

Alternative synthesis of the chiral atypical β -adrenergic phenylethanaminotetraline agonist SR58611A using enantioselective hydrogenation

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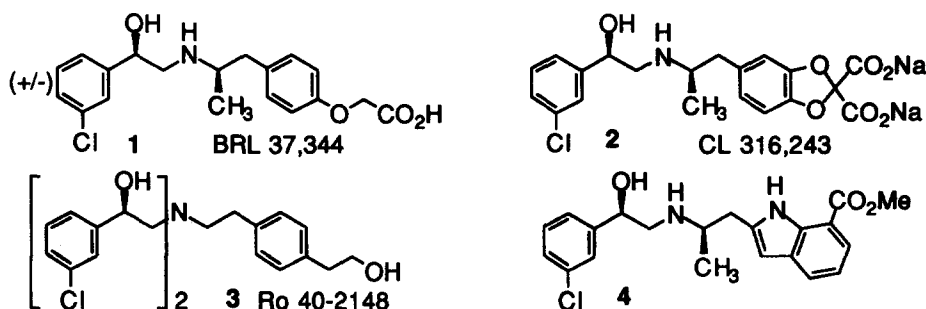
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Received 16 March 1999; accepted 24 April 1999

Abstract: We have developed an alternative synthesis of the atypical β -adrenergic phenylethanaminotetraline agonist SR58611A. Two key intermediates have been synthesised involving enantioselective hydrogenation of an aminoketone and an enamide providing the corresponding amino alcohol and amide in >96 and >98 % ee respectively. © 1999 Elsevier Science Ltd. All rights reserved.

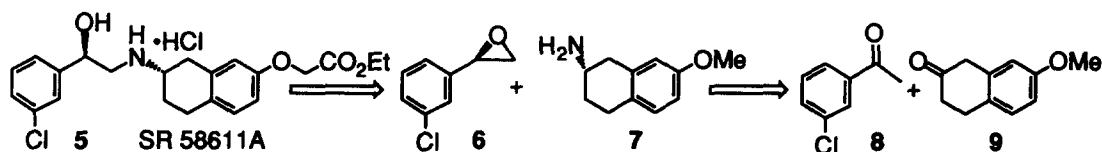
Amino alcohols play a critical role as building blocks for organic synthesis and in biological processes as some are recognised as β_1 - and β_2 -adrenoreceptor agonists.¹ Recently, the discovery of atypical β -adrenoreceptor mediating lipolysis stimulated the research for new agents specific for such sites as they constitute compounds of commercial interest.² In this context, certain phenylethanamines possessing two stereogenic carbon atoms reported by Beecham Laboratories have been found to behave as potent agonists for stimulation of lipolysis.³ An example is given as **1** in Scheme 1. Following, several other derivatives belonging to that family have been synthesised and evaluated biologically for their potential as atypical β -adrenoreceptor agonists (examples **2**,⁴ **3**,⁵ and **4**⁶ Scheme 1).



Scheme 1

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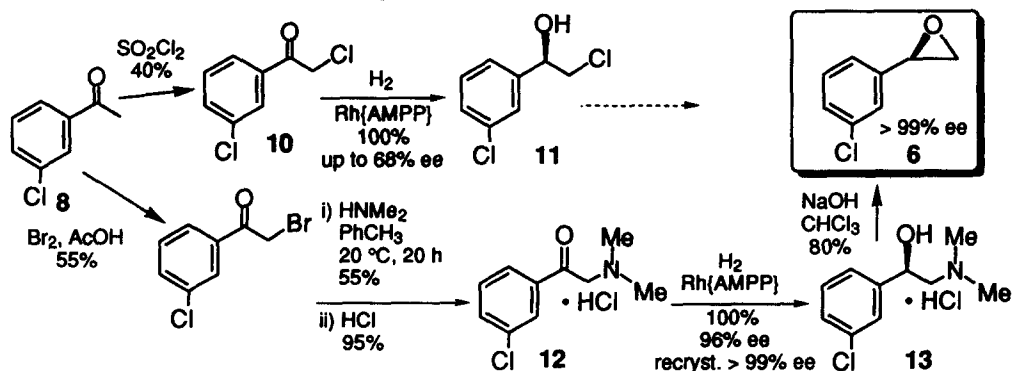
Atypical phenylethanolaminotetraline adrenergic agonists which are members of the above class of agents have been synthesised at Sanofi⁷ and are currently under biological investigation. Compound SR58611A **5** (Scheme 2) has been found to be the more potent and selective of the series. Interestingly, the multi-step syntheses of all of the above agonists 1-5 share generally in common the coupling between two chiral fragments: an epoxide and an amine. An example of retrosynthetic analysis is given for **5** (Scheme 2). Thus, the need for the two fragments in high optically pure form appears evident. Among the possible pathways to the chiral *m*-chloro epoxystyrene **6**,⁸ the cyclization of chiral functionalized hydroxy derivatives obtained through enantioselective hydrogenation of α -halo and α -dimethylamino ketones⁹ is a promising approach. On the other hand, even if the various strategies to the optically pure amines are highly dependant upon the overall structure of the latter, a hydrogenation step can be envisioned as well.



Scheme 2

As we have an ongoing interest in the enantioselective hydrogenation involving the chiral aminophosphine-phosphinite diphosphanes,¹⁰ we sought to apply such catalytic processes to the synthesis of SR58611A including the creation of the two chiral carbons. Here, we report the straightforward efficient and enantioselective synthesis of intermediates **6** and **7** (Scheme 2) involving two enantioselective hydrogenations.

We focused first on the access to (*R*)-*m*-chlorostyrene epoxide **6** following Noyori's strategy⁹ for the production of the intermediate hydroxy compound. As a matter of fact, two non-equivalently successful approaches were explored based on Rh{AMPP} catalyzed hydrogenations of α -functionalized ketones. The first involved the asymmetric hydrogenation of the α -chloro ketone **10** obtained easily from *m*-chloro acetophenone **8** (Scheme 3). Nonetheless, using AMPP ligands, the resulting hydroxy compound **11** could be obtained only, at best, in 68% ee (Table 1, entry 1). Thus, we turned our attention towards the reduction of the amino ketone **12** which was synthesised following standard procedures from **8** (Scheme 3).



Scheme 3

In summary, asymmetric hydrogenation is a highly efficient methodology for the introduction of chirality. More, for the synthesis of our target agent SR58611A, such a process proved to be particularly well

suited for the access to optically pure key intermediates. Further work is in progress for the synthesis of other key intermediates valuable for asymmetric synthesis using enantioselective hydrogenations.

Acknowledgements. The authors gratefully thank Pr. Dr. Bertrand Castro from Sanofi Chimie (Gentilly, France) for helpful discussions and both Sanofi Chimie (grant to M. D.) and the Centre National de la Recherche Scientifique for financial support.

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