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Synthesis of chiral β-methyl tryptamine-derived GnRH antagonists

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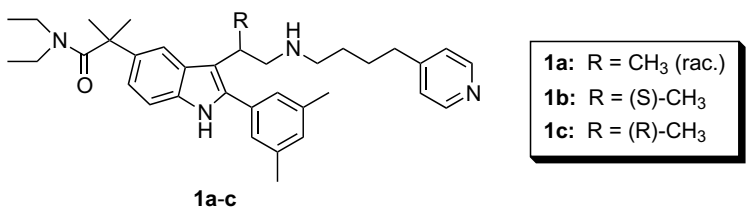
Abstract—The stereospecific formation of 2-aryl-β-methyl tryptamine derivatives **15** and **16** from chiral 4-chloro-1-(3,5-dimethylphenyl)-3-methylbutanones is described. These intermediates were further manipulated into the GnRH antagonists **1b** and **1c** in five steps. © 2001 Elsevier Science Ltd. All rights reserved.

During the course of our investigation into the development of potent non-peptide gonadotropin releasing hormone antagonists,[1a–c] we became interested in the synthesis of 2-aryl-β-methyl tryptamine derivatives. We found that the introduction of a methyl group β to the tryptamine nitrogen provided increased potency and selectivity over the non-substituted analogs, when evaluated in our screening protocol.[2] This discovery prompted us to develop a stereospecific synthesis of the tryptamine core, preferably with the 2-aryl group intact, to facilitate further SAR studies (Fig. 1).

The original synthesis[3] of 2-aryl tryptamine intermediates was designed to allow a facile modification of the aryl group. The tryptamine nitrogen was protected as a phthalimide, bromination at the 2-position of the indole was accomplished using pyridine hydrobromide perbromide, and the aryl group was introduced via a modified Suzuki coupling procedure. However, the focus of our efforts eventually shifted to modifications of other parts of the molecule. With this in mind, we turned toward a Fischer indole approach to construct the tryptamine with the aryl group in place and, in addition, a functional group at the 5-position to further elaborate the molecule.

Using this methodology, we were able to prepare the racemic compound **1a** (Scheme 1). Starting from commercially available 2-methylcyclopropane carboxylic acid **2**, treatment with oxalyl chloride followed by *N*,*O*-dimethylamine hydrochloride, yielded the Weinreb amide **3**. This was then converted to the ketone **4** via reaction with the lithium derivative of 5-bromo-*m*-xylene. With the ketone in hand, the next step was the formation of the indole core. Reaction with the previously prepared ethyl 2-(4-hydrazinophenyl)-2-methylpropanoate **5**[4] in the presence of concentrated HCl and *n*-butanol gave a 4:1 mixture of the β- and α-methyl isomers **6** and **7**. These were readily separated by silica-gel chromatography.[5] Reductive alkylation of tryptamine **6** with 4-pyridin-4-ylbutanal[6] resulted in the secondary amine **8** which was protected as the CBZ-carbamate before elaboration of the 'left-hand' side of the molecule. Saponification of the ethyl ester was achieved by refluxing overnight in a solution of water and 0.5N KOH in methanol. The PyBOP reagent was



1a-c

Figure 1.

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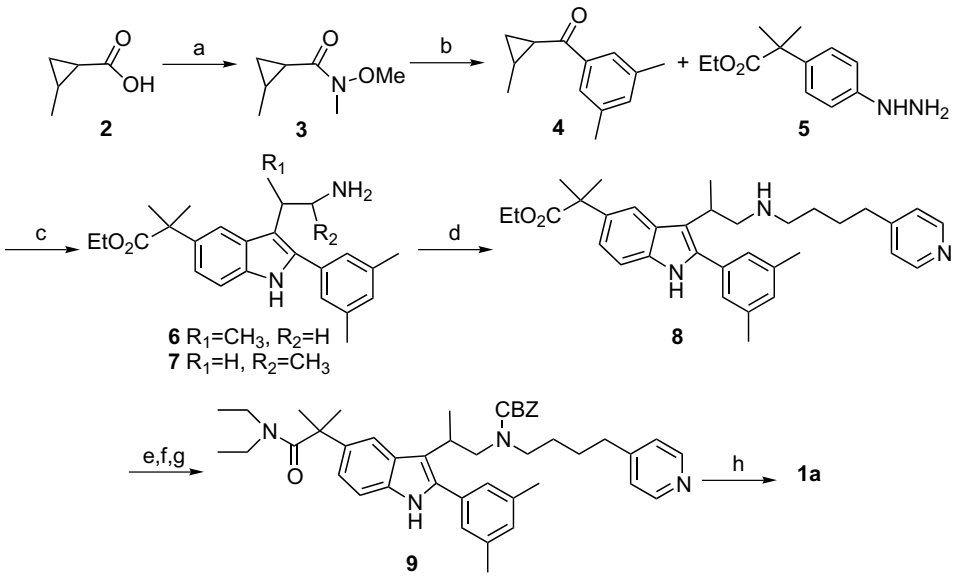


