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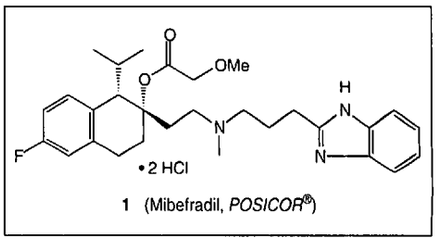
Asymmetric Hydrogenation *vs.* Resolution in the Synthesis of *POSICOR®*, a New Type of Calcium Antagonist

Yvo Crameri, Joseph Foricher, Urs Hengartner, Christian-Johannes Jenny, Frank Kienzle, Henri Ramuz, Michelangelo Scalone, Markus Schlageter, Rudolf Schmid*, and **Shaoning Wang**

Abstract. The pilot-plant-scale synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid ((*S*)-**5**) by asymmetric hydrogenation of 2-(4-fluorophenyl)-3-methylbut-2-enoic acid (**12**) with the [Ru((*R*)-MeOBIPHEP)(OAc)$_2$]-catalyst is described. The hydrogenation was performed in a continuous mode in a cascade stirred-tank reactor system at 270 bar pressure. The acid (*S*)-**5** is an important optically active intermediate in the synthesis of mibefradil (**1**), a new type of calcium antagonist.

1. Introduction

Mibefradil (**1**) [1] is a new type of a calcium antagonist which has been approved in several countries. Having recently also obtained recommendation for approval by the FDA Cardiovascular Committee, it will soon be released under the trademark *POSICOR®* for treatment of hypertension and angina pectoris. Mibefradil is the first calcium antagonist known to selectively block T-type calcium channels [2]. Accordingly, it has been classified by the World Health Organization as a new category of calcium antagonist. The compound is highly effective in hypertension and angina pectoris, has an optimal pharmacokinetic profile, which makes it a once-a-day, long-acting drug, and has an excellent tolerability profile in both indications [3]. Moreover, it has the unique property of slightly lowering the heart rate without reducing cardiac contractility [4]. In comparison with other antihypertensive and antianginal drugs, a significant improvement in the benefit-risk ratio could be demonstrated. Therefore, once mibefradil is launched, it will represent a very important alternative treatment for patients with hypertension and angina pectoris.



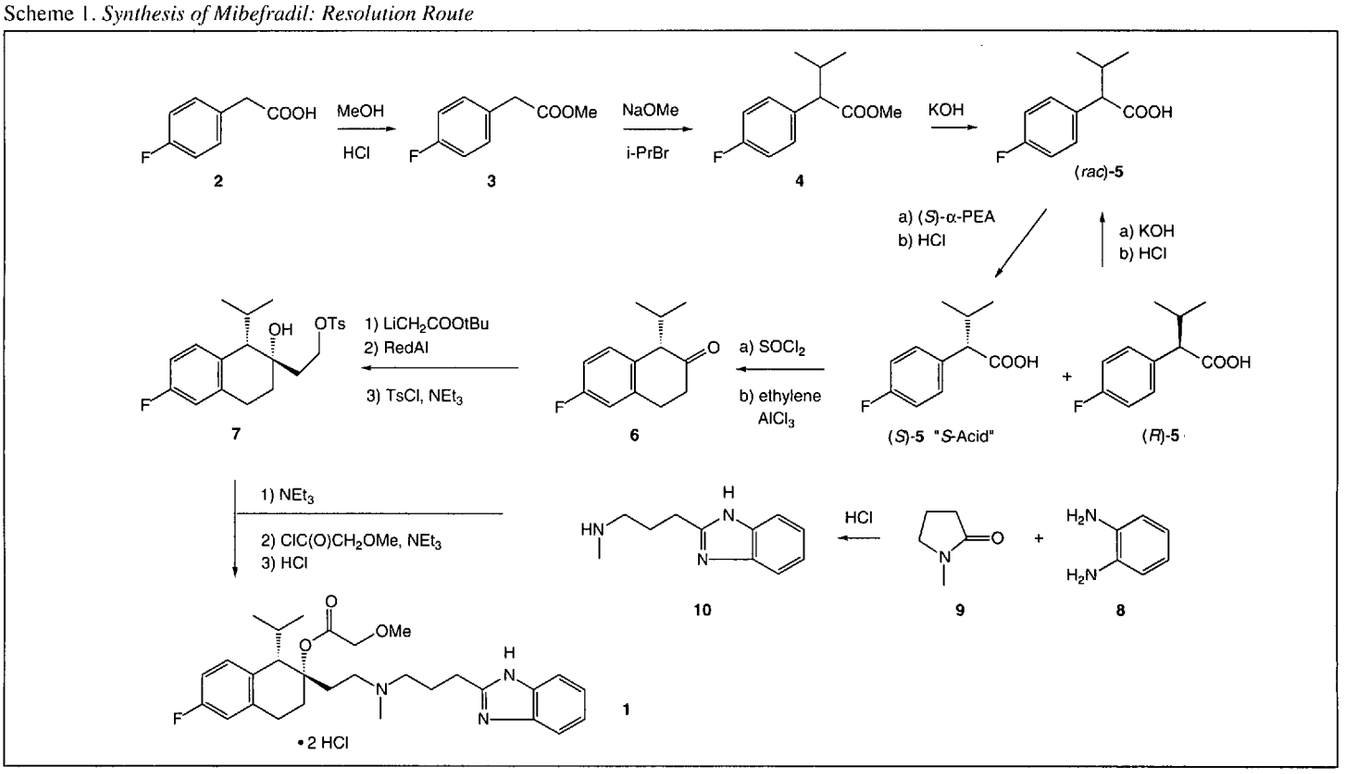
1 (Mibefradil, *POSICOR®*)

