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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.

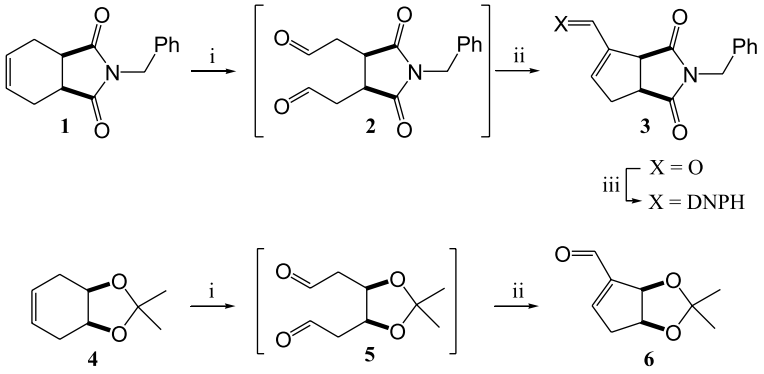
As a part of our study on the cyclopentanoid synthesis, an asymmetric version of the direct intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes, leading to the corresponding cyclopentene carbaldehydes, is presented herein.

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.

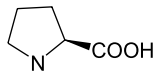
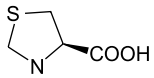
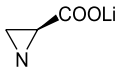
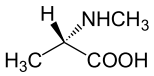
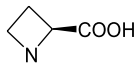
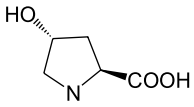
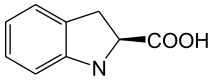
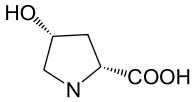
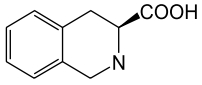
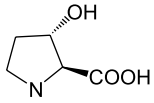
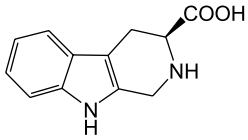
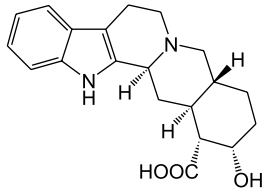
As a first series several amino acids activities were checked (Table 1), starting from (*S*)-proline as it has found to be a highly efficient catalyst in many transformations, including aldol cyclisation of heptanedials.[46] It was observed that it is also an effective catalyst in the formation of **3**, 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.

Table 1. Chiral amino acids and hydroxy amino acids, tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		73 (4)	0 (0)	7		58 (—)	36[a] (—)
2		73 (—[b])	0 (—)	8		85 (3)	16[c] (4[d])
3		88 (6)	0 (3[d])	9		26 (—)	52[a] (—)
4		57 (—)	58[a] (—)	10		19 (—)	66[c] (—)
5		42 (—)	26[a] (—)	11		60 (6)	30[a] (2[e])
6		18 (4)	6[a] (10[e])	12		10 (—)	4[c] (—)

[a] Major isomer $t_R = 52$ min.
[b] No reaction occurs.
[c] Major isomer $t_R = 60$ min.
[d] Major isomer $t_R = 29$ min.
[e] Major isomer $t_R = 22$ min.

the reaction media was observed, which could be an additional reason for the inefficiency of these compounds as catalysts. As phenylalanine has found to be an effective catalyst for the aldol condensation steps in the estrone[57] and (−)-ilimaquinone[58] syntheses, the primary amino acids (*S*)-valine and (*S*)-serine activities were ascertained, but racemic products in low reaction yields were isolated in both cases.

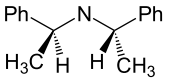
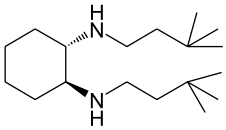
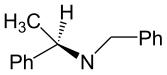
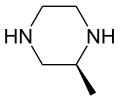
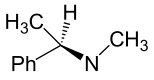
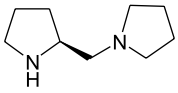
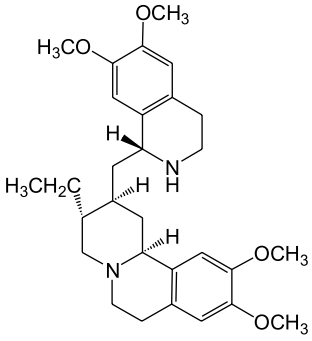
As a second series, the trifluoroacetates of various secondary amines were studied, due to their high effectiveness as catalysts in the non-chiral version. Starting with some chiral analogues of dibenzylamine (Table 2, entries 1–3), a strong dependence of the conversion on the steric hindrance in the catalyst molecule was observed, but without inducing stereocontrol. As all amines tested showed similar patterns, it could be summarised that these compounds, which have shown activity in Robinson annulation[45] but not in Manich condensation,[36] are not efficient catalysts for the asymmetric transformation, described herein.

