doi:10.2533/chimia.2009.265 Chimia 63 (2009) 265–269

Biotin – The Chiral Challenge#

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Sandmeyer Award Winners 2008
In honor of Leo H. Sternbach on the occasion of his 100th birthday

Abstract: In this contribution, the first examples of the catalytic highly enantioselective reduction of cyclic *meso*-anhydrides to lactones and of thioanhydrides to thiolactones are described. The N-benzyl protected key building blocks in the industrial synthesis of (+)-biotin were so far only accessible by usage of expensive reagents in multi-step procedures. In contrast, homogeneous catalytic enantioselective hydrogenation of the corresponding *meso*-anhydride mediated by a metal phosphane complex proceeds with high optical induction (*ee* >95%) and excellent yield. The catalytic system provides a generally applicable new method for the preparation of lactones from cyclic anhydrides.

Keywords: Asymmetric hydrogenation · Cyclic anhydrides · Dream reaction · Homogeneous catalysis · Vitamins

Sandmeyer Award team from left to right: Thomas Netscher, Werner Bonrath, Felix Spindler, Reinhard Karge, Felix Roessler

Werner Bonrath, born in 1959, is married and has three children. He studied chemistry in Bonn and Münster, Germany, and did his diploma thesis in organic chemistry with Prof. T. Kauffmann. In 1988 he completed PhD studies (Dr. rer. nat.) on butadiyne complexes of nickel, palladium and platinum under supervision of Prof. G. Wilke at the Max-Planck Institute for Coal Research in Mühlheim/Ruhr, Germany. After postdoctoral work at the University of Innsbruck, Austria, he started as a research chemist in the Vitamins and Fine Chemicals Division of F. Hoffmann-La Roche (later on Roche Vitamins and DSM Nutritional Products), Basel. His main fields of interest are processes for the synthesis of various vitamins and their intermediates and reactions under non-classical conditions. After promotion to Senior Scientist and Scientific Specialist (1996, 2001), Werner Bonrath became Competence Manager for heterogeneous catalysis in 2005. In parallel, he is lecturer at the Universities of Jena and Basel and completed his habilitation in technical chemistry in Jena in 2007. He is active in European COST network programs, board member of the European Society of Sonochemisty, and member of GDCh and Dechema.

Reinhard Karge, born January 12, 1959, is married and has two daughters. He completed his studies in chemistry and physics at the University of Heidelberg, Germany, with a doctoral degree (Dr. rer. nat.) in organic chemistry with Prof. G. Helmchen in 1990. Then he started his career at F. Hoffmann-La Roche in Basel as a research chemist in the Vitamins and Fine Chemicals Division. From 1997 to 1998 he worked at Roche Vitamins in Dalry, Scotland, working on capacity enhancement. After return to Basel, he took several positions in project management and management services, and was Center Manager of Process Research Chemistry of DSM Nutritional Products from 2004 to 2007. He was appointed to Vice Director and Director in 2004/2006. Since that time, a particular interest is directed towards collaborations with colleagues from academia and industry in China, dealing with production support and evaluation of new procedures. Reinhard Karge has broad experience in processes for the synthesis of various vitamins, fine chemicals and their intermediates.

Thomas Netscher was born in Constance, Germany, on 30 December 1954, is married, and has three children. Studies of chemistry at the Universities of Constance and Freiburg i.Br., Germany, were completed by a diploma thesis on polyolefins and a doctoral thesis (Dr. rer. nat.) on inositols, complex ligands and leaving groups under the direction of Prof. H. Prinzbach

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#This contribution is based on a lecture given at the Mitgliederversammlung der Division Industrielle Chemie der SCG, 5 June 2008 at the Société Suisse des Explosifs (SSE)/Valsynthese at Gamsen/Brig, Canton Wallis.

