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4-Phenylpyridine glucagon receptor antagonists: synthetic approaches to the sterically hindered chiral hydroxy group

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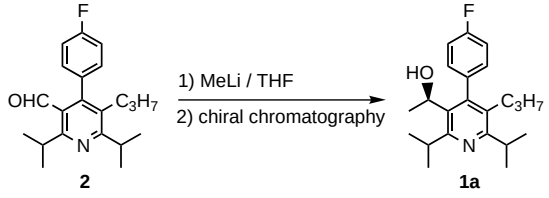
Abstract—Systematic evaluation of the structure–activity relationships of a new class of 4-aryl-pyridine glucagon antagonists led to the discovery of potent analogues bearing a key secondary hydroxy moiety as seen in compound **1a**. Due to the importance of this new class of compounds, it became necessary to establish an efficient synthesis of the pure enantiomer. A resolution and two chiral syntheses of alcohol **1a** were discovered and herein presented. © 2002 Elsevier Science Ltd. All rights reserved.

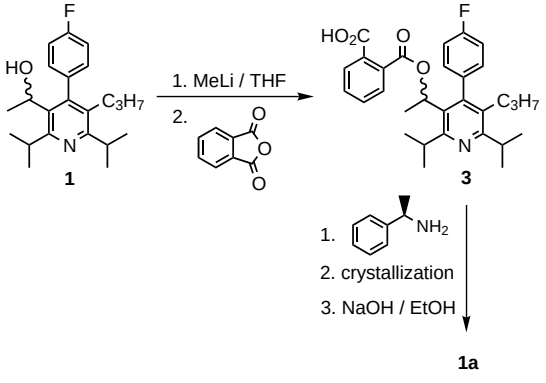
Recently, we reported our research efforts in the diabetes area which led us to the discovery of a new series of potent non-peptidic human glucagon receptor antagonists.[1] Compound **1a**, which was a potent antagonist ($IC_{50}=110$ nM, Scheme 1), was chosen as a representative analog for in vivo efficacy and toxicological studies. Amongst the modifications investigated throughout the SAR optimization of our class of antagonists, the secondary hydroxy moiety was found to be the key pharmacophoric element affording high affinity to the glucagon receptor.

Compound **1a** was originally synthesized by direct alkylation of its aldehyde precursor (**2**) with methyllithium (Scheme 1). This procedure delivered a racemic mixture of alcohols (**1**) and the more active enantiomer (**1a**) was obtained by chiral chromatography.[2] Although this synthesis of the racemate was straightforward, it was difficult to obtain large quantities of the pure desired enantiomer (**1a**). The need for bulk quantities of the pure enantiomer to support several biological studies prompted us to explore alternative synthetic routes. We discovered that the high level of steric hindrance caused by the neighboring groups of the secondary alcohol dictated its unique reactivity and the approach of reagents to the sp^2 center.

Our initial attempts focused on a resolution of the racemic alcohol **1** by conventional methods. The alcohol group revealed itself as a poor nucleophile, reacting only partially with bulky chiral auxiliaries such as Mosher's reagent.[3] Thus, we decided to convert the alcohol into a salt-forming derivative with an electrophile lacking steric bulk. Accordingly, alcohol **1** was treated with a base, such as methyllithium, followed by phthalic anhydride to produce the ester **3** (Scheme 2). Resolution of these derivatives can be accomplished by



Scheme 1. Achiral synthesis of compound **1**.



Scheme 2. Chiral resolution of compound **1**.

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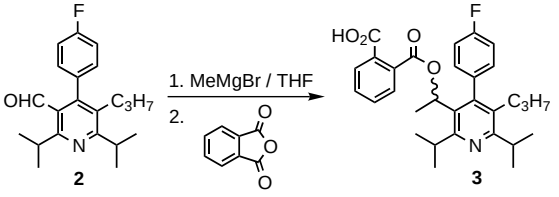
fractional crystallization in the presence of a chiral amine.[4] In our case, quick success was achieved by fractional crystallization of salts with *R*-(+)-α-methylbenzylamine.[5,6] Compound **1a** was then easily produced by a nearly quantitative cleavage of the ester group, giving an overall yield of about 30%.

The starting material remaining in the mother liquors (~70%), enriched with the undesired enantiomer, could be submitted to a recycling process. The starting material recovered was oxidized to the corresponding ketone (MnO_2/CH_2Cl_2), then reduced to the racemic alcohol **1** (LAH/THF) in a nearly quantitative yield. Alcohol **1** was submitted once more to the resolution procedure as described in Scheme 2.

