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New chiral auxiliaries in enantioselective heterogeneous catalytic hydrogenations: (−) and (+)-dihydro-apovincaminic acid. Comparison with (−)-dihydro-apovincaminic acid ethyl ester. III

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Abstract

The preparation, characterisation, use and comparison with (−)-dihydro-apovincaminic acid ethyl ester of (−) and (+)-dihydro-apovincaminic acid as chiral modifier in heterogeneous catalytic asymmetric hydrogenations are reported. The epimeric compositions were determined using NMR and HPLC methods.

Keywords: Dihydro-apovincaminic acid; Hydrogenation; Enantioselectivity; Chiral auxiliary; Ethyl pyruvate; Isophorone

1. Introduction

The known chiral auxiliaries for enantioselective hydrogenation can be classified into three main groups: alkaloids, hydroxy and amino acids. Notwithstanding the great number of chiral compounds, which are used as chiral auxiliaries or chiral ligands, only a few of them are effective in heterogeneous catalytic systems. The most well known examples are Ni catalysts modified with tartaric acid for the hydrogenation of β-keto esters [1] and Pt catalysts modified with cinchona alkaloids for the hydrogenation of α-keto esters [2]. Both systems are effective (ee's up to 95%) in the hydrogenation of C=O double bonds in a specific class of substrates. In order to find new chiral auxiliaries with different or broader substrate specificity, we have screened several vinca- and morphine-type alkaloids in the hydrogenation of various prochiral substrates [3]. A vinca-type alkaloid, (−)-dihydro-apovincaminic acid ethyl ester ((−)-DHVIN) proved to be an effective chiral additive in the hydrogenation of both C=C and C=O double bonds [4]. The starting unsaturated compound, apovincaminic acid ethyl ester (I) is a synthetic molecule, which is used in the treatment of oxygen-deficiency of the brain [5]. Af-

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ter testing the effect of reaction parameters and of the use of different catalysts on the performance of (−)-DHVIN [6,7], we tried to modify the molecule in order to find out how it works and perhaps to get a new chiral modifier with even better effect.

2. Experimental

Pd black catalyst was prepared according to the following procedure: 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and reduced at boiling point with 74 mmol (5.0 g) Na(HCOO) dissolved in 20 ml water. When the reduction was complete the pH of the suspension was basic (pH = 9). The catalyst was filtered and washed several times with distilled water. Its BET surface area is 8 m^2/g.

Platinum on alumina catalysts (E 4759, Engelhard) were heat-treated at 400°C for 3 h in hydrogen flow under atmospheric pressure in a glass reactor and subsequently cooled down to room temperature and flushed with nitrogen.

Apovincaminic acid ethyl ester (0.02 mol) (**I**) was dissolved in 60 ml 20% HCl solution and boiled for 3 h. The pure HCl salt of **II** precipitated (yield 5 g, 75%). This salt was dissolved in 100 ml water. After neutralisation with NaOH solution and extraction with dichloromethane, the organic phase was evaporated. The residue consisted of yellow crystals (**II**), melting point: 212–240°C. The hydrogenation reactions of a 2% aqueous solution of apovincaminic acid (**II**) HCl salt were carried out in an autoclave equipped with a magnetic turbine stirrer, under 6 bar H_2 pressure and at room temperature. The product composition (ratio of **II / III + IV** and **III / IV**) was determined with HPLC. The filtrate was neutralised with NaOH solution to pH = 7 and left to stand overnight at 5°C in a refrigerator. Compound **IV** crystallised and was filtered (purity 90%), melting point: > 254°C, $[\alpha]_{20}^{D} = +55{,}0°$. The remaining filtrate was partly evaporated and cooled, whereupon compound **III** crystallised in 85% purity, melting point: 210–222°C, $[\alpha]_{20}^{D} = -55{,}2°$ ($c = 1$, $CHCl_3$).

Ethyl pyruvate and cinchonidine were supplied by Merck. Apovincaminic acid ethyl ester was supplied by Richter Gedeon.