in 1986. From 1987 he worked as a lab head in research at F. Hoffmann-La Roche, Basel. From 1991 to 1992 he was an exchange scientist at the Roche Research Center in Nutley, New Jersey, USA. After return to Basel, the synthetic studies were continued mainly in the field of terpenoid chemistry at Research and Development of F. Hoffmann-La Roche (later on at Roche Vitamins and DSM Nutritional Products). Thomas Netscher held the Roche Lecture in 1997/98 at 25 European universities and research institutions. He was promoted to Senior Scientist/Scientific Specialist in 1994/1999. Since 2008 he is responsible for fat-soluble vitamins and isoprenoid natural products synthesis as a Principal Scientist at DSM. In recent years he acts as a jury member in the international DSM Science and Technology Awards for PhD students. He is currently Lehrbeauftragter at the University of Freiburg i. Br., and member of the German, the Swiss, and the American Chemical Societies.

Felix Roessler was born on 13 February 1947. He studied chemistry at the University of Zurich, where he graduated in 1975. In 1978 he completed his PhD thesis with Prof. M. Hesse in the field of mass spectrometric investigations and plant alkaloids. During postdoctoral studies 1978/79 with Prof. I. Fleming at Cambridge, GB, he contributed to the development of new synthetic methods for organic synthesis. From 1980 to 1986 he worked in the Central Research Unit of F. Hoffmann-La Roche at Basel in the heterogeneous catalysis field, and in 1987 at the Swiss Federal Research and Test Laboratories EMPA in Dübendorf. From 1988, again at Roche Basel, he was involved in the organisation of heterogeneous catalysis laboratories first for the Pharma, and later for the Vitamins Division, where he has led the hydrogenation laboratories since 1990, also continuing under Roche Vitamins and DSM Nutritional Products. His main interests were directed towards environmentally friendly industrial synthesis and application of chemical reaction engineering concepts to development and scale-up, as well as production of various compounds for vitamins, carotenoids, fine chemicals, and pharma markets. In 1997, Felix Roessler received his first Sandmeyer Award for the contributions to the economic and ecologic synthesis of the first HIV-protease inhibitor Saquinavir.

Felix Spindler did his chemistry studies at the ETH Zürich from 1971 to 1981, where he completed his PhD thesis under supervision of Prof. P. Pino. After a postdoctoral stay at the same institute (1982/83), he started in 1983 at Ciba-Geigy, Basel. In the Central Research Laboratories and in Scientific Services he was a Chemist, Senior Chemist, and Project Leader in the Department Homogeneous Catalysis, where he worked mainly on research and custom projects related to homogeneous enantioselective hydrogenation until 1996. From 1997 to 1999, now under Novartis Services, and as of 1999 at Solvias, Basel, he continued his engagement as a project leader in homogeneous enantioselective hydrogenation projects. Felix Spindler received the Sandmeyer Prize in 1999 as a member of a Novartis Services und Novartis Crop Protection team. As a member of the Merck&Co/Solvias team, he was awarded the ICHEME Award, AstraZeneca Award for Excellence in Green Chemistry and Engineering in 2005, and the Presidential Award Green Chemistry in 2006.

1. Introduction

(+)-Biotin (**1**) is a water-soluble B-vitamin that plays an important role as a coenzyme in carboxylation reactions and is an essential growth factor in every living cell. The daily need for an adult is about 0.03–0.1 mg per day. Biotin has three stereogenic centres, but only the isomer with the configuration (3a*S*,4*S*,6a*R*), D-(+)-biotin (**1**, Fig. 1), has full biological activity.[1]

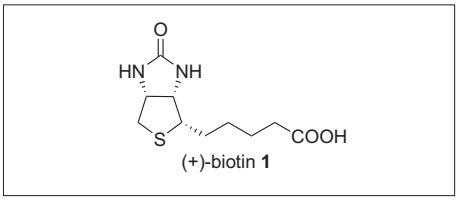


Fig. 1. (+)-Biotin (**1**).