Based on the observed better selectivities using hydroxy prolines in respect to proline, the trifluoroacetates of some amino alcohols activities were tested (Table 3). Variable conversion was observed without substantial selectivity, but some comments could be done. Comparing the efficiencies of some cyclic amino alcohols (Table 3, entries 1–3) with those of the corresponding carboxylic acids (Table 1, entries 1, 4 and 5), it could be summarised that while prolinol is more effective than proline, creating some stereocontrol in almost the same reaction extent, the indolyl derivatives show the opposite behaviour. As hydroxy pyrrolidine (Table 3, entry 5) catalysed the **2**→**3** conversion in the same extent as 3-hydroxy proline (Table 1, entry 11) but loosing the stereoselectivity (0 vs 30% ee), it could be suggested that the carboxylate functionality plays a crucial role in this case. Taking in consideration the stereochemistry of the major products in ephedrine and pseudoephedrine catalysed aldol condensation (Table 3), where (1*S*,2*R*)-(+)-ephedrine (entry 9) and (1*S*,2*S*)-(+)-pseudoephedrine (entry 10) originate mainly the product with a positive value of $[\alpha]_D$, while (1*R*,2*S*)-(−)-ephedrine (entry 8) led to the negative one, it could be suggested that the carbon, connected to the hydroxyl group, controls the selectivity in this case, where a carboxylate functionality does not exist. To ascertain this suggestion, as well as to study as wide as possible range of catalysts, several open chain secondary amino alcohols were prepared from commercially available primary ones (Fig. 1).

The racemic products were formed with all catalysts of this series, where the hydroxyl group is connected with a non-chiral centre. The latter supports the suggestion that the configuration of the carbon, bearing the hydroxyl group, is crucial for induction of stereocontrol in substrates studied.

Applying a part of the catalysts tested in **2**→**3** conversion to the construction of **6** from **5**, it was observed that the

Table 2. Chiral amines[a], tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		—[b]	—	5		78 (6)	4[c] (6[d])
2		59	0	6		10 (—)	4[e] (—)
3		97	0				
4		(8)	(14[d])	7		73 (10)	6[c] (0)

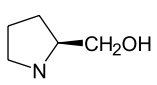
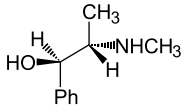
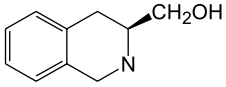
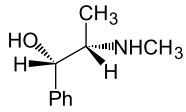
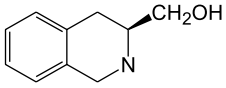
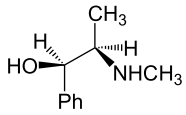
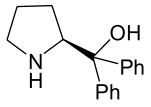
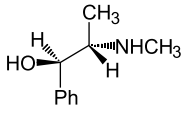
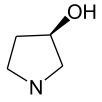
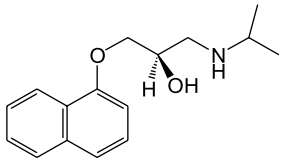
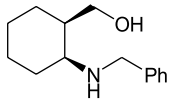
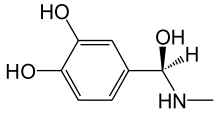
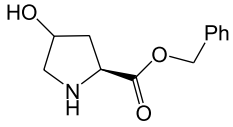
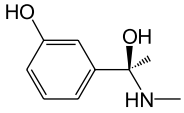
[a] As trifluoroacetates.
[b] No reaction occurs.
[c] Major isomer t_R=52 min.
[d] Major isomer t_R=22 min.
[e] Major isomer t_R=60 min.