2. Synthesis

Mibefradil (**1**) is a moderately complex molecule containing a substituted tetralin scaffold with two chiral centers. It has been developed as a single enantio-

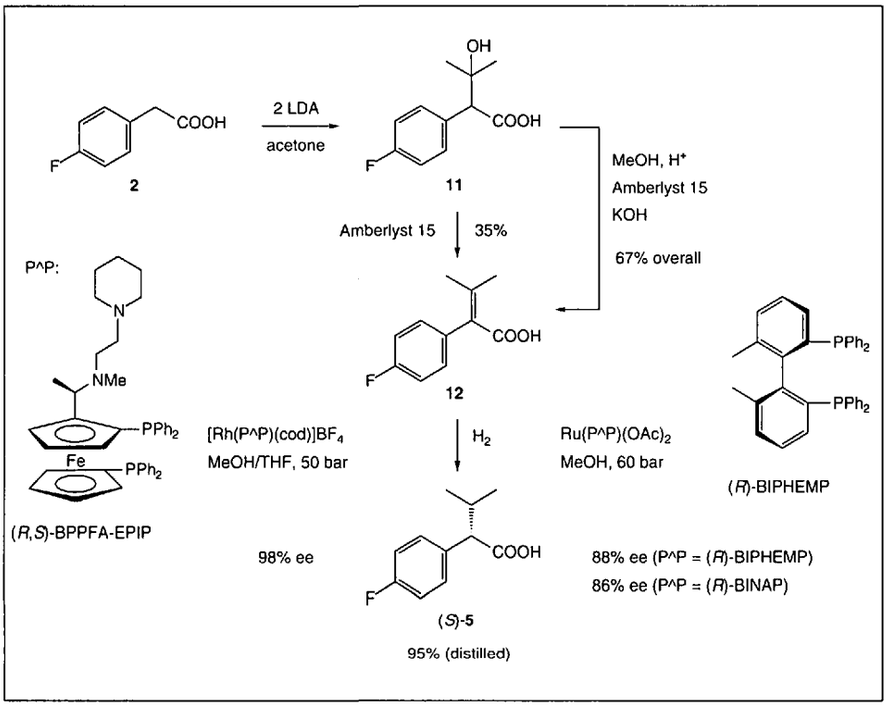
**Correspondence*: Dr. R. Schmid
Pharmaceuticals Division, Preclinical Research
F. Hoffmann-La Roche Ltd.
CH–4070 Basel