Historically important dates from a chemical point of view are the publications of the first (stereochemically unspecific) total synthesis by Harris, Folkers *et al.* at Merck in 1943,[2] and the first commercially applicable biotin synthesis by Goldberg and Sternbach (Hoffmann-La Roche) in 1949.[3–5] The world market for **1** is about 100 tonnes per year. Decades of research work in academia and industry were directed towards either an optimum synthetic approach or a biotechnological method. Current manufacturers of (+)-biotin (**1**) are DSM and several Chinese producers. The general production method still applied today is multi-step chemical synthesis. For such a low-cost process, being in line with economy as well as ecology, the general problems accompanied with efficient routes to **1** have to be solved: Introduction of nitrogen and sulphur to build up the highly functionalized bicyclic heterocycle, introduction of the side chain, and determining the correct stereochemistry (Fig. 2). Several approaches for the total synthesis of biotin, including industrial, large-scale processes, were compiled in the excellent review of De Clercq.[6]

2. The First Industrial Syntheses of (+)-Biotin

In 1946 Goldberg and Sternbach at Roche filed their patents on the first commercially applicable biotin synthesis.[3–5] From a concept viewpoint, this lactone–thiolactone approach is still of interest today. Starting from cheap fumaric acid (**2**), the cyclic anhydride **6** is obtained *via* the *meso*-compounds **3**, **4**, and **5** (Scheme 1). After several steps, the intermediate *rac*-**8** was obtained from racemic thiolactone (*rac*-**7**). The early stage of the optical resolution (on the racemic sulfonium salt *rac*-**9**) was acceptable and not a drawback, since the 'wrong' isomer was used as a pharmaceutically active compound for another product stream at that time. (+)-Biotin (**1**) could be produced by deprotection of intermediate **11** obtained from chiral salt **10**.

Routes using chiral starting materials available from natural sources were also thoroughly investigated.[6] Some examples are shown in Scheme 2. Particularly attractive were cheap carbohydrates like D-mannose or D-glucose, which have been selectively derivatised in order to introduce the nitrogen and sulphur functionalities. Also L-cysteine was extensively studied for its suitability in industrially feasible routes.[7]

In general, however, none of such procedures made the way to a commercial process. Even the use of very cheap starting materials with already established stereochemistry did not prove cost competitive, mainly due to the large number of steps, often accompanied with protective group chemistry on highly functionalized intermediates.

