CHIMIA 51 (1997) Nr. 6 (Juni)

Chimia 51 (1997) 300–302
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ISSN 0009–4293

Catalytic Asymmetric Hydrogenation in the Manufacture of d-Biotin and Dextromethorphan

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Abstract. Two enantiomerically pure products, (+)-biotin and dextromethorphan, have been chosen to illustrate the acquisition, development, and implementation of the catalytic asymmetric hydrogenation technology at *Lonza* Fine Chemicals. Taking advantage of the recently developed *Ciba-Geigy* ferrocenyl-type phosphine ligands, processes for the stereoselective hydrogenation of a C=C- and a C=N bond, respectively, have been developed and successfully scaled up.

Introduction

As the leading manufacturer of fine chemicals for the life science industries, *Lonza* is continuously enlarging and extending its technological capabilities. To position ourselves in the fast growing market segment of enantiomerically pure intermediates, we have acquired and developed a range of new chemical and biochemical technologies. In view of its broad application potential, its high chemoselectivity, and its minimal environmental impact, catalytic asymmetric hydrogenation is one of the most valuable tools for industrial application. Over the last five years, we have developed large-scale asymmetric hydrogenations for the synthesis of d-biotin and dextromethorphan. The vitamin d-(+)-biotin has found widespread application in the growing food/feed market. The alkaloid dextromethorphan is an established antitussive. The presence of three contiguous stereogenic centers is common to both molecules.

Lonza d-(+)-Biotin Process: Heterogeneously Catalyzed Hydrogenation

A considerable number of total syntheses of d-Biotin have been carried out and new ones continue to be published [1]. The *Lonza* process as outlined in *Scheme 1* starts from our raw material tetronic acid (**1**) which is readily available from diketene. The strategy chosen for the setting-up of the relative configuration consists of two stereoselectively controlled hydrogenations of the intermediates **3** and **5**, respectively. The absolute configuration is controlled by the sacrificial group (*R*)-α-methylbenzylamine.

Electrophilic amination using a diazonium salt followed by condensation with the chiral auxiliary (*R*)-α-methylbenzylamine were chosen as method for introducing the N-containing substituents at the tetronic acid (**1**). With the correct substitution pattern in place, the diaminated lactone **2** is transformed into the critical bicyclic intermediate **3** through heterogeneously catalyzed hydrogenation and subsequent urea formation with phenyl chloroformate.

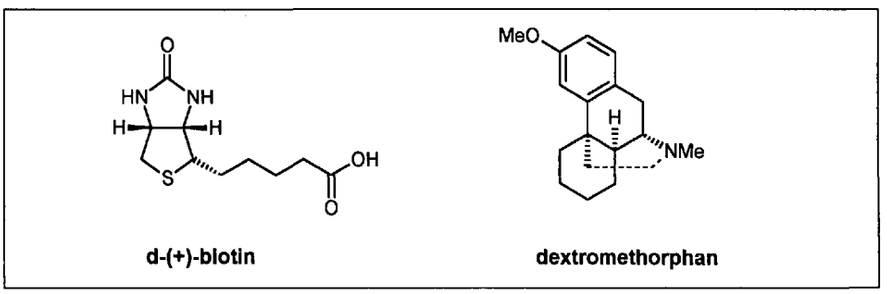
For the original manufacturing process a heterogeneously catalyzed hydrogenation using Rh metal on Al_2O_3 was used. The diastereoisomeric ratio achieved under the directing influence of the (*R*)-α-methylbenzylamino group was 70:30. Under optimized conditions, we were able to isolate the desired single diastereoisomer **4** in 58% yield after crystallization. Given the unsatisfactory yield due to the low stereoselectivity a second generation approach, namely homogeneously catalyzed asymmetric hydrogenation, was undertaken (see below).

Preceding the introduction of the side chain, the N-atom is benzylated and the lactone is transformed into a thiolactone using potassium thioacetate as a sulfurating agent. The most efficient tool for the introduction of the side chain on an industrial scale is the di-*Grignard* reagent prepared from 1,4-dichlorobutane. Under carefully controlled conditions, the resulting intermediate mono-*Grignard* substrate can be trapped by carbon dioxide giving, after elimination of water, the unsaturated carboxylic acid **5**. Catalytic hydrogenation of the exocyclic double bond sets up the correct relative configuration at the stereogenic center adjacent to the S-atom. After removal of both benzylic groups, enantiomerically pure d-(+)-biotin is obtained.