Scheme 1. *Synthesis of Mibefradil: Resolution Route*

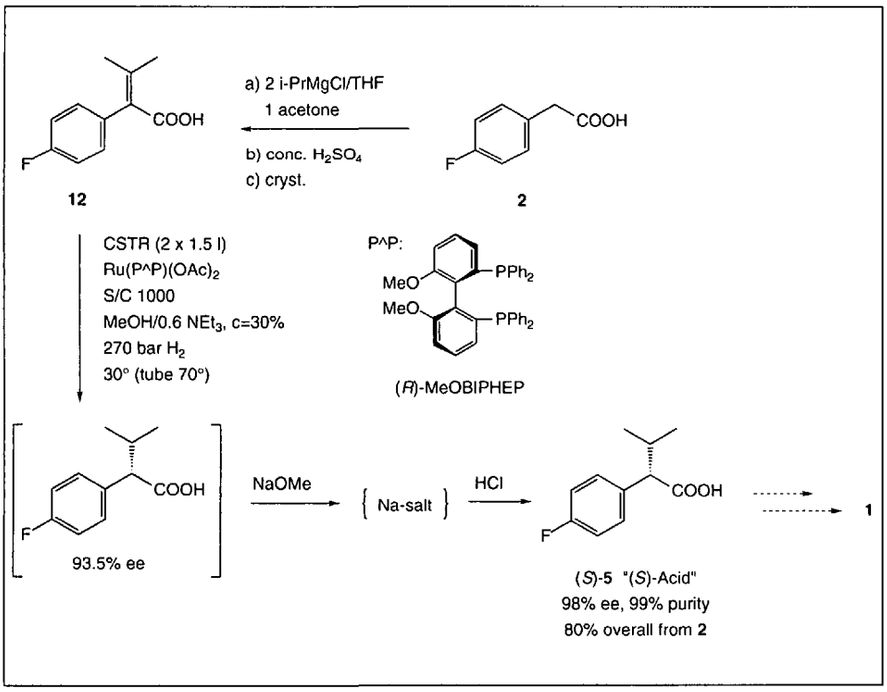


mer. The synthesis of **1** is based upon the original research route [1] and upon improvements elaborated by Process Research and Kilolaboratory [5] (*Scheme 1*). Separation of enantiomers was performed at the stage of the 2-(4-fluorophenyl)-3-methylbutanoic acid (*rac*-**5**) by resolution with (*S*)-1-phenylethylamine. The resolution has been developed into a highly efficient process in which undesired (*R*)-**5** is recycled by base-catalyzed racemization. Thus, an overall yield of 70% of (*S*)-**5** is attained in the five-step sequence starting from **2**. (*S*)-**5** is then converted into the optically active tetralone **6** *via* the acid chloride and reaction with ethylene [1a]. The side chain is diastereoselectively introduced by addition of *tert*-butyl lithioacetate. Further elaboration to tosylate **7** [1a], amination with the appropriate amine building block **10** [1b, 5b], and esterification of the tertiary alcohol function then lead to **1**.

Scheme 2. *Asymmetric Hydrogenation Approach to* (S)-**5**



Scheme 3. *Pilot-Plant-Scale Process*



3. Asymmetric Hydrogenation Approach

Whilst the synthesis is quite efficient overall, it remains lengthy (12 steps). Cost of goods, on the other hand, have to be low in order to successfully compete with products already introduced onto the antihypertensive market. Therefore, any shortening and improvement of the synthesis becomes beneficial. One major avenue followed was an asymmetric hydrogenation approach to (*S*)-**5** (*Scheme 2*) [6]. It had been previously shown by *Hayashi et al.* [7] that trisubstituted acrylic acids of the type **12** – although not **12** itself – can be hydrogenated using Rh-catalysts derived from modified ferrocenyl-type diphosphine ligands (BPPFA type). Otherwise, little precedent existed for asymmetric hydrogenation of trisubstituted acrylic acids [8]. In the event, the unsaturated acid **12**, prepared from **2** as shown in *Scheme 2*, could be asymmetrically hydrogenated with the *Hayashi* Rh(BPPFA-EPIP)-catalyst [7] or with a Ru(BIPHEMP)-catalyst [9] to afford (*S*)-**5** of 98% and 88% ee, respectively, in high yield. Having thus demonstrated the principal feasibility of the asymmetric hydrogenation approach, the next goal was to develop a technically feasible process.

4. Asymmetric Hydrogenation Development

In the course of the development of the asymmetric route, various issues had to be addressed and solved, amongst them *a*) the establishment of an efficient synthesis of the hydrogenation substrate **12**, *b*) the choice of catalyst which would be appropriate in terms of selectivity, activity, availability, cost, and patent independence, *c*) the evaluation and development of the optimal hydrogenation conditions, and in particular also *d*) the choice and design of the appropriate high-pressure equipment. The final result of the development work is summarized in *Scheme 3*.

As to the synthesis of **12**, it was found after considerable experimentation that dehydration of alcohol **11** could be effected cleanly and smoothly in conc. H_2SO_4 [10]. Decarboxylation (which occurred with weaker acids, to give β,β-dimethyl-*p*-fluorostyrene) was thus completely sup-