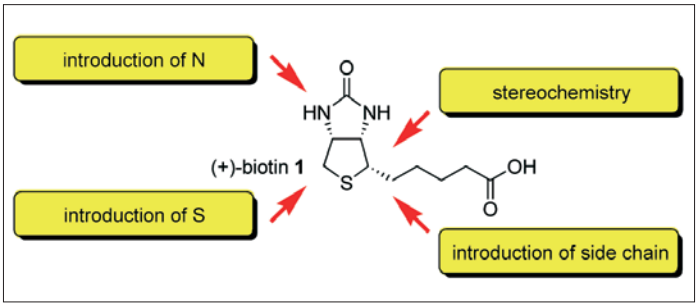
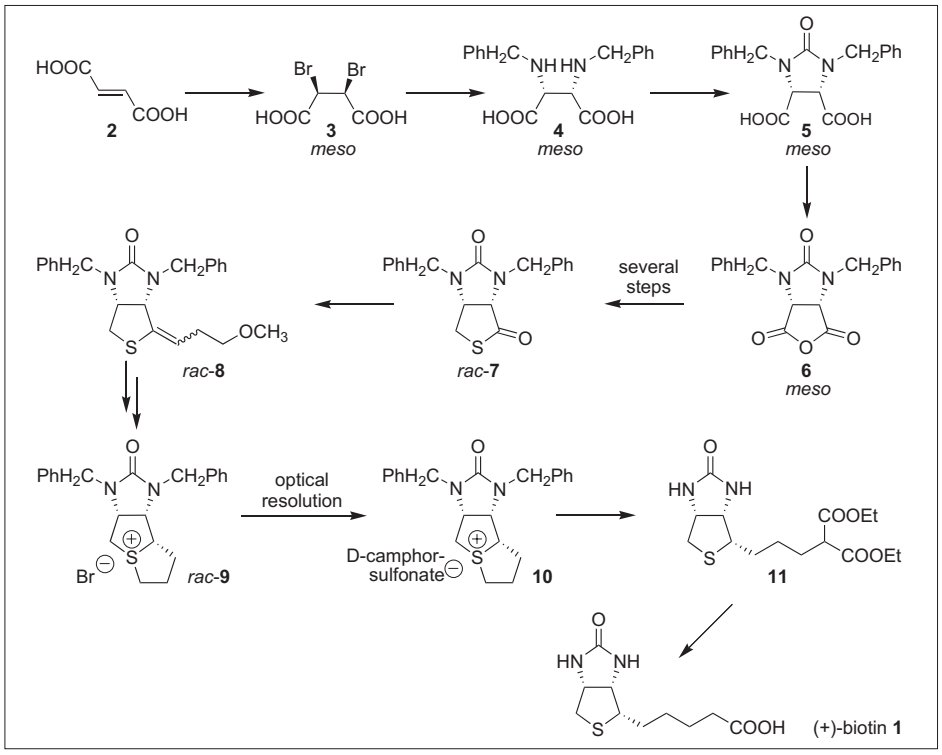
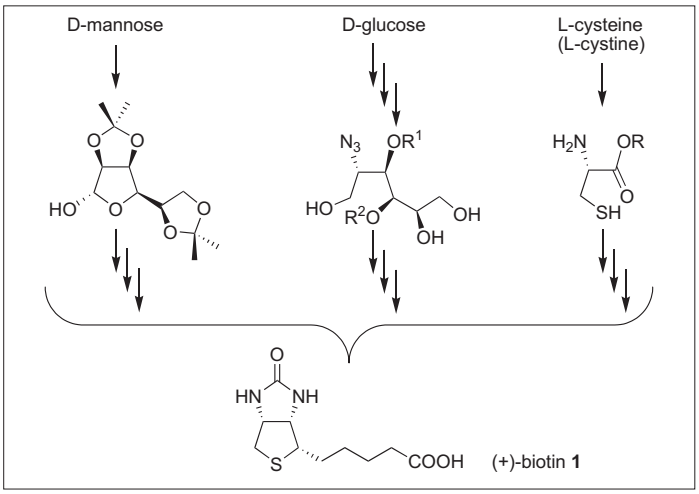


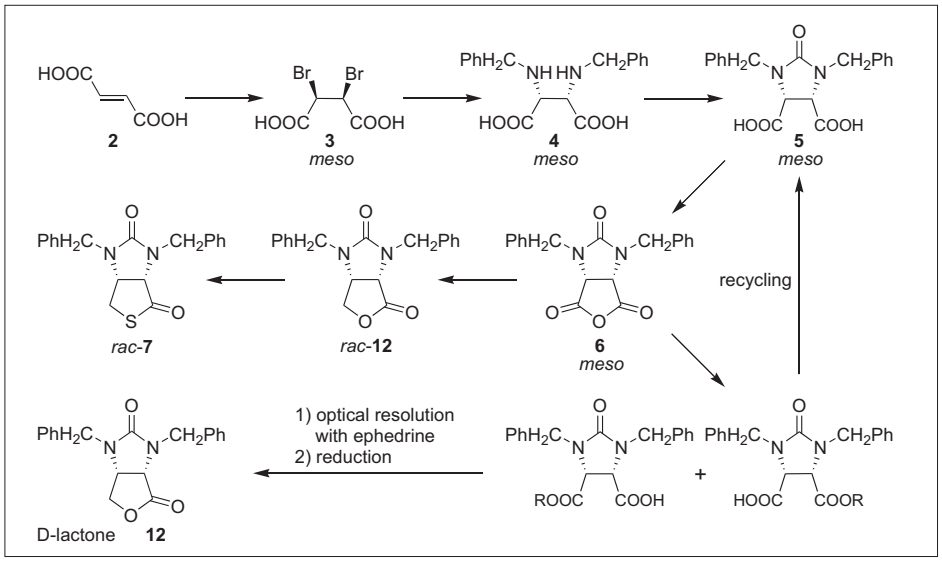
Fig. 2. Routes to (+)-biotin (**1**): General problems to be solved.



