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A NON-STEROIDAL DIENE ACID INHIBITOR OF HUMAN TYPE 2 STEROID 5α-REDUCTASE

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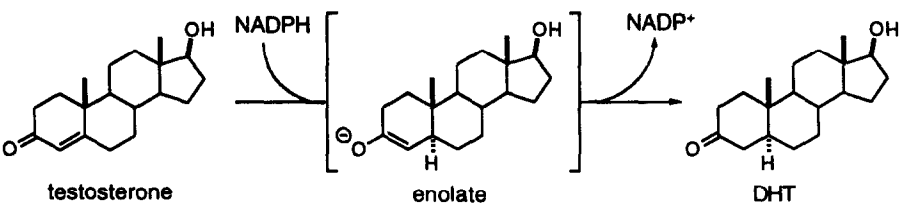
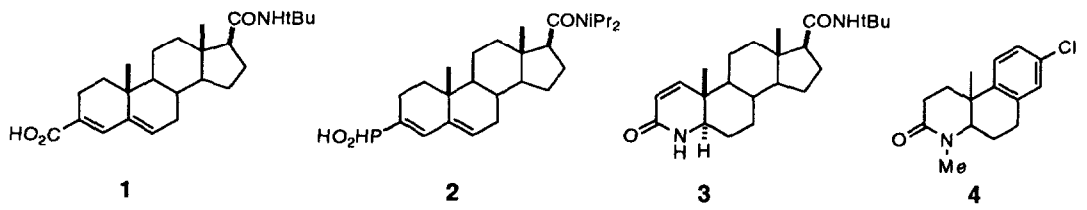
Abstract: A series of 4a-methyl-3,4,4a,9-tetrahydrophenanthrene-2-carboxylic acids and 2-phosphinic acids has been prepared and evaluated *in vitro* as inhibitors of human recombinant steroid 5α-reductase. 7-Chloro-4a-methyl-3,4,4a,9-tetrahydrophenanthrene-2-carboxylic acid, **5**, is a marginally selective inhibitor of human type 2 steroid 5α-reductase ($K_{i,app}$ = 260 nM). The phosphinic acid compounds, **8** and **9**, are weak inhibitors of types 1 and 2 steroid 5α-reductase.

Steroid 5α-reductase is an NADPH-dependent enzyme which catalyzes the stereospecifc reduction of testosterone to dihydrotestosterone (DHT) (Scheme 1). Inhibition of steroid 5α-reductase has attracted considerable interest as a potential therapeutic treatment for the pharmacological disorders associated with elevated levels of DHT. These disorders include benign prostatic hyperplasia[1], some prostatic cancers[2], skin disorders such as acne,[3] male pattern baldness,[4] and hirsutism.[5] Two isozymes of steroid 5α-reductase, differing in the pattern of tissue distribution and with distinct biochemical and pharmacological properties, have been identified,[6] although the precise roles of each of these isozymes in DHT-dependent diseases are yet to be fully elucidated.

Stable mimics of the putative enolate intermediate in the formation of DHT (Scheme 1) have been reported as mechanism-based reversible inhibitors of steroid 5α-reductase.[7] These mimics include anionic carboxylic acids[8] (e.g. epristeride, **1**, $K_{i,app}$ type-1 = 410 nM, type-2 = 0.2 nM), phosphorous acids[9] (e.g. **2**, $K_{i,app}$ type-1 = 4900 nM, type-2 = 0.8 nM) and sulfonic acids,[10] neutral nitrosteroids[11], A-ring pyridine oxides,[12] and azasteroids[13] (e.g. finasteride[13a], **3**, $K_{i,app}$ type-1 = 100 nM, type-2 = 2 nM). Recently a series of non-steroidal benzoquinolinones, typified by compound **4**, were reported as specific inhibitors of human type 1 steroid 5α-reductase ($K_{i,app}$ type-1 = 20 nM, type-2 = >5000 nM).[14] Herein we report diene acids of the type **5** as non-steroidal inhibitors of human type 2 steroid 5α-reductase. The corresponding phosphinic acid derivatives, **8** and **9**, show only weak activity against both types 1 and 2 human steroid 5α-reductase (Table 1).