transformation in this case is rather slow in general and without inducing significant stereocontrol. The only exception is in the case of 2-(diphenylhydroxymethyl)pyrrolidine (Table 3, entry 4), where 70% ee was observed but in very low conversion. An attempt to increase the reaction yield by prolonging the reaction time resulted in a significant decrease in the selectivity. The fact that no reaction occurred with several amino acids and ammonium trifluoroacetates is in accordance with the observed in our previous work[56] that dibenzylammonium trifluoroacetate does not catalyse the aldol condensation of **5**. As it was found that dibenzylamine itself is an efficient catalyst, the basic components of some of the catalysts used were checked. Thus, 2-methylpiperazine (Table 2, entry 6), which salt was inactive, created the product in almost the highest chemical yield, observed in this case, but with very low selectivity (34 and 8% ee). On the other hand, the ephedrines did not catalyse the reaction at all. The (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine, which salt gave the best chiral excess, generated the product in better extent but with reduced stereocontrol (6 and 70% ee vs 18 and 36% ee). The latter could be an indication that the faster reaction in this case leads to a loose of selectivity and/or that the acidic component of the catalyst controls it, but as such behaviour was observed only with this catalyst, no substantial conclusions could be done in general. Surprisingly, it was observed that the catalyst (*S*)-(−)-2-(pyrrolidinomethyl)-pyrrolidine, apart of giving some desired transformation (21 and 2% ee), originated 7,7a-dihydro-4-hydroxy-2,2-dimethylbenzo[*d*][1,3]dioxol-5(6*H*)-one as a main product. The same compound was found to be a side product in the non-chiral variant of this reaction performed in wet dichloromethane and the main one if hydroxycyclohexene was used as a starting material.[56]

Additionally, in a search of better catalysts, some chiral phosphites and phosphines were studied in both **2**→**3** and **5**→**6** cyclodehydration (Table 4). It was found that the transformation occurs in moderate to excellent yield, but without stereocontrol. The only exception was (2*S*,4*S*)-(−)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine (entry 6), which gave moderate selectivity (24% ee).

In an attempt to determine the absolute configuration of the aldol product **3**, which is explicit if a chiral centre with known configuration exists in the molecule as a norm, several derivatisations and transformations were performed. Chiral hydrazones (using SAMP and RAMP), chiral enamines and subsequent reduction to the corresponding amines, hydrogenation of the aldehyde followed by chiral ether or ester formation etc. were done, but a crystal of pure enantiomer was not isolated. When providing the cyclodehydration, starting from an analogue of **1**, having (*S*)-phenylethylamino group instead of benzylamino in the substituent part, the dinitrophenylhydrazone of the corresponding cyclopentene carbaldehyde was isolated in the same extent and stereochemistry as **3**. After several recrystallisations from ethylacetate, where racemic crystals were always formed, the enriched to the major isomer mother liquors were submitted to a PTLC using multiple developments of the plates, as both isomers have the same R_f-values. A pure isomer was isolated, but the crystals, created in several different solvent systems, were always rather small and thus, X-ray data were not obtained.

Table 3. Chiral amino alcohols[a], tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		81	12[b]	8		64 (11)	18[c] (20[d])
2		45	27[b]	9		73 (10)	44[b] (0)
3		70	22[b]	10		73 (25)	16[b] (6[e])
4		71 (6)	12[b] (70[e])	11		(14)	(6[d])
5		63 (12)	0 (10[d])	12		27 (15)	0 (2[d])
6		37 (—[f])	8[c] (—)	13		44 (3)	24[c] (32[d])
7		96 (16)	1[b] (8[e])	14		(9)	(10[d])

[a] As trifluoroacetates.
[b] Major isomer $t_R = 52$ min.
[c] Major isomer $t_R = 60$ min.
[d] Major isomer $t_R = 29$ min.
[e] Major isomer $t_R = 22$ min.
[f] No reaction occurs.

3. Conclusions

A first direct intramolecular asymmetric catalytic aldol cyclodehydration of 1,6-dialdehydes to the corresponding cyclopentene carbaldehydes was accomplished. Variable conversion was observed with dialdehyde **2**, having amide substituents, while in the case of acetonide protected diol **5**, the transformation was rather slow in general and without inducing substantial selectivity. Among the broad range of the catalysts tested, it appears that for the substrates studied some hydroxy amino acids, like hydroxy prolines, as well as amino alcohols, like ephedrines and pseudoephedrines, are the most efficient chiral ones for insertion of asymmetricity at the β-carbon in respect to the aldehyde. The results obtained clearly demonstrate that the chiral version is feasible and that to reach stereocontrol, the presence of a hydroxyl group in the catalyst's molecule seems to be crucial. The chiral centre in hydroxy amino acids, bearing the carboxylate functionality, 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 found that chiral phosphines and phosphites are effective catalysts for this cyclodehydration but without inducing stereocontrol.