Lonza d-(+)-Biotin Process: Homogeneously Catalyzed Asymmetric Hydrogenation

The rather unsatisfactory result obtained with the Rh/Al_2O_3-catalyzed hydrogenation of the bicyclic intermediate **3** initiated an intensive research program on the application of chiral, non-racemic catalysts. To achieve a high enough yield, we set the ambitious target of > 95% stereoselectivity. Exploratory experiments were carried out at our research labs using known homogeneous catalysts based on commercially available ligands. The reaction was found to proceed with homogeneous Rh-based catalysts; the best selectivity was, however, a modest 83:17, achieved by using a modified diop derivative.

To accelerate the research program, we chose a different tactic: technology acquisition through partnership. We approached the Catalysis Group of the former *Ciba-Geigy* in order to assist us. Having a large number of catalysts at their disposal, they were able to perform a screening within a short period of time. Selected results of the ligand screening are listed in *Scheme 2*.



d-(+)-biotin **dextromethorphan**

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Surprisingly, Rh-binap or Ir complexes did not function as catalysts, the highly substituted double bond was simply not reduced. In terms of activity, Rh-diphosphine complexes are the catalysts of choice with little difference between neutral or cationic complexes [2]. The reduction with the achiral bppf ligand gave a selectivity of 44:56 in favor of the unwanted diastereoisomer. The chiral acetoxyethyl-substituted bppf derivative led to a selectivity of 60:40. To our surprise, the *Ciba*-proprietary bis(diphenylphosphino) derivative **6** was unable to act as a catalyst. The real breakthrough was finally achieved when the more basic diphosphine **7**, bearing a dialkylphosphino group, was employed. The selectivity jumped up to 94:6. An even better ratio of > 99:1 was attained using the corresponding di(*tert*-butyl) derivative **8**. After a short period of optimization, the results were successfully verified on an industrial scale. The isolated yield of the desired diastereoisomer **4** increased from 58 to 95%.

