An efficient asymmetric synthesis of the potent β-blocker ICI-118,551 allows the determination of enantiomer dependency on biological activity†‡

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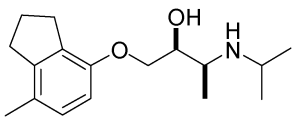
A highly efficient, practical and flexible two-step asymmetric synthesis of the β_2-selective β-blocker ICI 118,551 is reported, allowing an unambiguous determination of the dependency of biological activity with optical activity, revealing the *S*,*S*-enantiomer to be the most potent.

The β-adrenergic receptors (βARs) are G-protein-coupled receptors (GPRCs) that exist as three subtypes, β_1, β_2 and β_3. The recently reported crystal structures for the β_1AR[1] and β_2AR[2–4] have led to an upsurge in structural and biophysical studies on these receptors. βAR antagonists (β-blockers) are important drugs for the treatment of a range of diseases including heart failure,[5] ischemic heart disease,[6] and hypertension.[7] Most clinically used β-blockers are either selective for the β_1AR subtype or nonselective for the β_1AR and β_2AR. However, β_2AR-selective antagonism is useful as a pharmacological tool to probe the receptor and could potentially represent an important pharmacotherapy in its own right. By far the most potent and selective β_2AR antagonist currently known is the experimental compound ICI-118,551.[8–10] ICI 118,551 has been reported to have 550 times higher affinity for β_2AR over β_1AR.[9] The structure of ICI 118,551 consists of an indane core with a pendant propanolamine chain incorporating an α-methyl substituent (Fig. 1).

We were interested in ICI 118,551 as a basic starting point for a programme of molecular design to develop new β_2-selective antagonists. However we were surprised to find that there was ambiguity in the literature reports describing the stereochemistry of ICI 118,551. In the original patent describing (±)-ICI 118,551, and related synthetic work, the compound is described as the *erythro* isomer.[8,11] This leads to the assignment of the relative stereochemistry of (±)-ICI 118,551 as *S**,*S** (Fig. 1). It appears that this compound was incorrectly drawn and assigned in chemical abstracts[12] as the *R**,*S** diastereomer and this is where the confusion in the literature originates. For example docking studies on models of the β-adrenergic receptors were carried out using the incorrect *threo* diastereomer *R**,*S**-ICI 118,551.[13] It is worth noting that the *threo* diastereomer was also found to be an active β_2-selective blocker,[8] so in this case the work remains valid.



(±)-ICI 118,551

Fig. 1 (±)-ICI 118,551 shown with the correct *S**,*S** relative stereochemistry.

In the course of this investigation it became clear that the absolute configuration of the more active enantiomer of ICI 118,551 had never been reported conclusively. The chromatographic resolution of ICI 118,551 has been reported by Quaglia *et al.*, who reported a difference in the activity of the enantiomers, but without determination of the absolute stereochemistry.[14] The authors of this paper postulated that the most active enantiomer should be the 2*S* configuration by analogy with other aryloxypropanolamine β-blockers.[15] Unfortunately the authors then suggest that the active enantiomer to be 2*S*,3*R* which as discussed above is the wrong relative stereochemistry.

ICI 118,551 remains a very important pharmacological tool for studying β-receptor biochemistry and the purpose of this paper is to present our results which (a) clarify the ambiguity relating to the biological activity of the enantiomers of ICI 118,551; (b) provide a practical and flexible asymmetric synthesis of ICI 118,551; and (c) provide an assessment of the β_1 : β_2 receptor antagonism of each enantiomer of ICI 118,551 compared with the racemate. The results of this work, we believe, will aid investigators using ICI 118,551 and the simplicity of the synthetic route will offer opportunities for generating a wide range of analogues for biological applications and the development of therapeutics.

