Pergamon

Tetrahedron Letters 40 (1999) 4551–4554

TETRAHEDRON LETTERS

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

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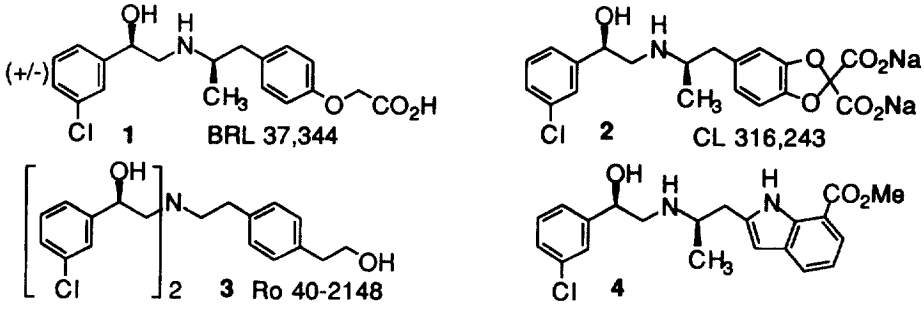
Received 16 March 1999; accepted 24 April 1999

Abstract: We have developed an alternative synthesis of the atypical β-adrenergic phenylethanolaminotetraline 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.

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 lipolylis stimulated the research for new agents specific for such sites as they constitute compounds of commercial interest.[2] In this context, certain phenylethanolamines 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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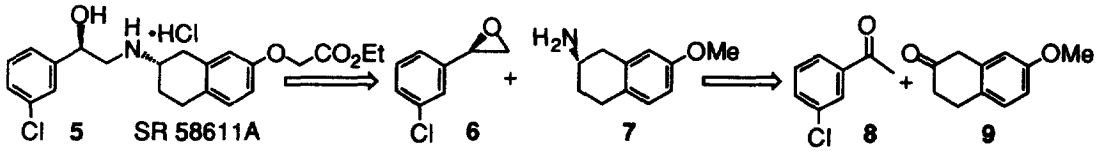
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00807-2

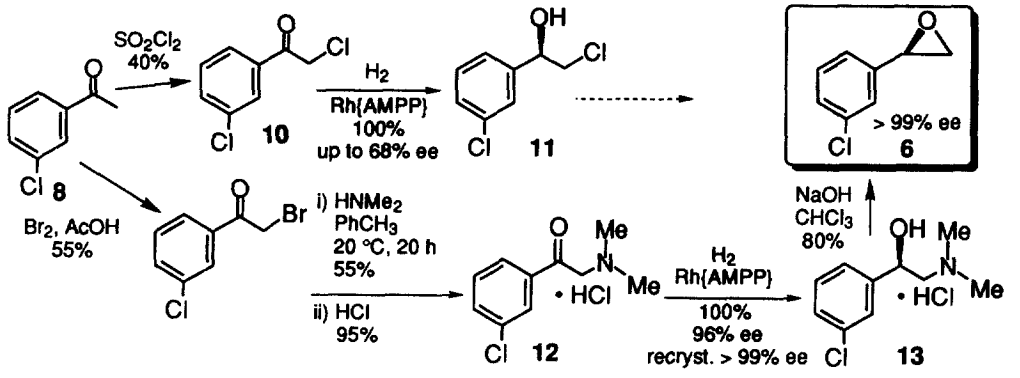
Atypical phenylethanolaminotetraline adrenergic agonists which are members of the above class of agents have been synthesised at Sanofi[7] and are currently under biological investigation. Compound SR58611A **5** (Scheme 2) has been found to be the more potent and selective of the series. Interestingly, 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 epoxistyrene **6**,[8] the cyclization of chiral functionalized hydroxy derivatives obtained through enantioselective hydrogenation of α-halo and α-dimethylamino ketones[9] 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.