Scheme 1. The Goldberg-Sternbach concept.



Scheme 2. Chiral pool concepts.



Scheme 3. The improved Goldberg-Sternbach concept: Direct conversion of lactone to thiolactone and late optical resolution.

3. Further Developments

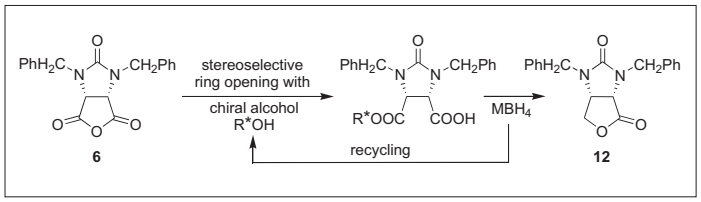
A major step forward to improve the original Goldberg–Sternbach concept was the finding of Gerecke, Zimmermann and Aschwanden[8] that (chiral) lactone **12** can be directly converted to (chiral) thiolactone **7** by treatment with potassium thioacetate (Scheme 3). The main advantage of this pathway to D-lactone **12** was based on the resolution step, which takes place at a very late stage of the synthesis. This procedure with recycling of the unwanted half-ester *via meso*-diacid **5** and the resolving agent ephedrine was carried out on commercial scale until the 1990s.

A further improvement replacing this procedure was invented by Pauling and Wehrli.[9] Diastereoselective ring opening of anhydride **6** with a chiral alcohol, followed by reduction of the selectively formed diastereoisomeric half-ester by a complex hydride and ring closure provides an efficient route to key intermediate **12** (Scheme 4), operated on industrial scale.

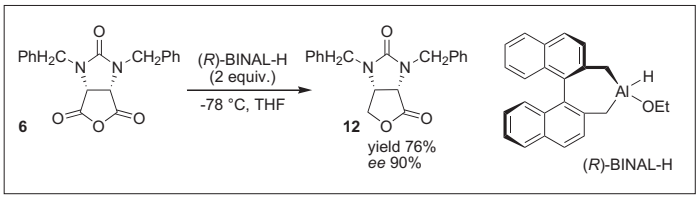
An alternative concept applied at Lonza used tetronic acid (**13**), which is easily available from diketene (Scheme 5[10–13]), as a starting material. The heterogeneous diastereoselective hydrogenation of intermediate **14** (originally delivering a 70:30 mixture of diastereomers **16a**/**b**), was further developed in cooperation with the colleagues from the catalysis group of the former Ciba-Geigy. With the diphosphane josiphos2 (**15**) as a ligand, the stereoselective Rh(I)-catalysed asymmetric hydrogenation resulted in a >99:1 ratio. The production, operated on multi-tonne scale, had to be terminated due to loss of chirality in the final hydrogenolysis deprotection step, which led to destruction of the (expensive) chiral auxiliary.