Lonza Dextromethorphan Process: Resolution of Enantiomers

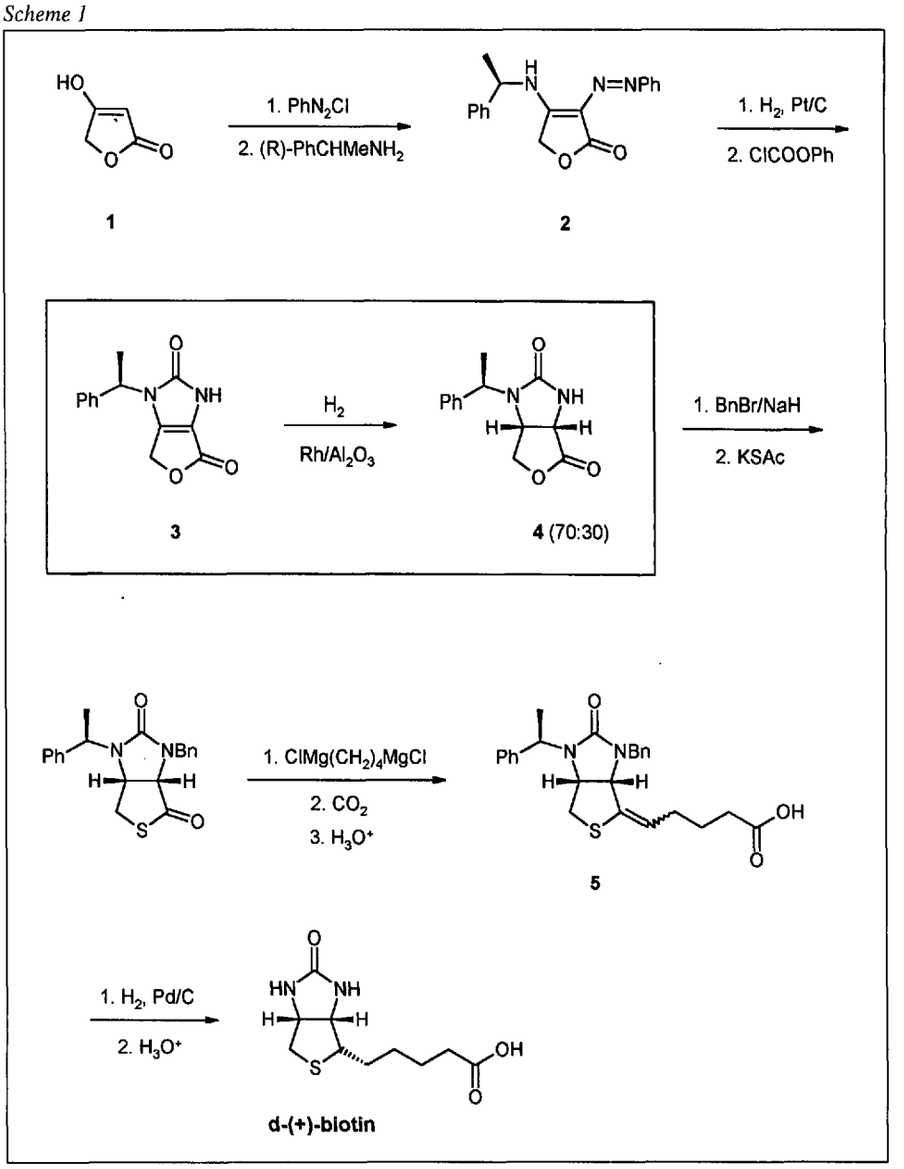
The dextromethorphan process is outlined in *Scheme 3*. Starting from 2-cyclohexen-1'-ylethylamine and 4-methoxyphenylacetic acid the critical hexahydroisoquinoline intermediate **9** is obtained *via* a *Bischler-Napieralsky* reaction. The C=N bond of this rather unstable derivative is reduced by $NaBH_4$, leading to the racemic octahydroisoquinoline. The racemic mixture is then resolved by fractional crystallization of the corresponding (–)-mandelic-acid salt.

This is a very tedious, resource-intensive (labour, equipment) low-yielding step. A more efficient process was highly desirable (see below). Through a series of transformations including a *Grewe* cyclization, the morphinane derivative dextromethorphan is finally obtained in enantiomerically pure form.

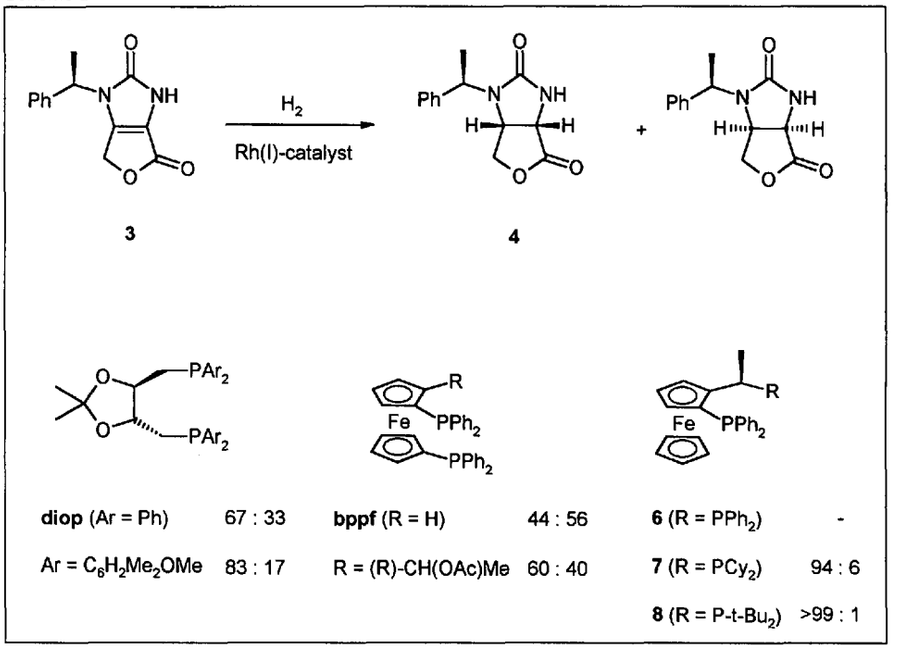
Lonza Dextromethorphan Process: Homogeneously Catalyzed Asymmetric Hydrogenation