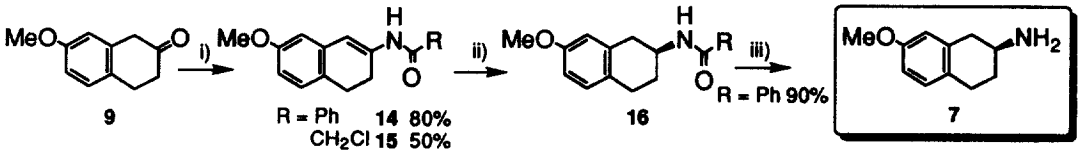
We focused first on the access to (*R*)-*m*-chlorostyrene epoxide **6** following Noyori's strategy[9] for the production of the intermediate hydroxy compound. As a mater of fact, two non-equivalently successful approaches were explored based on Rh{AMPP} catalyzed hydrogenations of α-functionalized ketones. 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

Subsequent hydrogenation in the presence of Rh{AMPP} catalysts led quantitatively to the corresponding amino alcohols **13** under mild conditions and in 96% ee (Table 1, entries 2-4)[11]. A single crystallisation of the product allowed to isolate the desired derivative **13** in >99% ee. The synthesis of the chiral epoxide **6** was then completed according to a procedure developed by Castedo *et al.*.[12]

For the asymmetric synthesis of the aminotetraline **7**, we also targeted the use of asymmetric hydrogenation. For that purpose, we applied the highly enantioselective procedure reported by Tschaen *et al.* involving the reduction of enamides **14** and **15** obtained from the substituted tetralone **9**.[13] As the reduction carried out in the presence of AMPP ligands gave only low enantioselectivities (Table 1, entries 5 and 6), ruthenium catalysts modified by the well known BINAP and MeO-BIPHEMP diphosphine were used. Accordingly, the enamides **14** and **15** were hydrogenated with up to 98% ee (Table 1, entries 7-10), substrate **14** providing the best results. Thus, the hydrogenated derivative **16** was converted to the optically active aminotetraline **7** in good yield. Subsequent transformations following reported procedures[7a] provided the expected 2-amino-7-ethoxycarbonylmethoxytetraline necessary for the final coupling with the chiral epoxide **6** leading to the target compound **5**.



i) H_2NCOR, PhMe, amberlyst 15, reflux 20h ; ii) H_2, "Rh" or "Ru"; iii) $MeSO_3H$, AcOH, 160 °C, 24h

Scheme 4

Table 1. Asymmetric hydrogenation of precursors of SR58611A.[a]

entry	substrate	catalyst[b]	solvent	P_{H2} (bar), temp (°C)	Time (h), conv. (%)[c]	ee (%)[d] config.
1	**10**	[Rh{(*R*)-Cy,Cy-oxoProNOP}(OCOCF$_3$)]$_2$	PhMe	50, 20	48, 100	68 (*R*)
2	**12**	[Rh{(*R*)-Cy,Cy-oxoProNOP}(COD)]BF$_4$	MeOH	50, 20	18, 100	96 (*R*)
3	**12**	[Rh{(*R*)-Cy,Cy-oxoProNOP}(COD)]BF$_4$	"	1, 20	18, 100	96 (*R*)
4	**12**	[Rh{(*R*)-Cp,Cp-oxoProNOP}(COD)]BF$_4$	"	50, 20	18, 100	96 (*R*)
5	**14**	Ru{(*S*)-Ph, Ph-oxoProNOP}(2-methylallyl)$_2$	MeOH/CH_2Cl_2	50, 50	22, 75	19 (*S*)
6	**14**	[Rh{(*R*)-Ph,Ph-ProNOP}(COD)]BF$_4$	"	50, 50	21, 58	37 (*S*)
7	**14**	[Ru(*R*)-BINAP(C_6H_6)Cl]Cl	"	50, 50	24, 100	95 (*S*)
8	**14**	Ru{(*R*)-MeO-BIPHEMP}Br$_2$	"	50, 20	64, 100	98 (*S*)
9	**15**	[Ru(*R*)-BINAP(C_6H_6)Cl]Cl	"	50, 50	21, 28	69 (*S*)
10	**15**	Ru{(*R*)-MeO-BIPHEMP}Br$_2$	"	50, 20	48, 35	78 (*S*)

[a]The reactions were carried out by using 1.5 to 2 mmol of recrystallized substrate, 0.1 M in dry degassed solvent. Substrate/M (M = Rh or Ru) : 200/1. [b]See ref 10e for the AMPP's structures. [c]Determined by ^1H NMR. For complete reactions, the times reported are not necessarily optimized. [d]Determined by HPLC analysis (Chiralcel OD (Daicel)) , on the free amine for **13**.

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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