Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 267–273

A direct intramolecular asymmetric catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes

Vanya B. Kurteva[a,b] and Carlos A. M. Afonso[c,*]

[a]*Institute of Organic Chemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev str., block 9, 1113 Sofia, Bulgaria*
[b]*REQUIMTE/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal*
[c]*CQFM, Departamento de Engenharia Química, Instituto Superior Técnico, 1049-001 Lisboa, Portugal*

Received 21 April 2004; revised 29 July 2004; accepted 1 October 2004

Available online 6 November 2004

Abstract—The intramolecular asymmetric catalytic aldol cyclodehydration of 1,6-dialdehydes to the corresponding cyclopentene carbaldehydes was accomplished for the first time on the cases of *meso*-3,4-disubstituted hexanedials. It was found that the presence of a hydroxyl group in the catalyst's molecule seems to be crucial to reach stereocontrol. The chiral centre, bearing the carboxylate functionality, in hydroxy amino acids controls the stereochemistry of the final product. In the case of amino alcohols, where carboxylate functionality does not exist, the configuration of the carbon, connected with the hydroxyl group, seems to be the key one. Additionally, it was observed that chiral phosphines and phosphites are effective catalysts for this cyclodehydration but without inducing stereocontrol.

1. Introduction

In recent years the synthesis of carbocyclic nucleoside analogues has been the subject of great interest, due to their wide range of biological activity profiles.[1–4] In the same time, these compounds are chemically and enzymatically more stable than the corresponding nucleosides, according to the absence of a typical glucoside bond in their molecules.[5] The role of the methylene group in the carbocycle as a bioisostere of oxygen is justified by the observed antiviral and antitumor efficacies of some natural carbocyclic nucleosides, such as Arystomicin[6] and Neplanocin A,[7] as well as synthetic ones, as Carbovir[8–10] and Abacavir.[11–14] The latter shows great anti-HIV activity and therefore, it is used clinically to treat AIDS and AIDS-related complex.

As precursors of the carbocyclic moieties of compounds like nucleosides, carbohydrates and many other products of biological importance, cyclopentanoids play a fundamental role in synthetic organic chemistry. Among the broad range of organic transformations for the five-membered ring construction, the aldol condensation is an exceptionally useful C–C bond-forming reaction.[15–17] Its catalytic asymmetric variant is a strategic one both in chemistry and in biology, where it presents a critical biological transformation in the context of metabolism. The enzymatic reactions, catalysed by Type I aldolases, which accept hydrophobic organic substrates, utilise an enamine mechanism.[18] The aldolase antibodies synthesis and application in aldol reactions,[19–24] as well as their chemical oversimplified versions, have received considerable attention in recent years. Proline-catalysed asymmetric intramolecular condensation of dicarbonyl compounds, well known as Hajos–Parris–Eder–Sauer–Wiecher reaction, was discovered in the 1970s,[25–29] and afterward widely exploited both in its intermolecular[30–37] and intramolecular[38–46] variants. This reaction involves an enamine intermediate, with the C–C bond formation as the rate determining step and the stereodifferentiation occurring in this step, before dehydration. In the case of the Robinson annulating reaction it was found[45] that while proline, as well as a number of similar chiral compounds, like hydroxy proline, azetidine carboxylic acid etc., catalyse both steps of the transformation, the chiral amines tested catalyse the annulation but not the dehydration. It was suggested that chiral compounds containing a secondary amine of pyrrolidine type and a carboxylate functionality are the most efficient catalysts and that the carboxylic acid functionality appears to be the key to the dehydration step.

The asymmetric aldol reactions of diketones and ketoaldehydes are widely investigated, while the condensation of

Keywords: Cyclopentenecarbaldehydes; Aldol; Cyclodehydration; Asymmetric catalysis; 1,6-Dialdehydes.
* Corresponding author. Tel.: +351 21 8417627; fax: +351 21 8417122; e-mail: carlosafonso@ist.utl.pt

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.034

dialdehydes, well known in its non-chiral version reaction, is much less studied. To the best of our knowledge, the only paper on this subject reports the direct intramolecular asymmetric catalytic aldol condensation of dialdehydes on the case of proline-catalysed cyclisation of heptanedials.[46] The corresponding hydroxy cyclohexanecarbaldehydes are isolated with stereocontrol at the carbons, bearing the hydroxyl and carbaldehyde functionalities, while no dehydration products are detected, like in the most part of the cases of six-membered ring formation. In contrast, the direct catalytic intramolecular cross-aldol cyclisation of 1,6 dialdehydes, a widely exploited non-chiral transformation in the synthesis of a broad range of biologically active products,[47–55] leads to dehydration products in general, the corresponding cyclopentenecarbaldehydes. However, the asymmetric variant, requiring an asymmetricity to be induced at the β-carbon in respect to the aldehyde, is still unknown.

