

# Large-scale manufacturing of chiral cyclopentendiol acetates, versatile prostaglandin building blocks

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Via Cesare da Sesto, 10  
20123 Milano - Italy  
Tel. 0039 02 83241119  
Fax 0039 02 8376457  
www.b5srl.com

**ANDREAS MEUDT** <sup>1</sup> \*  
**RICHARD WISDOM** <sup>2</sup>  
**JÖRG JUNG** <sup>2</sup>

**1. Archimica Group**  
Am Limespark 2  
D-65843 Sulzbach am Taunus,  
Germany  
Tel +49(0)69 305 34519  
Fax +49(0)69 305 34518  
Andreas.Meudt@archimica.com

**2. Archimica GmbH**  
Industriepark Höchst  
65926, Frankfurt am Main,  
Germany

\* Corresponding author

For the first time, enantiopure 1,4-cis-cyclopentendiol monoesters are available at large scale from Archimica. The synthesis of these long sought-after compounds has generated considerable attention over the last decades, as they offer completely new synthetic opportunities in pharmaceutical fine chemicals synthesis, especially in the manufacturing of prostaglandins. The synthetic methods developed to date suffer from severe disadvantages, especially from safety and economic standpoint. They have now become available after the first development of a stereo- and chemo-selective catalytic Luche reduction of hydroxycyclopentenone, accessible by the acid-catalysed rearrangement of furfuryl alcohol, and followed by the enzymatic formation of the title compounds. We expect that the ready availability of these compounds will enable the pharmaceutical industry to develop new synthetic pathways to several highly interesting compound classes.

**O**ptically active 1,4-cis-cyclopentendiol monoesters are highly versatile starting materials for the synthesis of prostaglandins, carbocyclic nucleosides and other biologically active products, hence of outstanding interest for pharmaceutical and fine chemical companies. In general, these enantiopure products can be accessed by enzymatic partial cleavage of diesters of cis-cyclopent-4-ene-1,3-diols or by enzymatic partial esterification of the diol (Scheme 1) (1).

Commercially available enzymes can be used for these operations. By careful control of the process parameters and workup conditions, the two enantiomers of the semi-esters can be obtained in high yields and with enantiomeric excess of more than 99.5%.

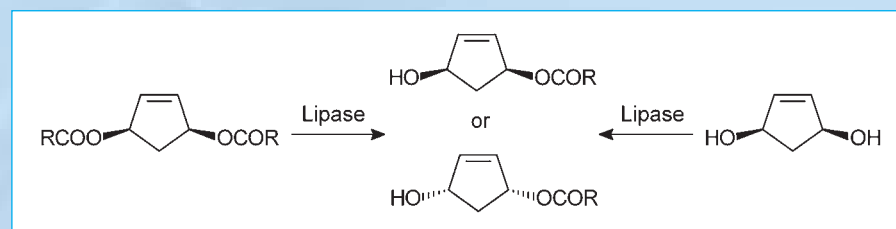
Surprisingly, the biggest issue in our initial attempts for developing these products was the availability of the starting materials, the cis-cyclopentene diol or its esters. Due to the huge potential of these building blocks in the pharmaceutical fine chemical industry, several academic and industrial groups have already worked on the synthesis of these basic building blocks. A variety of

different approaches have been developed over the last decades.

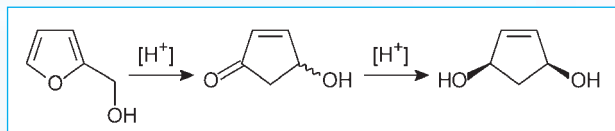
Probably the most well-known approach uses epoxidation of cyclopentadiene with peracids or peroxides, followed by copper- or palladium-catalysed rearrangements (2). As a result of a very thorough safety analysis, our own conclusion of this pathway was that there are huge safety hazards connected with this approach, and that any attempts to scale this chemistry would pose severe risks. Whereas peroxide handling can be managed by special precautions, the combination with hazardous cyclopentadiene was considered to result in uncontrollable risks. As a conclusion, we decided to stop all further work on this chemistry.

Another synthesis for such cis-cyclopentene diols consists in the reaction of cyclopentadiene with singlet oxygen, followed by reduction of the adduct with thiourea (3). This reaction sequence was disregarded as being unsuitable for scale-up, for obvious reasons.

