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Synthesis of the Individual Enantiomers of the Benzoquinolinone Human Type 1 Steroid 5-α-Reductase Inhibitors LY191704 and LY266111

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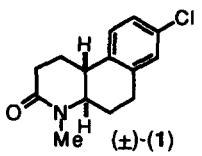
Key Words: asymmetric aza-annulation; enamine; steroid 5-α-reductase; enzyme inhibitor; α-phenethylamine.

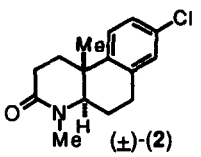
Abstract. The first syntheses of the individual enantiomers of the benzoquinolinone class of selective inhibitors of human Type 1 steroid 5-α-reductase are described. For benzoquinolinones lacking an angular substituent, the approach relies upon an enamine acryloyl chloride cyclization followed by non-stereoselective reduction and diastereomer separation. Absolute configuration was established by single crystal x-ray diffraction analysis. The angularly methylated benzoquinolinones are prepared in an enantiospecific (deracemizing) fashion from 1-methyl-6-chloro-2-tetralone in 5 steps, employing a " formal 3 + 3 aza-annulation " sequence, with (R) or (S) α-phenethylamine as the source of chirality.

Dihydrotestosterone is produced from testosterone in an NADPH-dependent reduction catalyzed by steroid 5-α-reductase (EC 1.3.99.5) and differs substantially from testosterone in its physiological role as an androgen in humans and other mammalian species.[1] While testosterone possesses anabolic activities leading to increases in bone and muscle mass, and effects on sexual differentiation leading to the development of the vas deferens, epididymis and seminal vessicles, dihydrotestosterone mediates the androgenic effects on formation of external genitalia and the prostate.[2] Two isozymes of human steroid 5-α-reductase, differing in structure, biochemical properties, patterns of expression, and pharmacology, have recently been identified .[3-5] Although the role of each 5-α-reductase isozyme has yet to be delineated, preliminary findings suggest that both forms are produced in human prostate,[6] while the Type 1 predominates in scalp tissue[7] and in the liver.[8] This differential distribution offers opportunity for potential selective modulation of the androgenic effects of dihydrotestosterone resulting from local synthesis in androgen target cells.[2]

The human genital skin fibroblast cell line Hs68 has been shown to express the Type 1 steroid 5-α-reductase isozyme, and has been used to identify and evaluate a series of novel, selective, non-steroidal inhibitors of this enzyme.[6,8] Herein we discribe syntheses of the single enantiomers of LY191704 (**1**) and LY266111 (**2**), members of the benzoquinolinone series of selective human Type 1 steroid 5-α-reductase inhibitors.

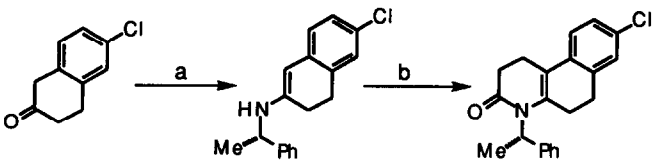


(±)-(1)



(±)-(2)

The synthetic strategy for the angularly unsubstituted series is based upon the enamine acryloyl chloride cyclization protocol previously described by Hickmott[9] and more recently refined by Stille.[10] We sought to extend this methodology, utilizing an enantiomerically pure primary amine such as (*R*)- or (*S*)-α-phenethylamine for the direct incorporation of a chiral auxiliary into the cyclization product, allowing for either stereocontrolled reduction or eventual separation of diastereomeric products.[11] In the event, condensation of (*S*)-α-phenethylamine and 6-chloro-2-tetralone (**3**) gave a quantitative yield of the enantiomerically pure enamine (**4**). Acylation with acryloyl chloride under Schotten-Baumann conditions directly afforded the optically pure tetrahydobenzo[f]quinolin-3-(2*H*)-one (**5**) in a single operation in excellent yield.[12]



(**3**) (**4**) (**5**)

Reagents: a)(s)(-)-α-phenethylamine, toluene,110°C,100 %,b) acryloyl chloride, 1:1 $CHCl_3$/Sat. $NaHCO_{3(aq)}$, R.T,79 %.

Attempted ionic hydrogenation of (-)-(**5**) with trifluoroacetic acid/triethylsilane[13] unfortunately resulted in concomitant auxiliary cleavage and olefin reduction to afford racemic (**8**), albeit in high yield. We therefore screened reduction conditions to circumvent cleavage of the auxiliary and