2.1. Hydrogenation

The hydrogenation of ethyl pyruvate and isophorone was carried out at 25°C and under 50 bar hydrogen pressure in a conventional apparatus or in a Büchi Bep 280 autoclave equipped with a magnetically driven turbine stirrer and a gas-flow controlling and measuring unit. Prior to hydrogenation the reaction mixtures were stirred under nitrogen for 15 min in the reaction vessel.

The reaction mixtures were analysed with a gas chromatograph equipped with a β-cyclodextrin capillary column (analysis temperatures: ethyl lactate at 90°C, dihydroisophorone at 110°C) and FID. The chromatograms and peak areas were recorded and peak areas were calculated with Chromatography Station for Windows V1.6 (DataApex, Prague). Enantiomeric excess was defined as:

$$ee(\%) = ([R] - [S])/([R] + [S]) * 100$$

2.1.1. HPLC chromatography

The analysis was carried out on a chiral AGP column, at room temperature, the eluent was 80% Sörensen buffer and 20% acetonitrile. The adsorbance of the eluent was measured at 230 nm.

2.1.2. NMR spectroscopy

The NMR spectra were recorded on a Bruker Ac-500 spectrometer in $CDCl_3$.

3. Results and discussion

The naphthyl ester of dihydro-apovincaminic acid seemed to be an appropriate derivative as the necessity and usefulness of a naphthyl or

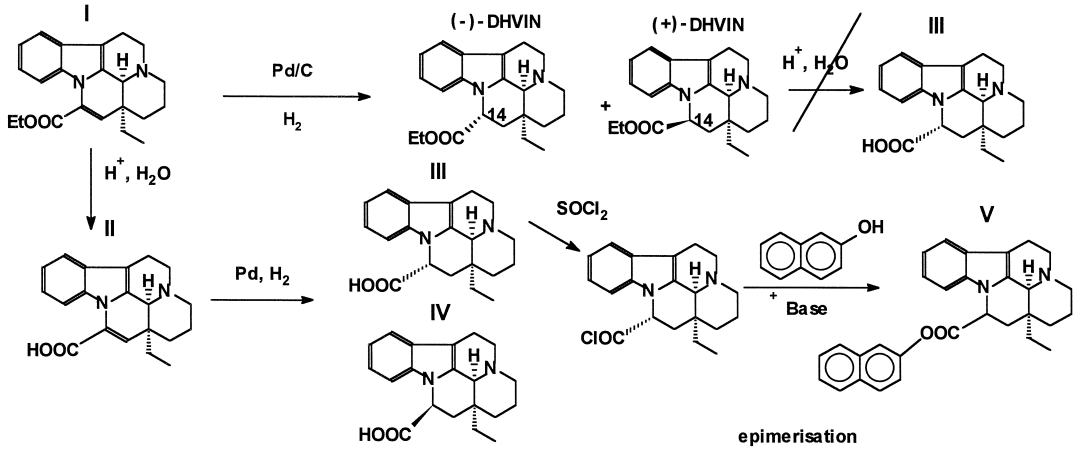
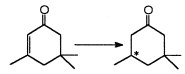
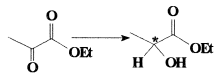


Fig. 1. The reaction-scheme of the preparation of modifiers **II, III, IV** and **V**.

quinolyl group in modifiers for the enantioselective hydrogenation of ethyl pyruvate was verified [8]. However, the first route (Fig. 1) stranded already at the second step, namely the hydrolysis of (−)-DHVIN was incomplete and (−)-dihydro-apovincaminic acid could not be isolated in pure form. The hydrolysis of the unsaturated ester, in contrast, was facile, and the hydrochloride salt of the apovincaminic acid (**II**) precipitated in pure form from the hydrochloric acid solution.