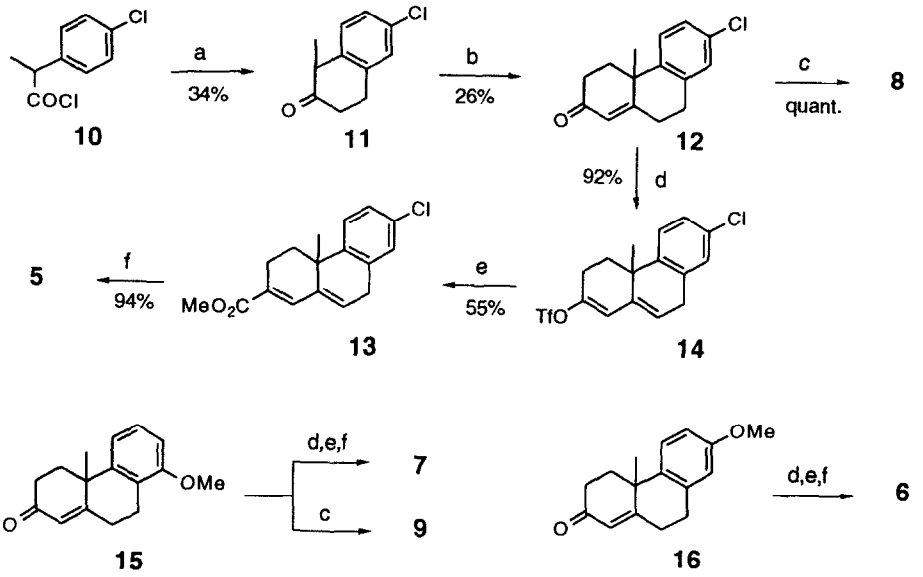
Scheme 1





Chemistry. The α,β-unsaturated carboxylic acid and phosphinic acid derivatives **5-9** were prepared as racemates as shown in Scheme 2.[19] Reaction of the acid chloride **10** with $AlCl_3$ and ethylene gave 6-chloro-1-methyl-2-tetralone **11** in modest yield. The tetralone **11** has also been prepared by alkylating the sodium hydride-derived anion of 6-chloro-2-tetralone with iodomethane.[14a,15] Compound **11** gave the key enone intermediate **12** using a Mannich base and methyl iodide annulation sequence.[16] Treatment of **12** with 95% H_3PO_2 by the literature method[9,17] gave the phosphinic acid **8**. Alternatively, **12** was treated with triflic anhydride and base to give the triflate **14**. Palladium-catalyzed carbonylation and subsequent hydrolysis gave the diene acid **5**. Compounds **6**, **7** and **9** were similarly prepared from the enones **15**[18] and **16**[15] (Scheme 2).

Scheme 2

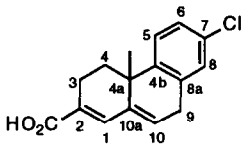
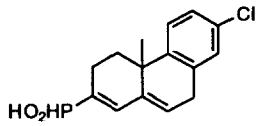
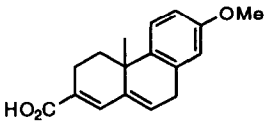
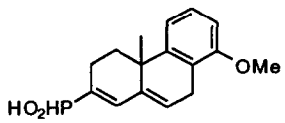
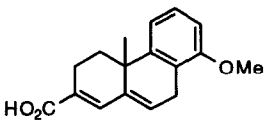


(a) $AlCl_3$, CH_2CH_2; (b) I^- $Et_2MeN^+(CH_2)_2COMe$, KOMe, MeOH, toluene; (c) 95% H_3PO_2, THF; (d) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine; (e) $(Ph_3P)_2Pd(OAc)_2$, CO, Et_3N, MeOH, DMF; (f) K_2CO_3, H_2O, MeOH.

Enzyme Inhibition. The apparent inhibition constants ($K_{i,app}$) were determined for compounds **5-9** using recombinant type 1 and type 2 human steroid 5α-reductases as previously described.[20] The diene acid **5** shows preferential (*ca.* 5-fold) inhibition of the type 2 over the type 1 isozyme of steroid 5α-reductase (Table 1). However, in comparison to its steroidal progenitor **1**, tricyclic **5** is a much weaker inhibitor of the type 2 isozyme (by three orders of magnitude). The previously reported benzoquinolinone inhibitors, by contrast, are 10-fold more potent inhibitors than **5** and are extremely selective for the type 1 enzyme activity.[14] Like the benzoquinolinones, 7-chloro substitution appears to give optimum inhibitory activity. 7-Methoxy and 8-methoxy substitutions (diene acids **6** and **7**, respectively) result in both a decrease in isozyme 2 selectivity and potency (Table 1). The phosphinic acid compounds **8** and **9** exhibit only weak inhibition of types 1 and 2 steroid 5α-reductases irrespective of the nature of the aromatic ring substitution.

In conclusion, the reported A-ring structure/steroid 5α-reductase inhibitory activity relationships between the 4-azasteroid and benzoquinolinone series do not directly translate to the 3-carboxysteroid inhibitors and their tricyclic analogs. While one of the acids described exhibits modest activity, the structural elements governing potency and isozyme selectivity are yet to be fully understood. Ongoing work in the area of non-steroidal inhibitors should help to illuminate these factors.

Table 1. Inhibition of recombinant types 1 and 2 human steroid 5α-reductase.

Compound	$K_{i,app}$ (nM) type-1	type-2	Compound	$K_{i,app}$ (nM) type-1	type-2
 **5**	1200	260	 **8**	1900	1600
 **6**	NI[a]	>2500[b]	 **9**	1900	1600
 **7**	1900	1600			

[a] no inhibition observed at 2.5 μM
[b] 30% inhibition at 2.5 μM

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