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New data on the effect of steric constraints on the chiral induction in the Orito reaction: Hydrogenation of activated steroid ketones

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ABSTRACT

Hydrogenation of α-ketoesters containing steroid groups at the ester side and at the keto carbonyl function of substrates was investigated the first time on Pt–alumina–cinchona alkaloids chiral catalysts using mild experimental conditions (room temperature, 1 bar hydrogen pressure, modifier concentration 1 mM) in the presence of acetic acid. Catalysts modified by cinchona alkaloids ensured enantioselective hydrogenation with 10–70% ee, depending on the steric structure of the substrate. In the absence of cinchonas racemic hydrogenation takes place, i.e. the chiral centers of the substrates do not participate in chiral induction. Experimental data so far obtained support the assumption that under stereochemical conditions not inhibiting adsorption of the substrate and after optimization of the experimental conditions, the Orito reaction may be rendered suitable for the asymmetric hydrogenation of bulky activated ketones. These results also supply additional evidence for the determinant role of the H-bonded adsorbed intermediate, the 1:1 complex of cinchona alkaloid and substrate in chiral induction under protic conditions.

1. Introduction

It is an important research area to increase the selectivities (regio-, stereo-, enantioselectivities) of the organic catalytic transformations [1]. Among these it is no more necessary to underline nowadays the significance of asymmetric syntheses for a readership of professionals well versed in chemistry and biology. Due to its well-known advantages, the preparation of chiral compounds using heterogeneous catalytic hydrogenation is a synthetic method of outstanding significance. Two methods have been applied in heterogeneous catalytic hydrogenations (which have been reviewed regularly): (i) enantioselective hydrogenation [2], (ii) diasteroselective hydrogenation [3]. Industrial application of the enantioselective hydrogenation of activated ketones (Orito reaction [4] (Fig. 1) in which enantioselectivities exceed 90% [5]) has already been realized [6].

Since the present manuscript describes the results of the diastereoselective hydrogenation of α-ketoesters with steroid skeletons not studied before, Section 1 only summarizes the preliminaries of the hydrogenation of steroid ketones. Hydrogenation of the keto-groups of steroids can be achieved both by chemical reductants (e.g.) [7] and catalytic hydrogenation [8]. The data in the special literature on the metal-catalyzed hydrogenation of steroid ketones suggest that the determinant factor in the stereochemistry of the hydrogenation is the mode of adsorption of the steroid molecule on the surface.

In this respect a characteristic example is shown in Fig. 2, demonstrating the determinant role of the adsorption of molecule. In the case illustrated in Fig. 2 the C_{12} alcohol of equatorial orientation is formed in 100% regio- and diastereoselectivity, because, in the starting diketone the C_{12} ketone is on the α-face and the C_{11} ketone is on the β-face. Since the adsorption of C_{11} ketone is prevented and only the C_{12} ketone could be in contact with the metal surface, this oxo group is hydrogenated [9].

As regards the stereochemistry of the hydrogenation of compounds with the oxo group positioned outside the steroid skeleton under the conditions of the Orito reaction, to our best knowledge only two papers have been published in this field. According to one of these [10a] trigemestone was synthesized in 72% diastereoselectivity (de) after optimizing the experimental conditions of the hydrogenation of oxoprogemestone and varying the chiral modifier (Fig. 3). It has to be specially emphasized that the molecule to be hydrogenated contains five hydrogenable bonds. It was estab-

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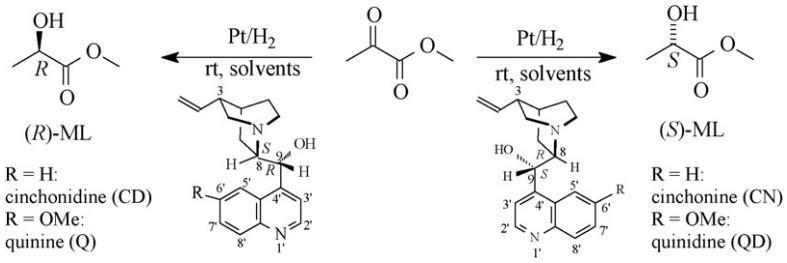

Fig. 1. The Orito-reaction [4].

lished on the stereochemistry of the hydrogenation that "... the chirality of the modifier plays a secondary role in diastereoselectivity; the main factor is the chirality of the substrate itself" [10a]. The other paper [10b] describes preliminary studies on a derivative of lithocholic acid.