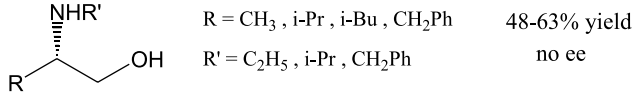
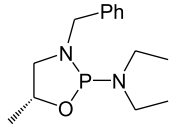
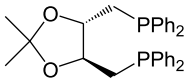
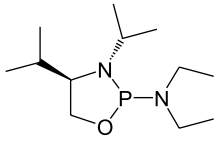
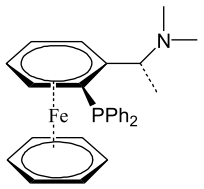
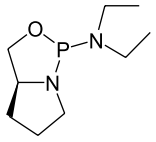
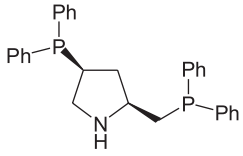


Figure 1. A series of chiral secondary amines.

4. Experimental

All reagents and the most part of the catalysts were purchased from Aldrich and Fluka and were used without any further purification. The chiral phosphites were prepared in the laboratory.[59] The amino alcohols, shown in Figure 1, were synthesised from (*S*)-(+)-alaninol, (*S*)-(−)-phenylalaninol, (*S*)-(+)-leucinol and (*S*)-(+)-valinol by azomethyne formation with benzaldehyde, acetaldehyde

Table 4. Chiral phosphites and phosphines, tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		83 (17)	2[a] (0)	4		48 (—[b])	0 (—)
2		97 (13)	0 (4[c])	5		50	4[a]
3		64 (25)	0 (4[c])	6		93	24[d]

[a] Major isomer $t_R = 60$ min.
[b] No reaction occurs.
[c] Major isomer $t_R = 29$ min.
[d] Major isomer $t_R = 52$ min.

and acetone and subsequent $LiAlH_4$ reduction, following standard procedures. The dichloromethane was dried over P_2O_5. The ozonolysis were performed on a Fischer Ozon Generator 500 M using dry (in-steam molecular sieve-silica gel blue tube) oxygen. The HPLC analyses were carried out using Merck and Hitachi components L-600A, L-4250, T-6300, D-600 on a Chiralpak AD column, Diacel Chemical Industries, Ltd (0.46 and 25 cm). The optical rotations were recorded on a AA-100 Polarimeter, Optical Activity, Ltd (Na-lamp, $\lambda = 589$ nm, 0.5 dm cell, $c = 1$ in $CHCl_3$).

All experimental details and physical and spectroscopic data for the starting materials, intermediately formed dialdehydes and final products are given in our previous report.[56]

General procedure for **1**→**3** *and* **4**→**6** *transformation*. Through a solution of an alkene (1 mmol) in dry dichloromethane (5 ml) a steam of ozone in oxygen was bubbled at −78 °C until the solution turned blue. The system was purged with argon until the colour disappeared and dimethylsulphide (4 mmol, 0.3 ml) was then added. The solution was kept at rt for 2 h and a catalyst (0.2 mmol, 20%), was added. After 18–20 h at rt the solvent was removed in vacuo and the product was purified by chromatography directly in the case of **6** and after derivatisation as DNPH for **3**.

The selectivities were determined by chiral-phase HPLC analysis at 25 °C using the following conditions: (a) for the DNPH derivative of **3**: mobile phase 50% *i*-PrOH and 50% hexane, flow rate 0.6 ml/min, wave length 372 nm, retention times $t_R = 52$ min and $t_R = 60$ min; (b) for the product **6**: mobile phase 1% *i*-PrOH and 99% hexane, flow rate 1.5 ml/min, wave length 240 nm, retention times $t_R = 22$ min and $t_R = 29$ min.

Optical rotations of selected samples of the DNPH of **3**: Table 1, $[\alpha]_D = +137.0°$ (entry 4), $+59.0°$ (entry 5), $+79.3°$ (entry 7), $-38.7°$ (entry 8), $+119.5°$ (entry 9), $-169.0°$ (entry 10), $+61.7°$ (entry 11), $-11.9°$ (entry 12); Table 3, $[\alpha]_D = -48.4°$ (entry 8), $+97.2°$ (entry 9), $+39.2°$ (entry 10), $-56.1°$ (entry 13).

Acknowledgements

We thank Fundação para a Ciência e Tecnologia and FEDER (Ref. SFRH/BPD/5531/2001) for the financial support. We also thank Dr. Eurico Cabrita for supplying us with samples of the chiral phosphites.

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