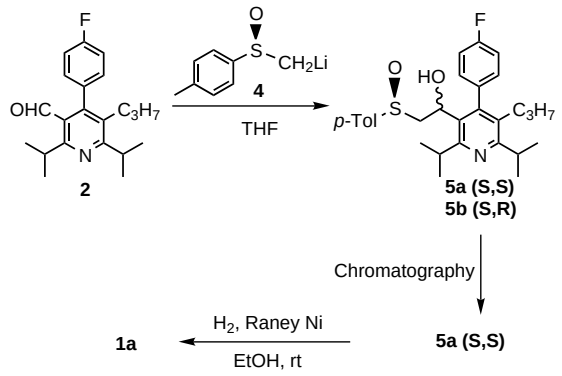
We later improved this process by synthesizing compound **3** in a one-pot procedure directly from the aldehyde **2** (Scheme 3), instead of a two-step sequence.

We also investigated enantioselective syntheses through chiral alkylation, since several research groups have been successful with this approach. We were particularly interested in the work of Braun and Hild,[7] who have shown that the zinc derivative of methyl-*p*-tolyl sulfoxide can be added to benzaldehyde with high diastereoselectivity. The resulting β-hydroxysulfoxide can undergo reductive cleavage by Raney Ni to give a secondary alcohol as in compound **1a**. However, no reaction occurred when we treated aldehyde **2** with the same reaction conditions, or with harsher conditions, such as refluxing tetrahydrofuran. On the other hand, aldehyde **2** reacted cleanly with lithiated (*S*)-methyl sulfoxide **4**, but gave only a 1.3:1 ratio of desired (**5a**) to undesired (**5b**) diastereomers (Scheme 4). The diastereomers were separated by standard chromatography and the desired isomer was treated with Raney nickel in ethanol to give **1a** (96% yield, 99% e.e). This reduction proceeded without racemization, in contrast to a published report.[7]

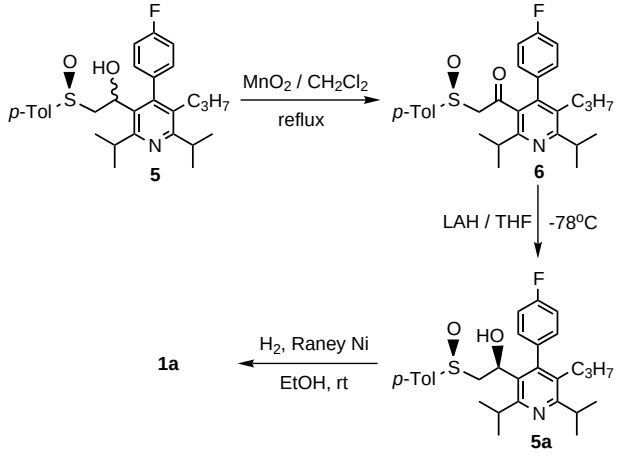
In an alternative process, **1a** was obtained through a stereoselective reduction of a β-ketosulfoxide (Scheme 5). Oxidation of the alcohol **5** with manganese dioxide provided the corresponding ketone **6** in 87% yield. Reduction of **6** with lithium aluminum hydride[8–11] at −78°C gave the desired diastereomer in >98% diastereomeric excess as determined by ^{1}H NMR. The rate of this reaction was extremely slow, unless a large excess of lithium aluminum hydride was used (14 equiv.). Allowing the reaction mixture to warm to 0°C did not hasten the reaction but instead led to decomposition. The resulting large amounts of aluminum salts generated by this excess might account for the relatively modest yield (72%).



Scheme 3. Alternative synthesis of compound **3**.



Scheme 4. Chiral synthesis compound **1**.



Scheme 5. Inversion of the chirality of the secondary alcohol.

The high diastereoselectivity achieved during the reduction of the ketone **6** offered the option to eliminate the chromatographic separation of the two diastereomers (**5a** and **5b**) obtained in Scheme 4. Both diastereomers were oxidized together by manganese dioxide to give ketone **6** (87%), then submitted to the same desulfurization process as previously described.

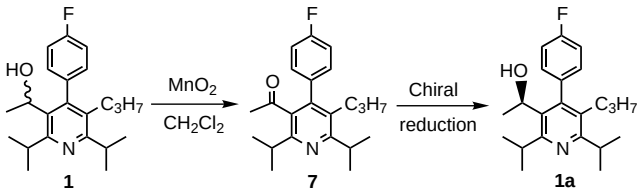
This sequence was convenient for producing a few grams of **1a**. However, several problems were encountered when a larger scale synthesis was attempted. In particular, both methylsulfoxide intermediates (**5** and **6**) were poorly soluble and required very large amounts of solvent, making the process impractical for scale-up. Furthermore, the (*S*)-methyl *p*-tolyl sulfoxide precursor was available only in small quantities and at a high cost. Therefore, we continued to explore other synthetic approaches. We were also intrigued by the unique features of the molecule and were anxious to learn more about its reactivity towards other enantioselective reagents.