A third sequence uses cheap and readily available furfuryl alcohol, which can be rearranged under slightly acidic conditions, to form 4-hydroxycyclo-



Scheme 1



Scheme 2

pent-2-enone. After purification and, depending on the reducing agent, protection of the free hydroxyl group, this intermediate can be selectively reduced to yield cis-cyclopent-4-en-1,3-diol and derivatives (Scheme 2) (4). Whereas this looked like an attractive synthesis route on paper, also this literature sequence included several severe scale-up issues.

First of all, the reduction itself typically results in insufficient selectivity with regards to cis- / trans- selectivity. Additionally, over reduction occurs, producing saturated cyclopentane derivatives, which have proven to be highly problematic in purification attempts for this material. To make things even worse, the rearrangement product of furfuryl alcohol is formed in a purity of only 40-60% and, due to its poor stability, cannot be purified in an economic manner. As a conclusion, a reduction method which could be a candidate for successful upscaling requires reduction of the crude product with high selectivity and in good yields without necessitating the need for purification the crude hydroxy ketone.

Best results in this reduction can be achieved by using aluminium or boron hydrides. Aluminium hydrides suffer from the disadvantage that the free hydroxy group of the substrate has to be protected before the reduction and deprotected at the end of the sequence, making the whole reaction lengthy (five or six steps from furfuryl alcohol to the two enantiomeric monoacetates) and uneconomic.

Using borohydrides appears to be economically much more viable on first sight, obviating the need for OH protection. However, only LUCHE conditions (4) have been proven to show sufficient selectivities. Using this protocol, over-stoichiometric quantities of cerium(III) salts are used. As an example in following the above publication, the reduction of 10 g of 4-hydroxycyclopent-2-enone would require 38 to 76 grams of cerium(III) chloride as its heptahydrate. It is obvious that such conditions cannot be used in an economically attractive process, not only because of high costs for the rare earth metal and resulting

waste disposal costs, but also because of the difficulties in separating the highly hydrophilic product from the salts.

This problem does not

allow for an aqueous workup for removal of the large salt load.

As a conclusion, none of the protocols was considered useful in making large quantities of the title compounds or derivatives economically accessible.

For reasons described above, we selected the last mentioned protocol as the starting point of our optimisation work. As already described, the rearrangement and the enzymatic step at the end of the sequence had to be improved as well, but the most crucial aspect of the sequence was the reduction step. The prime target of this program was to develop conditions under which the reduction could be performed without protecting group strategies, and without the need of large quantities of cerium(III) or other transition metals – hence avoiding the respective large waste stream loadings of such metals. A further requirement was to obtain attractive yields in an easy process with few process steps, despite having a “crude” starting material. Additionally, high selectivities with regards to over-reduction and cis- / trans-selectivities were required, to avoid lengthy and costly purifications.

To the best of our knowledge, the process we have developed is the very first catalytic LUCHE reaction (5). The breakthrough was possible by very careful optimisation of the solvent mixture and the reaction temperature, but probably most important by slow addition of the reducing agent, sodium borohydride, over the course of the reduction. After these conditions had been fully optimised, it was proven possible to successfully use the un-purified starting material, hydroxy cyclopentenone – purities as low as 40-50% could be used without issues if the solvent mixture contained methanol. The best reducing agent is sodium borohydride, and the catalyst can be used in catalytic quantities, often much less than 20 mol%.

To overcome the problem of isolation of the highly hydrophilic product after reduction, the material was esterified by adding acid anhydrides, acid chlorides or acids and water-

removing agents.

The requirement of an easy process with few operational steps was fulfilled by using the acylating agent in excess, to convert methanol residues into the respective methyl ester. This step makes the isolation much easier.

The cerium salts can be isolated by a filtration after completion of the reduction.

In general, isolated yields in this reduction are higher than 70%, which is particularly surprising because of the utilisation of very impure rearrangement product. The cis selectivity is very high, and less than 5% of the trans compound are observed if the reduction is performed under cryogenic conditions (<-50°C). Also the extent of over-reduction is controlled to less than 10% by working at low temperatures. These low impurity levels, as described, can be readily removed in the normal workup procedure and in the following steps of the sequence.

The overall process has already been scaled to the pilot plant (>100 kg). The enantiopure products were obtained in good overall yields and in outstanding purity. No scale up issues were observed and production of much larger quantities should not be an issue.

To the best of our knowledge, this is the first large-scale synthesis of these broadly applicable and highly useful building blocks. The availability of these materials from Archimica should allow broad new applications of these compounds, not only in prostaglandin synthesis, but also on a much broader basis in pharmaceutical fine chemicals synthesis.

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