The most obvious way to avoid the resolution mentioned would be the substitution of the $NaBH_4$ reduction by an asymmetric hydrogenation of **9**. In contrast to the rather well established asymmetric hydrogenations of C=O and C=C bonds, the corresponding reduction of C=N bonds is much less developed [3]. Taking advantage of the knowledge and experience gained in the d-(+)-biotin case, we quickly

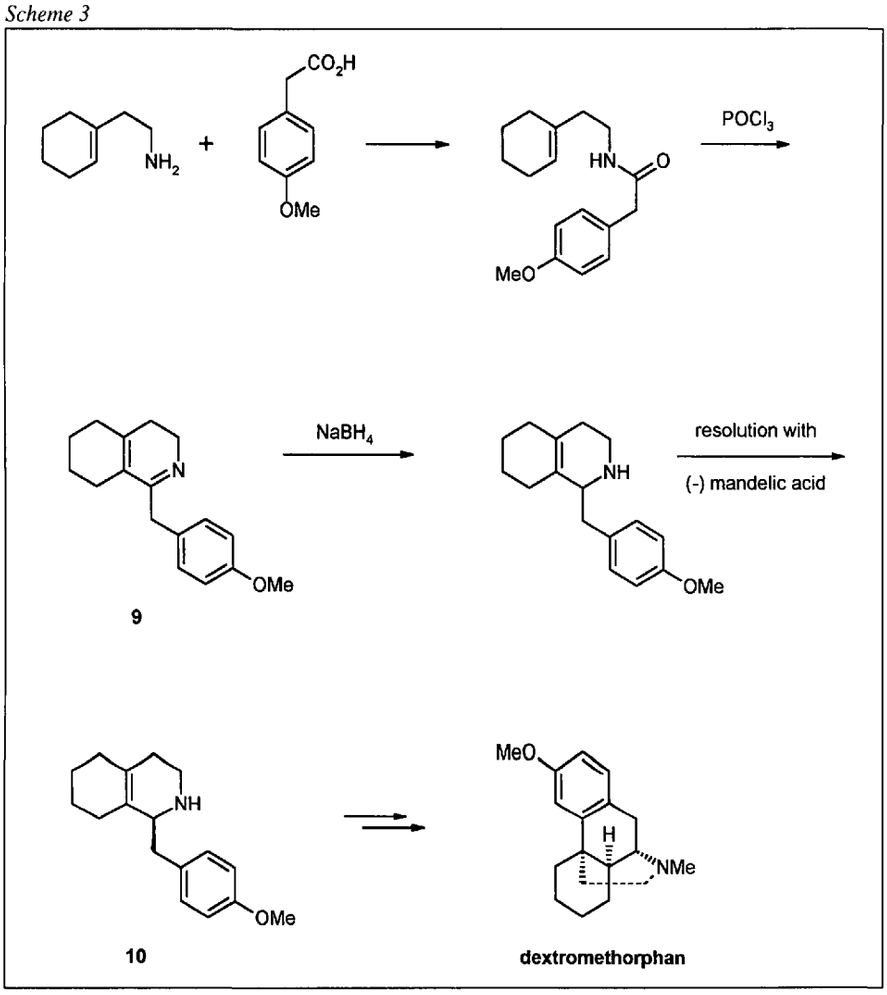
Scheme 1



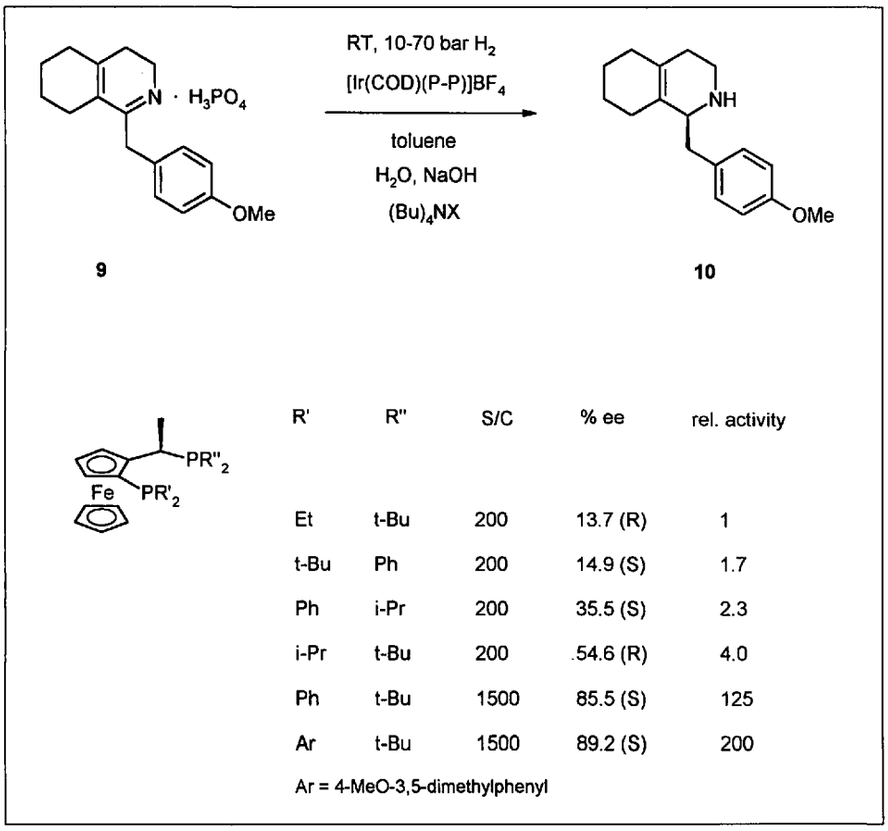
Scheme 2



Scheme 3



Scheme 4



realized that ferrocenyl-type ligands would again do the best job!

It was found that the very sensitive hexahydroisoquinoline **9** is best used as its phosphoric-acid salt to ensure reliable quality for the hydrogenation step [4]. Of the various metals tested, Ir^I complexes performed best. A selection of the ferrocenyl-type ligands tested is depicted in *Scheme 4*.

The activity and the selectivity of the corresponding [Ir(cod)(ferrocenyldiphosphine)]BF_4 complexes can easily be tuned through simple variation of the groups R^1 and R^2 at the P-atoms illustrating the tremendous power and versatility of this type of ligands which were developed by *Togni* and *Spindler* [5]. In terms of activity and selectivity, the best result was achieved with the *tert*-butyl/4-methoxy-3,5-dimethylphenyl derivative. The final level of 89% enantioselectivity was attained only after careful optimization of