We then decided to investigate enzymatic resolutions as they offer several potential advantages: low cost (catalytic), simplicity and high selectivity.[12] Enantioselective

esterification of the racemic alcohol of **1** appeared to be the most interesting procedure because the reactions are usually performed in organic solvents. Unfortunately, alcohol **1** did not esterify when treated with a wide variety of enzymes; PPL,[13] *Bacillus subtilis*,[14] *Candida cylindracea*,[15] *Pseudomonas fluorescens*,[16] lipoprotein lipase,[17] lipase PS-30[18] and chymotrypsin.[19] The lack of reactivity of the compound is probably related to the steric effects caused by the bulky groups adjacent to the alcohol. Similarly, the reverse reaction, the enantioselective saponification of the corresponding acetate of **1**, was unsuccessful. However, this type of reaction must be performed in a buffer solution, which gives inadequate solvation for the highly lipophilic phenylpyridine acetate.

We then focused our efforts on exploring enantioselective reduction of ketone **7** (Scheme 6). This field has been extensively studied and, in general, has been very successful with rigid chiral hydride reagents, such as the efficient CBS reduction.[20] However, when we tried these conditions on the ketone **7**, no reaction occurred. In fact, sodium borohydride itself was reacting only very slowly with ketone **7** (<50% conversion after 3 days). Likewise, DIP Chloride[21] and Binal[22] did not react with ketone **7**. In any case, we always faced the same problem, the chiral reagents used were too sterically hindered to react efficiently with the bulky ketone. Limited success was finally obtained with a procedure developed by Terashima (LAH, ethylaniline and *N*-methyl ephedrine).[23,24] Although the conversion was poor (<10%), we could demonstrate that some enantioselectivity was achieved during the course of the reaction (~2:1 mixture of enantiomers) and we decided to investigate this reaction further.

As we tried to explain the very low yield of the reaction, a key discrepancy was noted: the alcohol produced was not the result of a reduction of the ketone (**7**) by Terashima's reagent but rather by its less hindered precursor, the complex LAH/*N*-methylephedrine. Indeed, during the preparation of the chiral reducing agent, a small portion of the reagent did not react with ethylaniline (<10%) which readily reduces the ketone where Terashima's reagent does not, even at higher temperature. In order to take advantage of this observation, the reduction was subsequently performed with the complex LAH/*N*-methylephedrine, which yielded approximately 90% of the corresponding alcohol with the same enantiomeric ratio as previously observed. To our knowledge, no one else has reported an enantioselective reduction with this complex and the mechanistic approach of the reagent toward the substrate remains unclear.



Scheme 6. Enantioselective synthesis of alcohol **1a**.

Compound **1a** was predominantly obtained when (+)-*N*-methylephedrine was used while its enantiomer is obtained with (–)-*N*-methylephedrine. The next objective was to improve the enantiomeric excess (e.e.) of the reduction. Enantioselective reactions are often temperature and solvent dependent. Accordingly, we attempted this reaction at 0°C and a ratio of 7:3 was then obtained with a comparable yield (~90%). This interesting result clearly demonstrated the direct effect of the temperature on the enantioselectivity of the reduction. It was then obvious to try even lower temperatures. At –78°C, the desired product was produced with a ratio of 97:3 (94% e.e.) with an excellent yield (90–95%). This highly enriched alcohol can then be recrystallized from a mixture of ethanol and water to give **1a** (>99% e.e.). This new procedure became the most efficient and simple sequence thus far and has been successfully applied on several other analogs bearing the same sterically hindered secondary alcohol.

This new chiral reducing agent could potentially have other applications on similar sterically hindered ketones. A detailed procedure is included as additional information.[25]

Acknowledgements

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2. Chiralpak AD column; isocratic elution 1.5 ml/min. (99% hexane/methyl *t*-butyl ether), retention times (**4a**, 7.3 min; **4b**, 9.9 min).
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6. Methanol (5.25 mL) was added to compound **3** (23.1 g, 47 mmol) in hot hexane (350 mL), then the suspension was heated to reflux. The suspension dissolved after addition of (*R*)-(+)-α-methylbenzylamine (6.06 mL, 47 mmol) and the salt precipitated after a few minutes. After 45 min stirring, the precipitate was filtered and washed with cold hexane (2×10 mL) to afford 11.36 g (40%, 91% ee) of the salt. The salt was dissolved in hot methanol (150 mL) then hot hexane (300 mL) was added. The methanol was removed with a cooled Dean–Stark trap. The heat bath was removed as soon as the solution became turbid. After 1 h of stirring at room temperature the precipitate was filtered and washed with cold hexane (2×10 mL) to afford 7.95 g (70%, 98.5% ee) of the salt. The salt was cleaved with a mixture of 20% aqueous sodium hydroxide solution (50 mL) and ethanol (50 mL)