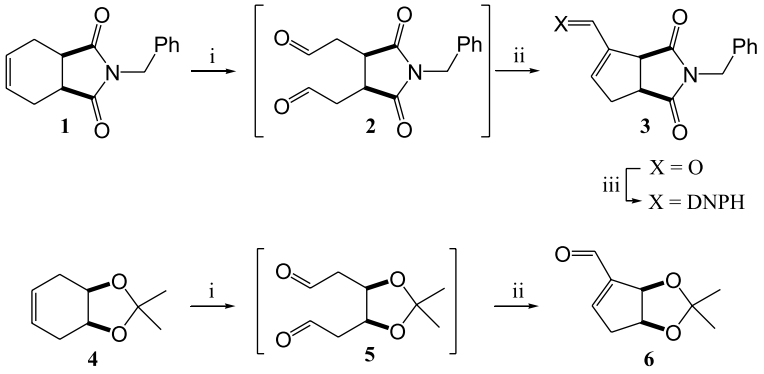
As a part of our study on the cyclopentanoid synthesis, an asymmetric version of the direct intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes, leading to the corresponding cyclopentene carbaldehydes, is presented herein.

2. Results and discussion

The *meso*-3,4-disubstituted-1,6-dialdehydes were readily obtained by olefin oxidation of a series of differently *meso*-4,5-disubstituted cyclohexenes, applying ozonolysis and subsequent dimethyl sulphide (DMS) reductive work-up. Their asymmetric aldol cyclodehydration was conducted at ambient temperature in a time scale of 18–20 h, using different groups of compounds as catalysts (Scheme 1). In our previous work[56] several alkenes were tested in a non-chiral transformation. Among them the cyclic amide **1** appeared to be a good model compound for the detailed preliminary investigations, according to the observed high stability of the 2,4-dinitrophenylhydrazone of the aldol product (**3**, X=DNPH). Afterward the same catalysts were applied in the cyclodehydration of the dialdehyde **5**, where the corresponding cyclopentenecarbaldehyde **6** presents a direct precursor of a more functionalised cyclopentanoid unit with its two hydroxyl groups in the molecule. The difference in the behaviours of the dialdehydes **2** and **5** in respect to the catalysts used, observed in the non-chiral version,[56] gave an additional reason to concentrate our attention on the asymmetric transformation of these compounds.

As a first series several amino acids activities were checked (Table 1), starting from (*S*)-proline as it has found to be a highly efficient catalyst in many transformations, including aldol cyclisation of heptanedials.[46] It was observed that it is also an effective catalyst in the formation of **3**, but without including stereocontrol (entry 1). By testing other amino acids it was observed, that **2**→**3** transformation is catalysed by simple acids, like (*S*)-(−)-aziridine carboxylic acid (entry 2), (*S*)-(−)-azetidine carboxylic acid (entry 3) and *N*-methyl-(*S*)-alanine (entry 8), leading to relatively high chemical yields but without enantiomeric excess. On the other hand, aromatic amino acids, such as (*S*)-(−)-2-indoline carboxylic acid (entry 4) and (*S*)-(−)-tetrahydro-3-isoquinoline carboxylic acid (entry 5), gave lower conversion but better stereoselectivities. The chiral yield observed with (*R*)-(−)-thiazolidin-4-carboxilic acid (36%, entry 7) in comparison with (*S*)-proline could be an indication that the sulphur atom in the catalyst molecule creates some stereocontrol. However, as the variability of commercially available sulphur containing chiral amino acids is very low, no further detailed investigation of this class of compounds were conducted.

The catalytic activities of different hydroxy prolines, which have shown similar efficiency to that of proline in an asymmetric Mannich reaction,[36] were studied (Table 1). It was observed that while both (2*S*,4*R*)-(+)-*trans*-4-hydroxyproline (entry 9) and (2*R*,4*R*)-(+)-*cis*-4-hydroxyproline (entry 10) catalysed the construction of **3** slowly but with significant stereocontrol, (2*S*,3*S*)-(−)-3-hydroxyproline (entry 11) promoted better conversion but with lower selectivity. When the diastereoisomers of 4-hydroxy prolines were used, where the difference in the configuration is only at C-2 centre, while that of the C-4 is the same, the major products showed the opposite stereochemistry. This could be an indication that the carbon, bearing the carboxylate functionality, controls the selectivity in this case, while that connected with the hydroxyl group has not significant influence. The latter is in agreement with the stereochemistry of the product of the reaction, catalysed by 3-hydroxy proline. In the cases of (*S*)-(−)-2,3,4,9-tetrahydro-1*H*-pyrido(3,4-*b*)indole-3-carboxilic acid (entry 6) and (+)-yohimbinic acid (entry 12), very low solubility in



Scheme 1. Aldol cyclodehydration of dialdehydes **2** and **5**: (i) O_3, dry CH_2Cl_2, −78 °C, DMS; (ii) catalyst (0.2 equiv), rt, 18–20 h; (iii) 2,4-dinitrophenylhydrazine, H_2SO_4, MeOH.