4. Asymmetric Hydrogenation of Cyclic Anhydride: The Dream Reaction

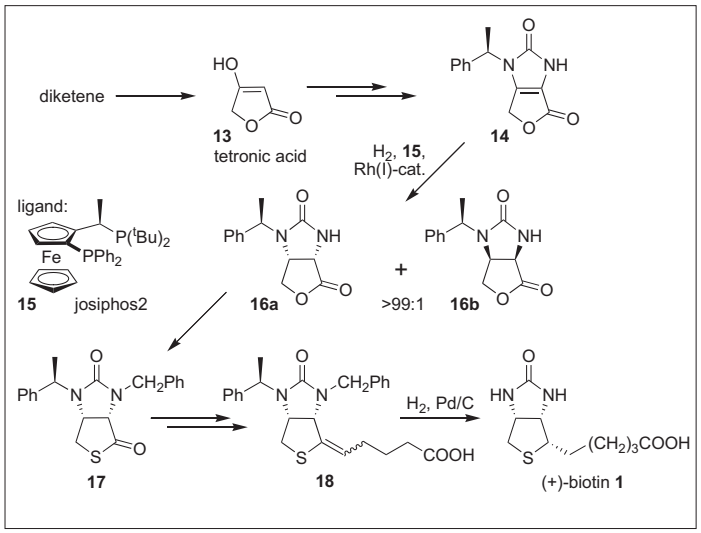
In all commercially attractive synthesis schemes, one central question has to be answered: At which stage should chirality be introduced? Concerning the methods for achieving this, classical optical resolution, chiral pool approaches, and the use of chiral auxiliaries (including enzymes) have been evaluated. When reviewing processes delivering (+)-biotin (**1**) on an industrial scale, it becomes apparent that D-lactone **12** is best suited for this task. It is, therefore, the common intermediate in technical syntheses (Scheme 6). The most attractive precursor of this compound, in turn, is the easily available cyclic anhydride **6**. When combining those two facts, consequently a further breakthrough would be an enantioselective catalytic approach,



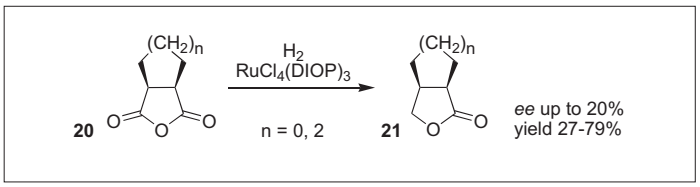
Scheme 4. The Pauling-Wehrli concept: Diastereoselective ring opening.



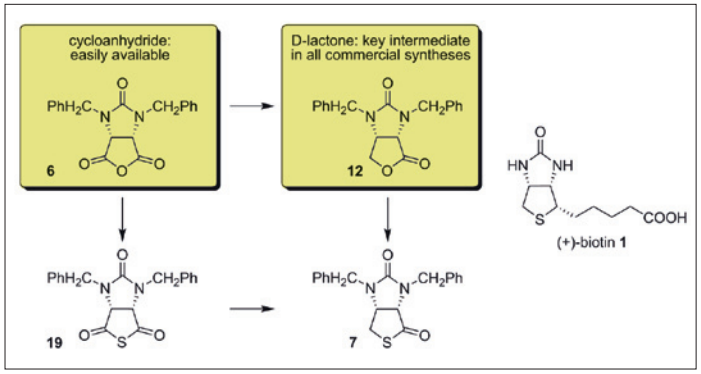
Scheme 7. Direct stoichiometric reduction of anhydride **6** to D-lactone **12**.



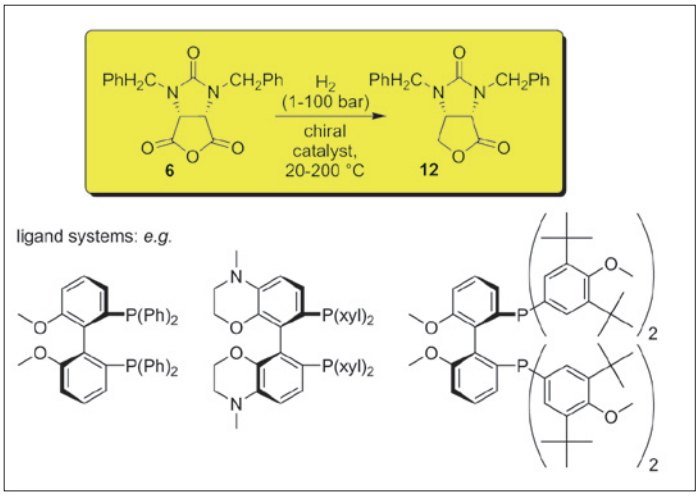
Scheme 5. (+)-Biotin process using asymmetric hydrogenation (Lonza concept).