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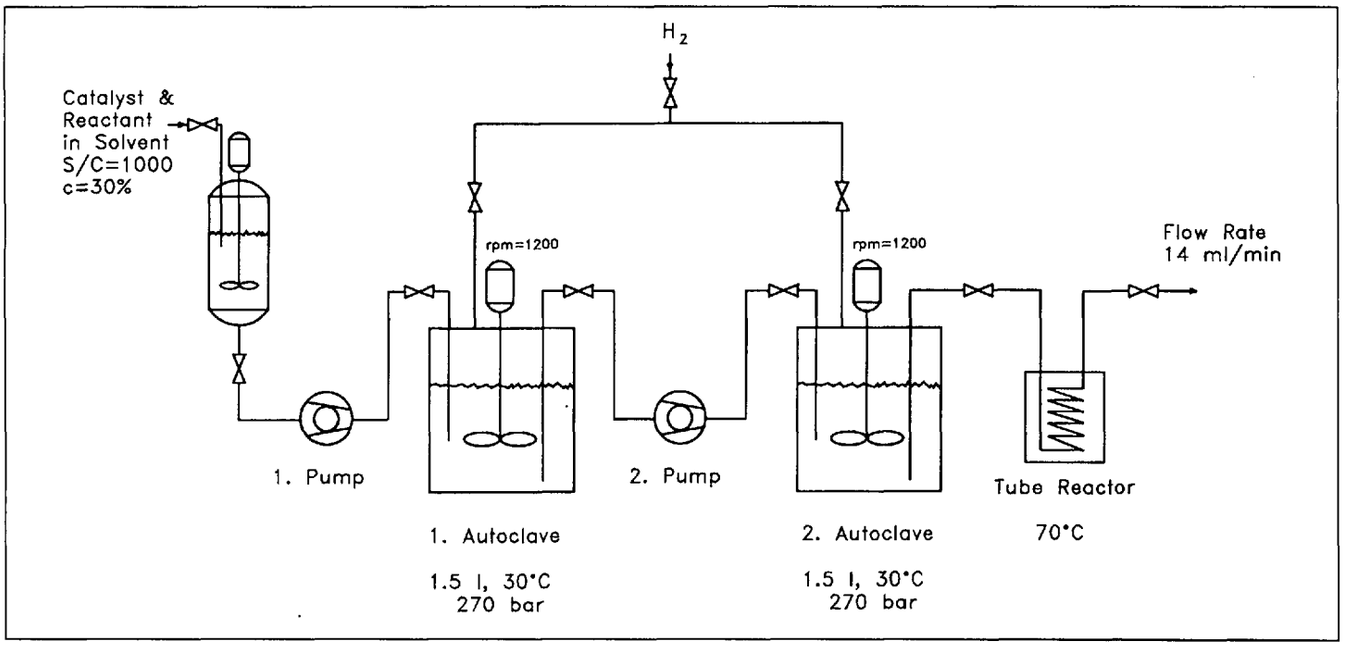

Figure. *Cascade continuous stirred-tank reactor system* (CSTR)

pressed, and the three-step indirect route shown in *Scheme 2* became obsolete. In addition, the expensive LDA base was replaced with isopropylmagnesium chloride in the preparation of **11**. Acid **12** was obtained in overall yields up to 94% from **2**. For the catalyst, it was decided (based on the above considerations and experimental evaluation) to pursue a Ru-catalyst derived from the MeOBIPHEP-diphosphine ligand [11]. This catalyst, like the one derived from BIPHEMP, showed increasing enantioselectivity with increasing pressure (up to 92% ee at 180 bar).

For the development of the hydrogenation step, a cascade continuous stirred-tank reactor (CSTR) system was chosen. The major advantage of such a system lies in the large reduction in total reactor volume as compared to the batch mode. Using this system (2 × 1.5-l autoclaves, see *Fig.*), 38 kg of **12** were asymmetrically hydrogenated at 270 bar pressure in seven days to afford (*S*)-**5** of 93.5% ee. Productivity for this relatively slow hydrogenation (average TOF *ca.* 40 h^{-1}) amounted to 1.8 kg l^{-1} day^{-1} (as opposed to *ca.* 0.2 kg l^{-1} day^{-1} for batch-mode hydrogenation). Final upgrading to 98% ee was achieved by crystallization of the Na-salt of (*S*)-**5**. The overall yield of the asymmetric route amounted to 80% based on **2** (*Scheme 3*).

5. Conclusion

In comparison with the resolution route, the asymmetric route to (*S*)-**5** is shorter (2 *vs.* 5 chemical steps), higher-yielding (80 *vs.* 70%), and requires less multipurpose equipment and much less unit operations. Consequently, a significant reduction in costs for (*S*)-**5** has resulted, and the process is under consideration now for technical implementation. Crucial for the successful development of the asymmetric hydrogenation route was, next to the substrate synthesis, the establishment and demonstration of the cascade CSTR system for the high-pressure asymmetric hydrogenation step.

The work on the asymmetric hydrogenation route presented here has been performed at the Process Research and Kilolaboratory units of the Basel Preclinical Research Department. Laboratories involved in addition to those of the authors were those of Dr. *Emil A. Broger*, Dr. *Josef Gabriel*, and Dr. *Reinhard Zell*. Their and their collaborators dedicated work and the technical assistance of all coworkers in the laboratories of the authors are gratefully acknowledged. Regulatory advice by Dr. *Wolf Brenner* and cost calculations by Mr. *Helmut Bömches* are also gratefully acknowledged.

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