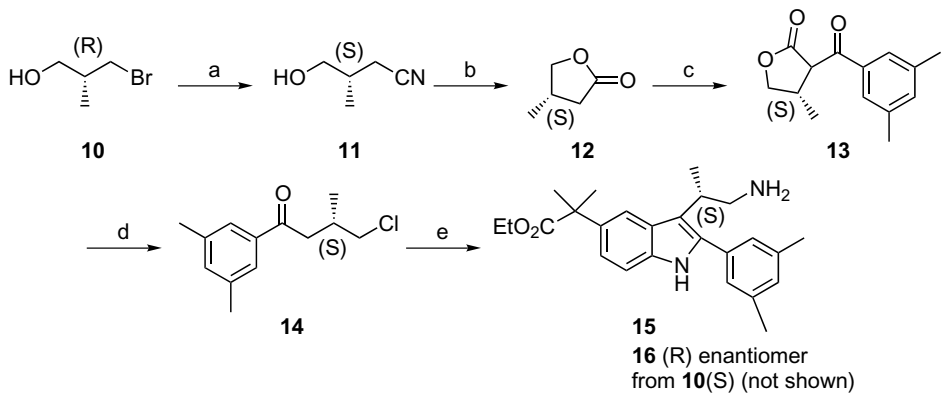
Scheme 1. *Reagents and conditions*: (a) (1) ClCOCOCl, DMF, benzene, 0°C, (2) *N,O*-dimethylamine hydrochloride, Et_3N, 0°C to rt, 62%; (b) 5-bromo-*m*-xylene, 1.6 M *n*-BuLi, THF, −78°C, 81%; (c) phenylhydrazine **5**, HCl, *n*-butanol, reflux, 16% **6**, 4% **7**; (d) 4-pyridin-4-ylbutanal, $MgSO_4$, $CHCl_3$, 0 to −10°C, 75%; (e) CBZCl, K_2CO_3, H_2O, THF, 0°C, 80%; (f) 0.5N KOH/CH_3OH, H_2O, reflux, 97%; (g) Et_2N, PyBOP, Et_3N, CH_2Cl_2, rt, 75%; (h) H_2, 10% Pd/C, CH_3OH, 97%.

used to couple the carboxylic acid with diethylamine. Finally, deprotection of carbamate **9** through hydrogenolysis of the CBZ protecting group led to the desired tryptamine **1a**.

At this time, we discovered that a variation of the Fischer indole synthesis could be used to obtain 2-aryl tryptamines directly in moderate yields. Using a model system involving the reaction of 4-chlorobutyrophenone with 4-nitrophenyl hydrazine, we were able to obtain 2-phenyl-5-nitro tryptamine in 40% yield. This result was contrary to the findings of Grandberg[7] and later Sannicolo[8] who both found that only tetrahydopyridazine products could be obtained from the reaction of phenyl hydrazines with 4-chlorobutyrophenones. Based on this result, we set out to prepare a 4-chlorobutyrophenone substituted with a chiral methyl group at the 3-position. This could then be subjected to the Fischer indole conditions in combination with phenylhydrazine **5** to give rise to our desired tryptamines with the methyl stereocenter fixed.

Starting from (*R*)-3-bromo-2-methyl-1-propanol **10**, one carbon homologation to the nitrile **11** was achieved via S_N2 displacement of the bromide with sodium cyanide in DMF (Scheme 2). A two-step 'one-pot' lactonization procedure[9] was then used whereby the nitrile was hydrolyzed with sodium hydroxide in aqueous ethanol, followed by cyclization of the acid through the action of PTSA in benzene.

The Claisen condensation of lactone **12** with methyl 3,5-dimethyl benzoate was at first problematic. The published procedure[10] called for a 3:2 excess of lactone to ester. This ratio resulted in sodium methoxide mediated degradation of the lactone leading to low yields of



Scheme 2. *Reagents and conditions*: (a) NaCN, DMF, 80°C, 88%; (b) (1) NaOH, EtOH, reflux, (2) PTSA, benzene, reflux, 61%; (c) NaOMe, methyl 3,5-dimethyl benzoate, dioxane, reflux; (d) conc. HCl, dioxane, reflux, 87% for two steps; (e) phenylhydrazine **5**, HCl, *t*-butanol, reflux, 16%.

the coupled product **13**. When we switched the ratio to 2:1 ester to lactone and used freshly prepared sodium methoxide in the same excess, we realized an 87% yield of chloroketone **14** after acid-catalyzed ring opening. An attempt was made to perform both transformations in a 'single pot' but this was complicated by our inability to separate the excess ester from the chloroketone product.

The chloroketone **14** was condensed with phenylhydrazine **5** under the Fischer indole conditions to give rise to the target 2-aryl-tryptamine **15**. Although the yields[11] for this step in the process are only modest, this method allowed us to prepare sufficient quantities of both enantiomers[12] in a timely fashion. From here, we followed the same procedure used for the racemic compound, as outlined above, to obtain optically pure **1b**. The entire process was repeated for the synthesis of the (*R*) enantiomer **1c**.

In summary, we have prepared racemic and optically active β-methyl substituted tryptamine derivatives making use of a novel synthesis of both enantiomers of 4-chloro-1-(3,5-dimethylphenyl)-3-methylbutan-1-one and a modified Fischer indole synthesis. These derivatives were transformed into the desired targets **1a–c** in five steps.

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11. Several different modifications of the reaction conditions were examined in an attempt to minimize the tetrahydropyridazine product. In all cases, yields of tryptamines varied from 10 to 40%, depending on the nature of the substituent at the 5-position.
12. Tryptamines **6**, **15**, and **16** were separately analyzed on a Chiralcel ODR column in 1:1 CH_3CN:1.0N $NaClO_4$ at 25°C. Under these conditions, the racemate **6** showed baseline resolution of both enantiomers, whereas analysis of both enantiomers **15** and **16** revealed none of the opposite enantiomer present.