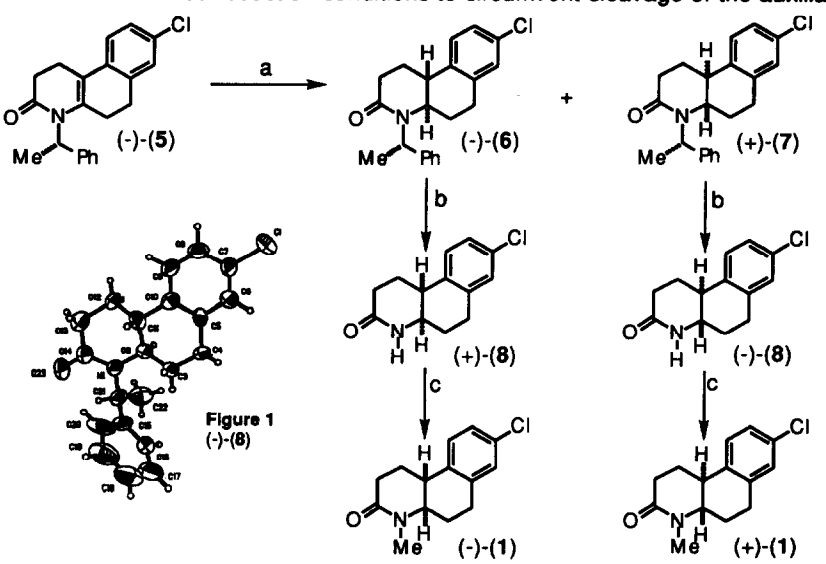


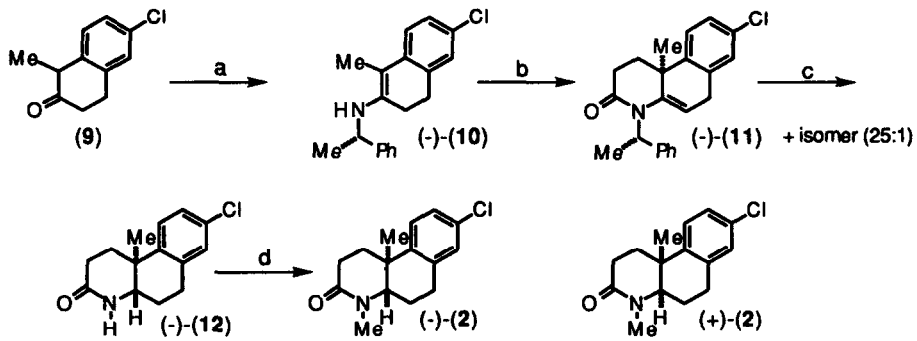
Figure 1
(-)-(8)

Reagents: a) 30equiv. $NaBH_3CN$, HCOOH, R.T.,33%,b) TFA, reflux,84%,c) NaH, DME, MeI, reflux,86%

found that treatment of (-)-(**5**) with excess sodium cyanoborohydride in neat formic acid[14] gave a 5:1 mixture of *trans/cis* diastereoisomers with a trace amount of (±)-(**8**) being formed (HPLC analysis).[15] Much to our satisfaction, MPLC of the mixture on silica afforded the two *trans* diastereoisomers (-)-(**6**) and (+)-(**7**) in essentially pure form (>99.5% de) (in 20 % and 13 % yield

respectively). The absolute stereochemistry of (-)-(**6**) was elucidated by a single crystal x-ray determination and the structure is depicted in **Figure 1**. Completion of the synthesis required removal of the chiral auxiliary and N-methylation. To this end, treatment of (-)-(**6**) with hot TFA[16] gave (+)-(**8**) as a highly crystalline solid. Subsequent N-methylation afforded (-)-(**1**), whose spectroscopic properties were identical in all respects save optical rotation with racemic LY191704 (**1**). In like fashion, the chiral auxiliary was removed from (+)-(**7**) to give (-)-(**8**) whose methylation provided the antipodal (+)-(**1**).[12,17]

The synthesis of the angularly methylated benzoquinolinones was more efficient, relying upon the stereospecific aza-annulation methodology currently under development in our laboratories to install the requisite C-10 stereochemistry directly in the cyclization reaction with acryloyl chloride.[18] While the precise mechanistic details (for example, the timing of N-acylation versus C-C bond formation) of this process have yet to be fully delineated, the cyclization has a predictable stereochemical outcome which parallels that observed by D'Angelo and coworkers in the asymmetric Michael addition of related enamines/imines.[19]



Reagents: a) (*s*)-(-)-α-phenethylamine, toluene, 110°C, b) acryloyl chloride, THF, -20°C, 70% from (**9**), c)TFA, triethylsilane, 100 °C, 48% from (**11**), d) KH, dimethoxyethane,MeI, 72%.

In the event, racemic 1-methyl-6-chloro-2-tetralone,[20] (**9**), was condensed with (*S*)-(-)-α-phenethylamine in toluene with azeotropic removal of water, affording the air sensitive enamine, (**10**), (in equilibrium with the corresponding imine tautomer) which was treated directly with acryloyl chloride in THF solution at low temperature. Workup with aqueous sodium bicarbonate solution afforded (-)-(**11**) and its C-10 epimer as a 25:1 mixture (capillary GC analysis). Although these adducts were not crystalline, the diastereomers were readily separable by flash chromatography on silica gel,[21] allowing for isolation of homogenous (-)-(**11**) in 70 % yield from tetralone (**9**).[12]

Removal of the chiral auxiliary with concomitant enamide reduction was accomplished by refluxing in neat trifluoroacetic acid/triethyl silane[13,16] affording the *trans* isomer (-)-(**12**), along with its corresponding cis isomer (6:1 by capillary GC analysis). Homogenous (-)-(**12**) was attained by direct crystallization from this "one pot " deprotection/reduction sequence in 48 % overall yield.[12] The enantiomeric purity was evaluated at this stage by proton NMR (300 MHz), employing (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral shift reagent.[17] By this technique, the optical purity was determined to be greater than 95%. Finally, N-methylation was accomplished by treatment

with KH and methyl iodide in dimethoxyethane, affording (-)-(**2**) in 72 % yield.[12] The enantiomer (+)-(**2**) was prepared in entirely analogous fashion, employing (*R*)-(+)-α-phenethylamine for the preparation of the enamine, (+)-(**10**) (not shown).[12]

Thus, benzoquinolinone inbititors of human Type 1 steroid 5-α-reductase can be prepared in high enantiomeric purity, employing aza-annulation protocols. For angularly unsubstituted benzoquinolinones such as (**1**), the stereochemistry is established by a non-stereoselective reduction followed by diastereomer separation. For the angularly substituted benzoquinolinones such as (**2**), the stereochemistry is directly established in the cyclization with a high degree of specificity. These syntheses have allowed for the determination of the absolute configurations (by single crystal x-ray analysis) of the individual enantiomers. The pharmacological characterization of these individual enantiomers will be disclosed in due course.

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