Knowing the above, and based on the results of varying the bulkiness of the substituents of the substrates (i.e. the substituent next to the oxo group to be hydrogenated and the one in the ester function) [11] the following objectives were set: (i) generalization of the above described conclusion [10a] regarding the de of the hydrogenation; (ii) studies of the effect of bulky groups on the diastereoselectivity of the Orito reaction and (iii) application of the Orito reaction for the hydrogenation of steroid ketones. From the results, novel information was expected to be obtained about the stereochemistry of the Orito reaction. The asymmetric hydrogenation of the steroid compounds **1**–**4** (see Section 2) was studied.

2. Experimental

2.1. General remarks

The cinchona alkaloids (CD, CN, Q, QD), solvents and compounds used in synthesis of **1**–**4** were Fluka or Aldrich products. All solvents were dried, purified and distilled according to conventional methods. The lithocholic acid methyl ester was synthesized according to a literature procedure [12]. β-ICN preparation has been described elsewhere [13]. Melting point was measured on Boëtius micromelting point apparatus (uncorrected value). Column chromatography was performed using hexane/acetone (5:2) solvent system on Fluka silica gel 60 (70–230 mesh ASTM), analytical TLC on Fluka Silica gel/TLC cards.

2.2. Syntheses

The steroid esters of pyruvic and phenylglyoxylic acids (**1**, **2**) were prepared by the reaction of the crude acid chloride and steroid alcohol in the presence of Et_3N (or pyridine) and DMAP in CH_2Cl_2 at room temperature. Literature procedures were followed in the preparation of pyruvic chloride [14] and phenylglyoxylic chloride [15].

5α-Cholestan-3β-yl pyruvate (**1**): white solid (65% yield), melting point: 388–389 K, TLC R_f: 0.67 (hexane/acetone 5:2).

5α-Cholestan-3β-yl phenylglyoxylate (**2**): 64% yield, melting point 376.5–377.5 K (lit. [16]: 376–378 K), TLC R_f: 0.86 (hexane/diethyl ether 8:2).

3-Phenylglyoxyloxy-lithocholic acid methyl ester (**3**): white solid (52% yield), melting point 339–341 K, TLC R_f: 0.52 (hexane/acetone 5:2).

Methyl 3α-acetoxy-23-oxo-5β-cholan-24-oate (**4**): white solid (67% yield), melting point: 389-391 K, TLC R_f: 0.55 (hexane/diisopropyl ether 7:3). The preparation was followed according to [10b].

2.3. Spectroscopic measurements

The NMR spectra were obtained by the use of (^{1}H at 500 MHz, ^{13}C at 125 MHz) in $CDCl_3$ solution, using Me_4Si as the internal standard. The ESI-MSD and ESI-MSD-ion-trap (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion and auto MS-MS mode as described earlier [17].

VCD spectra at a resolution of 4 cm^{-1} were recorded in chloroform-*d* solution with a Bruker PMA 37 VCD/PM-IRRAS module connected to an Equinox 55 FTIR spectrometer. The instrument was optimized for the fingerprint spectral region and calibrated for VCD intensity with a CdS multiple-wave plate. A BaF_2 cell with a pathlength of 50 μm and sample concentrations of 120 mg/mL were used. In order to improve the signal/noise ratio interferograms were accumulated for 7 h, corresponding to ~24,500 scans. Baseline correction was achieved by subtracting the spectrum of the solvent obtained under the same conditions.

2.4. Molecular modeling and computation of VCD spectra

Geometry optimizations and the computation of vibrational frequencies and VCD rotatory strengths were performed at the B3LYP/6-31G(d) DFT levels with the Gaussian 03 quantum chemical software package [18] the vibrational frequencies being scaled by a factor of 0.97. VCD curves were simulated from the calculated wavenumber and rotatory strength data by using Lorentzian band shape and a half-width at half-height value of 3 cm^{-1}.

2.5. Hydrogenation

From the pretreatment methods (high temperature reductive, ultrasound [17c,19]) used for activation of the catalyst we have used

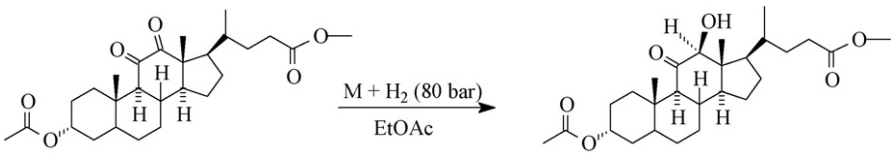

Fig. 2. Hydrogenation of a steroid-diketone catalyzed by supported catalysts (M = Pd-, Pt-, Rh-, Ru-SiO_2) [9].