Scheme 8. Asymmetric hydrogenation of cyclic anhydrides to lactones.



Scheme 6. Preferred key steps for introduction of chirality in commercial (+)-biotin syntheses.



Scheme 9. The dream reaction: Catalytic asymmetric hydrogenation of anhydride **6** to D-lactone **12**.

e.g. the reduction of **6** to **12** (or of **19** to **7**, respectively), representing the recommended method of the 21st century.

In general, asymmetric homogeneous catalysis with metal complexes is a key technology for the development of successful processes in the competitive field of vitamins and fine chemicals.[14,15] However, despite the numerous achievements in organic synthesis methodology, certain functional group transformations are still not achievable in an efficient manner that satisfy the criteria of green chemistry. As an example, only few reports are known for the direct conversion of cyclic *meso*-anhydrides to optically active lactones: For the stereoselective reduction of **6** to **12** with BINAL-H (Scheme 7[16]), over-stoichiometric amounts of the chiral reagent were used, and the hydrogenation of anhydrides **20** with a chiral ruthenium DIOP complex delivered the corresponding lactones **21** in low (up to 20%) *ee* only (Scheme 8[17]).

Therefore an efficient general catalytic method for such a transformation was lacking. When tackling this high-rewarding, but high-risk topic, the conditions and environment for such an invention were far from optimum. In times of limited man power and financial resources, *i.e.* with basically no company-internal support and almost no budget at DSM Nutritional Products, there was only a chance to demonstrate the feasibility of the so far unattainable with a rather limited number of experiments. Finally the aim could be achieved only in cooperation with the homogeneous catalysis group at Solvias, based on technical and scientific competence of contributors as well as personal contacts existing from former collaborations within the Basel chemical community.

The transformation of cyclic *meso*-anhydride **6** to D-lactone **12** (Scheme 9) was investigated as a first example of the catalytic highly enantioselective reduction of this kind:[18] The dream reaction indeed worked with high chemoselectivity, optical induction and yield! A limited screening of solvents, precursors for metal complexes and ligands, forming the active catalysts, reaction conditions (hydrogen pressure, time and temperature), and substrate-to-catalyst (s/c) ratio delivered excellent results in a surprisingly short period of time.

Iridium and rhodium complexes with atropisomeric ligands like the examples shown in Scheme 9 delivered complete conversion and *ee* values of >95% after some optimisation work. These results could be achieved at an s/c of 5'000. Laboratory scale-up, piloting on multi-kg scale, and production trials were performed without particular difficulties. The

breakthrough method can be used for the synthesis of a variety of lactones which are suitable for various applications in the fine chemicals area.[19] The corresponding thio case, *i.e.* the transformation of thioanhydride **19** to thiolactone **7** (Scheme 6) also worked, although with somewhat limited yield and selectivity under comparably more drastic conditions.[20] Investigations on the mechanism of the asymmetric reduction are underway.

5. Conclusions

An important step towards an environmentally benign production method for (+)-biotin has been taken by the enantioselective catalytic hydrogenation of the cyclic anhydride to the lactone intermediate. This method provides a tool for the efficient introduction of chirality in the synthetic scheme to biotin. Even more than 60 years after the first commercial synthesis of biotin, main elements of the original approach of Goldberg and Sternbach are still applicable. Even after more than hundred years of research on biotin, breakthrough inventions are still possible.

Acknowledgements

We would like to kindly acknowledge the contributions of our colleagues J. Fischesser, O. Stan, and S. Hottiger (research), R. Härter (development), and G. Schiefer (analytical department) from DSM Nutritional Products (Basel), H. Hartmann (production) from DSM Nutritional Products (Grenzach, Germany), J. Boogers, A. de Vries, and J.G. de Vries (pharma research) from DSM (Geleen, Netherlands), B. Winkler (pilot production) from DSM (Linz, Austria), and various colleagues from analytical departments of Solvias and DSM.

Received: March 5, 2009

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