the reaction conditions. The nonhomogeneity of the reaction mixture makes the choice of the optimal reactor geometry an important factor for the upscale process. Due to insufficient mass transport in a BUSS-type loop reactor, the activity of the Ir catalyst dropped by a factor of 2, although the selectivity remained unchanged. No difference was noticed between a 30-liter batch-type reactor and a laboratory reactor.

I would like to thank the coworkers of our research and development laboratories for making the above-mentioned innovative achievements on the catalytic asymmetric hydrogenation possible. The main players were Dr. *John McGarrity*, Dr. *Rudolf Fuchs*, Dr. *Martin Eyer*, Dr. *Holger Breitbach*, Dr. *Oleg Werbitzky*, Dr. *Hans-Peter Mettler*, and Dr. *W. Brieden*. This fast track approach would not have been possible without the valuable contribution of our colleagues at *Novartis* (former *Ciba-Geigy*) engineer *Rolf Bader*, Dr. *Hans-Ulrich Blaser*, and Dr. *Felix Spindler*.

Received: April 11, 1997

[1] For more recent examples with extensive referencing to previous syntheses of d-Biotin see: a) F.D. Deroose, P.J. DeClercq, *J. Org. Chem.* **1995**, *60*, 321; b) M.J. Moolenaar, W.N. Speckamp, H. Hiemstra, E. Poetsch, M. Casutt, *Angew. Chem.* **1995**, *107*, 2582; c) T. Fujisawa, M.Nagai, Y. Koike, M. Shimizu, *J. Org. Chem.* **1994**, *59*, 5865.

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