylations in general produced higher chemical yields than the corresponding hydrolyses. For a flexible synthesis of a particular target molecule and, in order to avoid protection/deprotection steps for a possibly required inversion of configuration it seemed attractive to screen for lipases, which could produce both enantiomers at will—starting from the same diol substrate (Scheme 4).

After some screening effort we were indeed able to realize this expectation. Using the 1,3 dithiane derivative **14** as model compound we were indeed able to identify two different lipases, which produced opposite enantiomers.

The transformations can be followed directly by HPLC on a chiral support (Chiralcel OD-H). While the lipase from *Candida antarctica B* produces the (*S*)—configurated monoester **17** (Fig. 2B), the (*R*)-enantiomer was obtained by using the lipase from *Mucor miehei* (Fig. 2C).



Scheme 4. Desymmetrization of achiral 1,3 diols by lipases—production of opposite enantiomers.

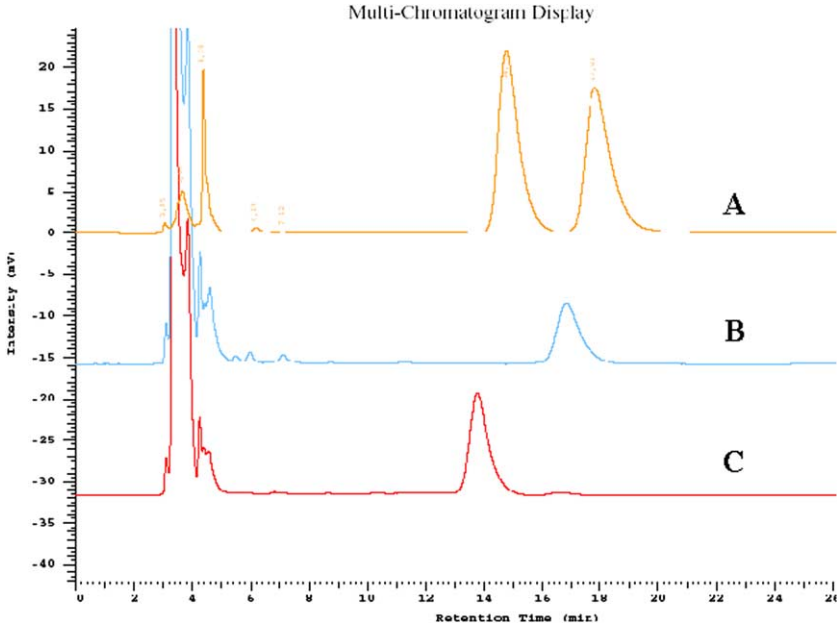
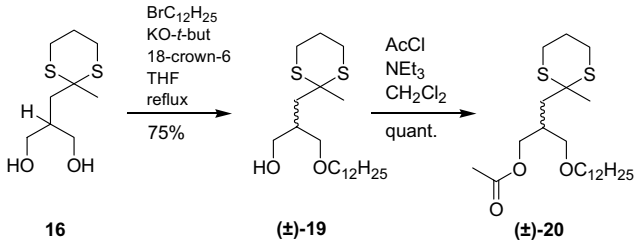


Figure 2. HPLC Multichromatogram of racemic compound (**A**), (*S*)-**17** (**B**), (*R*)-**17** (**C**). Conditions: Column: Daicel Chiralcel OD-H; *n*-heptane/2-propanol 99:1; flow: 1 ml/min; UV-249 nm.

The absolute configurations were tentatively assigned based on the resulting carba-analogous phospholipids (see Section 8) derived thereof, while attempting to obtain a crystalline derivate for an X-ray structure, the ultimate confirmation.

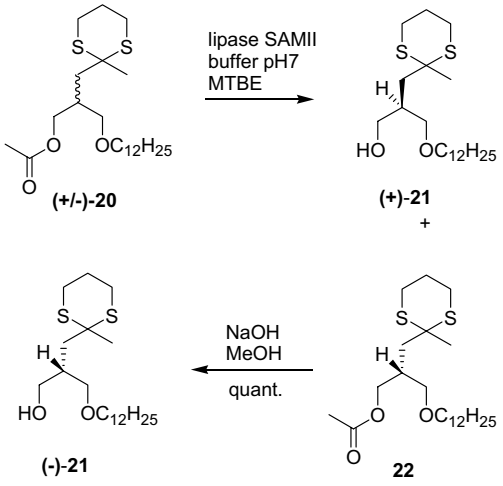
7. Building blocks for PAF analogues

For the synthesis of the corresponding ether lipids we had to resort to the lipase-catalyzed resolution of the corresponding racemic ether derivate (±)-**20**. Thus, mono alkylation of the 1,3-dithiane building block **16** led to racemic **19** from which **20** was obtained via classical chemical acylation (Scheme 5).



Scheme 5. Synthesis of the racemic precursor (±)-**20**.

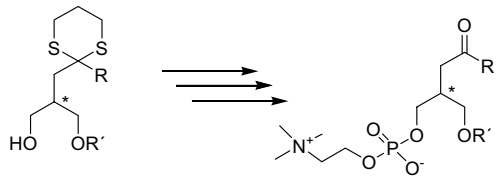
The kinetic resolution (Scheme 6) of (±)-**20**, using lipase *SAM II* (*Pseudomonas* sp.) proved to be the method of choice. The enantiomers (+)-**21** and (−)-**21** were obtained with >96 and 92% e.e., respectively as shown by HPLC on a chiral support (Chiralcel OD-H).



Scheme 6. Lipase catalyzed resolution of (±)-**20**.

8. Conclusion

In summary, we have demonstrated in this preliminary communication that lipase—catalyzed transformations can be used effectively to transform both achiral 1,3-diols and their racemic analogues into pure enantiomers of opposite absolute configurations. The here obtained chiral building blocks are now available as mimics of 1,2-*sn*- and 2,3-*sn*-diglycerides for coupling reactions with inositol phosphates to the corresponding carba-analogues of inositol phospholipids. They were also converted into the corresponding, enantiomeric carba-analogues of phospholipids and ether lipids (PAF analogues) (Scheme 7).[19]



Scheme 7. Syntheses of carba-analogues of phospholipids and etherlipids from the enzymatically prepared chiral building blocks.

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