at reflux for 30 min. The reaction mixture was extracted with diethylether (3×100 mL). The combined organic phases were washed with brine and dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by filtration through silica gel (∅ 1.5″×5″, 200 mL 30% CH_2Cl_2/hexane, 300 mL CH_2Cl_2) to afford 4.23 g (95%, 98.5% ee) as a white solid: mp 105–6.5°C; R_f=0.39 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (m, 3H), 7.04 (m, 1H), 4.64 (dq, J=3.7, 6.6 Hz, 1H), 3.73 (sept, J=6.6 Hz, 1H), 3.18 (sept, J=6.6 Hz, 1H), 2.15 (m, 2H), 1.56 (d, J=3.7 Hz, 1H), 1.39 (d, J=6.6 Hz, 3H), 1.28 (m, 14H), 0.73 (t, J=7.35 Hz, 3H); MS-FAB m/e Calcd for ($C_{22}H_{31}FNO$, M+H) 344, found 344; Anal. Calcd for $C_{22}H_{30}FNO$: C, 76.93; H, 8.80; N, 4.08; F, 5.53; Found: C, 77.20; H, 8.97; N, 4.01; F, 5.60; $[\alpha]_D$ +38.5 (c 1.35×10^{-2} M; CH_2Cl_2).

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25. To a solution of (1*S*,2*R*)-(+)-*N*-methylephedrine (31.1 g, 0.174 mol) in ether (208 mL) was added lithium aluminum hydride (1 M/Et_2O, 1.5 equiv., 174 mL) dropwise at 0°C under argon (gas evolution, the first 50 mL of lithium aluminum hydride reacted strongly). The reaction was refluxed for 1.5 h turning from a clear solution to a white milky solution. The reaction was cooled to −78°C for a dropwise addition of **7** (39.53 g, 0.116 mol) in diethyl ether (300 mL) cooled to 0°C, (∼2 mL/min; the reaction temperature was monitored, not allowing the temperature to rise above −60°C). After the addition was completed, the addition funnel was washed with another 50 mL of dry ether. The reaction was kept at −78°C for 4.0 h and then allowed to stir and warm to room temperature overnight. The reaction was quenched at 0°C with isopropanol (70 mL) and diluted with ether (700 mL), washed with water (4×500 mL), 10% HCl (2×500 mL), brine (2×500 mL), and dried with $MgSO_4$. Filtration and concentration afforded a white solid. The product was filtered through a pad of silica (600 g, 10% ether/hexane) to afford the desired alcohol (36.67 g, 92%). HPLC (chiralcel OD-H #066-013-50418 (4.6×150 mm)) showed 97% ee favoring the first alcohol enantiomer. R_f=0.4 (CH_2Cl_2); The alcohol (32.1 g, 93.5 mmol) was dissolved in ethanol (820 mL) and water (480 mL) was slowly added at 60°C. The solution was heated to 75°C for 5 min and the heating and the stirrer bar were removed. The solution was seeded with pure **1a** every 5 min while it was allowed to cool to room temperature. When the seeds did not dissolve any longer (after 1.5 h), more seeds were added. The crystals are filtered after 16 h, dried in the vacuum oven and dissolved in dichloromethane (50 mL). The solvent is removed in vacuo and the residue dried to afford 20.4 g (63%, 99.4% ee) as a white solid. mp=106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 3H), 7.04 (m, 1H), 4.64 (dq, J=3.7, 6.6 Hz, 1H), 3.73 (sept, J=6.6 Hz, 1H), 3.18 (sept, J=6.6 Hz, 1H), 2.15 (m, 2H), 1.56 (d, J=3.7 Hz, 1H), 1.39 (d, J=6.6 Hz, 3H), 1.28 (m, 14H), 0.73 (t, J=7.35 Hz, 3H). FAB-MS Calcd for ($C_{22}H_{30}FNO$) 343, found 344 (M+H). Anal. Calcd for $C_{22}H_{30}FNO$: C, 76.93; H, 8.80; N, 4.08; F, 5.53. Found: C, 77.02; H, 8.75; N, 4.02; F, 5.62. $[\alpha]_D$ +40.7 (c 1.22×10^{-2} M; CH_2Cl_2).