A concise asymmetric synthesis of ICI 118,551 was developed (Scheme 1). Epoxide **1** was prepared *via* a known one-pot Sharpless asymmetric epoxidation-*in situ* tosylation sequence on *trans* crotyl alcohol.[16] Displacement of the tosylate with the commercially available indanol **2** using caesium carbonate as the base led to epoxide **3** in high yield. The enantiomeric purity was determined by chiral HPLC (>95% ee). Ring-opening of the epoxide with isopropylamine gave (2*S*,3*S*)-ICI 118,551, for which a crystal structure was obtained and is shown below. The synthetic route is extraordinarily short from the commercially available indanol **2** and offers flexibility, given the commercial availability of amines.

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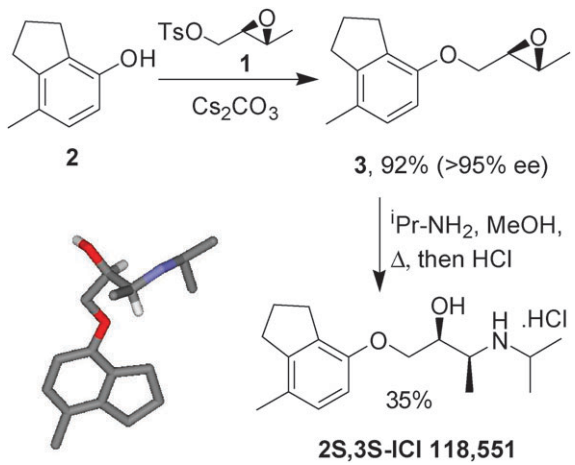

Scheme 1 Asymmetric synthesis and crystal structure of (2*S*,3*S*)-ICI 118,551. Hydrogens shown on chiral centres for clarity.

Table 1 The binding affinities (pK_i) of racemic and enantiopure preparations of ICI-118,551 for β_1AR and β_2AR, and their β_2AR/β_1AR-selectivity ratios, as determined by [^{3}H]CGP-12177 competition binding

Preparation	*n*	pK_i		β_2AR-selectivity ratio
		β_1AR	β_2AR	
(±)-ICI-118,551	3	6.54 ± 0.09	9.22 ± 0.1	474
(2*S*,3*S*)-ICI-118,551	4	7.51 ± 0.13	9.27 ± 0.06	58
(2*R*,3*R*)-ICI-118,551	3	5.63 ± 0.16	8.00 ± 0.06	234

By simply changing the chiral ligand in the Sharpless epoxidation to L-(+)-diisopropyltartrate we repeated this synthesis to afford (2*R*,3*R*)-ICI 118,551. The two enantiomers of ICI 118,551, in addition to the racemate,[15] were then tested for their activity and selectivity for the β_1AR *vs.* β_2AR. This was carried out using a [^{3}H]CGP-12177 competition assay on HEK293 membranes expressing either β_1AR or β_2AR.

(±)-ICI-118,551 bound with high affinity to β_2AR and considerably lower affinity to β_1AR, giving it a β_2AR/β_1AR selectivity ratio of 474 (Table 1). These results are in good agreement with those previously published.[9,17] At both βARs (2*S*,3*S*)-ICI-118,551 was found to bind with higher affinity, and (2*R*,3*R*)-ICI-118,551 was found to bind with lower affinity, than the racemate. The differences in pK_i values between the two enantiomers were highly statistically significant at both the receptors. We can thus conclusively confirm that the (2*S*,3*S*) enantiomer has the greatest βAR binding affinity. Interestingly, for both enantiomers the β_2AR-selectivity was found to be lower compared to the racemate. This was due to the relative changes in binding affinity being nonequivalent at the two receptors. For example, the gain in affinity of the (2*S*,3*S*) enantiomer was greater at β_1AR than β_2AR. This unexpected observation may suggest a complementary binding mode for the two enantiomers, and we are currently investigating this possibility further.

In conclusion we have developed a highly efficient asymmetric synthesis of ICI 118,551, and confirmed conclusively that the (2*S*,3*S*) enantiomer is the most potent. While varying in activities the 2*S*,3*S* and 2*R*,3*R* enantiomers are both selective for the β_2-adrenoceptor over the β_1-adrenoceptor. We are currently investigating the apparent drop in selectivity shown by the individual enantiomers relative to the racemate.

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