The hydrogenation of this salt (**II** HCl) was carried out in aqueous solution with Pd/C catalyst. The resulting mixture of the epimers {70% α,α (**III**) and 30% α,β isomer(**IV**)} could be separated after partial neutralisation with NaOH. The further conversion of the α,α-dihydro-apovincaminic acid into optically pure naphthyl

Table 1
The effect of different chiral auxiliaries on the ee of the hydrogenation of isophorone and ethyl-pyruvate

Reaction mol substrate	Catalyst g	Enantiomeric excess % modifiers (-)-DHVIN	(+)-DHVIN	I	II	III	IV	V ***
 0.05	Pd black 0.3	55	15	53 *	41 **	50	38	29
 0.1	Pt/Al_2O_3 0.1	30	14	14	7	29	22	6

Solvent 50 cm^3 MeOH, in the hydrogenation of isophorone 0.02 g modifiers, 0.2 g acetic acid, in the hydrogenation of ethyl pyruvate 0.1 g modifiers, 0.1 g acetic acid.

* The modifier consists of ca. 80% (−)-DHVIN and 20% (+)-DHVIN.

** The modifier consists of ca. 70% **III** and 30% **IV**.

*** Epimeric mixture.

ester was unsuccessful, however, owing to epimerisation under the acylation conditions.

We compared the asymmetric induction of (−) and (+)-DHVIN [6,7] with that of **I, II, III** and **IV** in the Pd catalysed hydrogenation of isophorone and in the Pt catalysed hydrogenation of ethyl pyruvate (see Table 1).

We previously reported [4] that Pd and Rh are active catalysts for the hydrogenation of the 14,15 C=C double bond of **I** but that Pt is inactive for this reaction. In the Pd catalysed hydrogenation of **I** the α,α-epimer constitutes ca. 80% of the product, while in the hydrogenation of **II**, the α,α-epimer (**III**) and the α,β-epimer (**IV**) were produced in 70% and 30%, respectively. Hence, during the hydrogenation of isophorone with Pd catalyst, the unsaturated modifiers **I** and **II** are hydrogenated in situ, giving a mixture of (−)- and (+)-DHVIN, or of **III** and **IV**, respectively. The asymmetric induction observed with the pure epimers of DHVIN were very similar to those obtained with the in situ generated epimeric mixtures which contained mainly the α,α-epimers (see Table 1).

In the Pt catalysed hydrogenation of ethyl pyruvate, in contrast, there is a significant difference between the unsaturated and saturated modifiers. In this reaction the true effect of the unsaturated modifier molecules can really be seen as Pt does not catalyse hydrogenation of the 14,15 double bond of these vinca alkaloids.

3.1. Structure of (−)-dihydro-apovincaminic acid

According to the NMR results the structure of **III**, (−)-dihydro-apovincaminic acid is similar to the structure of (−)-dihydro-apovincaminic acid ethyl ester [4]. The –COOH and the 16-ethyl group are both in α position (Fig. 2).

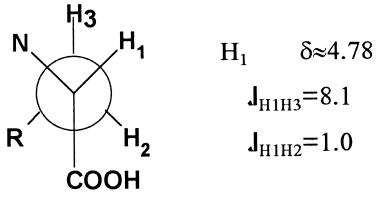


Fig. 2. The NMR dates of (−)-apovincaminic acid.

4. Conclusions

Relation between structure, substituents of the modifiers and their asymmetric effect in hydrogenations.

(1) The difference between the effect of α,α-isomers of saturated ester and acid is small suggesting that the ester and the carboxyl group have similar anchoring capabilities.

(2) The α,α-isomers of the saturated ester and acid give a larger asymmetric induction than that of the α,β-isomers, suggesting that an equatorial position is preferred for the ester or acid group.

(3) Asymmetric induction solely due to the unsaturated modifier compounds (**I, II**) could be observed only in the Pt catalysed hydrogenation of ethyl pyruvate, and was much smaller than that of the saturated molecules. A possible explanation for this difference can be that the ester or acid groups can exert their anchoring effect much better if they are not in the plane of the ring they are attached to.

(4) The difference in asymmetric induction observed with the two epimeric esters (−)- and (+)-DHVIN was much larger than that with the acid epimers (**III** and **IV**). This may be due to the different size of the ester and carboxyl groups.

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