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SYNTHESIS OF B-NOR-4-AZA-5α-ANDROSTANE COMPOUND AS 5α-REDUCTASE INHIBITOR

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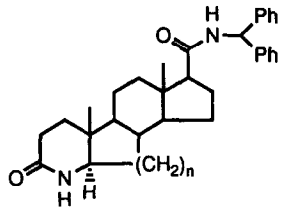
Abstract : B-Nor-4-aza-5α-androstane derivative **1** was synthesized. The compound **1** showed potent inhibition activity against testosterone 5α-reductase.

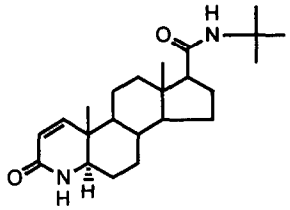
Testosterone 5α-reductase plays an important role in the pathology of benign prostatic hypertrophy. It converts testosterone in the prostate to 5α-dihydrotestosterone, whose accumulation is known to cause hypertrophy of the prostate.[1)]

A series of 4-azasteroid compounds have already been synthesized, and they were found to have 5α-reductase inhibition activity.[2)] Among them, N-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, MK-906, was recently launched as a drug for benign prostatic hypertrophy. These compounds have a nitrogen at the C-4 position and a backbone structure similar to that of testosterone. In relation to the structure-activity relationship we were interested in modifying the backbone structure, in particular the B-ring. Namely, we focussed attention on synthesizing a B-nor-4-aza-5α-androstane derivative. The conformation of B-nor-4-aza-5α-androstane, having a five-membered B ring, is not much different from that of 4-aza-5α-androstane based on molecular model inspection. In addition, we have already disclosed that the 4-azaandrostane derivative **2**, having a 17-benzhydrylcarbamoyl moiety, has highly potent inhibition activity against testosterone 5α-reductase.[3)] Therefore, the B-nor-4-aza-5α-androstane derivative **1** with a benzhydrylcarbamoyl moiety at the C-17 position was selected as a target compound. In this report we describe a synthesis of **1** and its 5α-reductase inhibition activity.

Figure 1



1 : n = 1
2 : n = 2



MK 906

The compound **1** was synthesized from **3** by the route described below. First we selected secodicarboxylic acid **12**, having a B-nor structure, as a key intermediate. The B-nor structure was constructed according to a method similar to that described by Morisawa et al..[4] Ester **3**[2a] derived from Pregnenolone was acetylated to provide **4**, which was oxidized with ozone to give **5** (81% from **3**). Aldehyde **5** was cyclized to **6** with basic alumina, which was oxidized to yield carboxylic acid **7** (75% from **5**). Heating **7** with acetic anhydride and triacetin under reflux afforded **8** (66%), via a formation of β-lactone, followed by elimination of carbon dioxide. Deacetylation of **8** afforded ester **9**. Oxidation of **9** by the Oppenauer method, followed by hydrolysis gave enone **11** (80% from **8**). In order to introduce the 4-aza function, dicarboxylic acid **12** was synthesized. Oxidative cleavage of **11** with $NaIO_4$ and $KMnO_4$ in aqueous *tert*-butyl alcohol afforded **12** (28 %).

Next, the cyclization of dicarboxylic acid **12** to **13** was attempted. Upon heating **12** with ammonia, as is described for the synthesis of MK 906, the desired enamido compound **13** was not obtained. Therefore, we investigated preparing the saturated compound **14a** directly from **12**. Following the Leuckart method, heating **12** with formamide and formic acid, a cyclization occurred, to give B-nor-4-azaandrostane compound **14b** (39%). But the compound **14b** had undesired 5β-H configuration. This was determined by the presence of Nuclear Overhauser Effect (NOE) between the hydrogen at the C-5 position and the methyl group at the C-19 position.

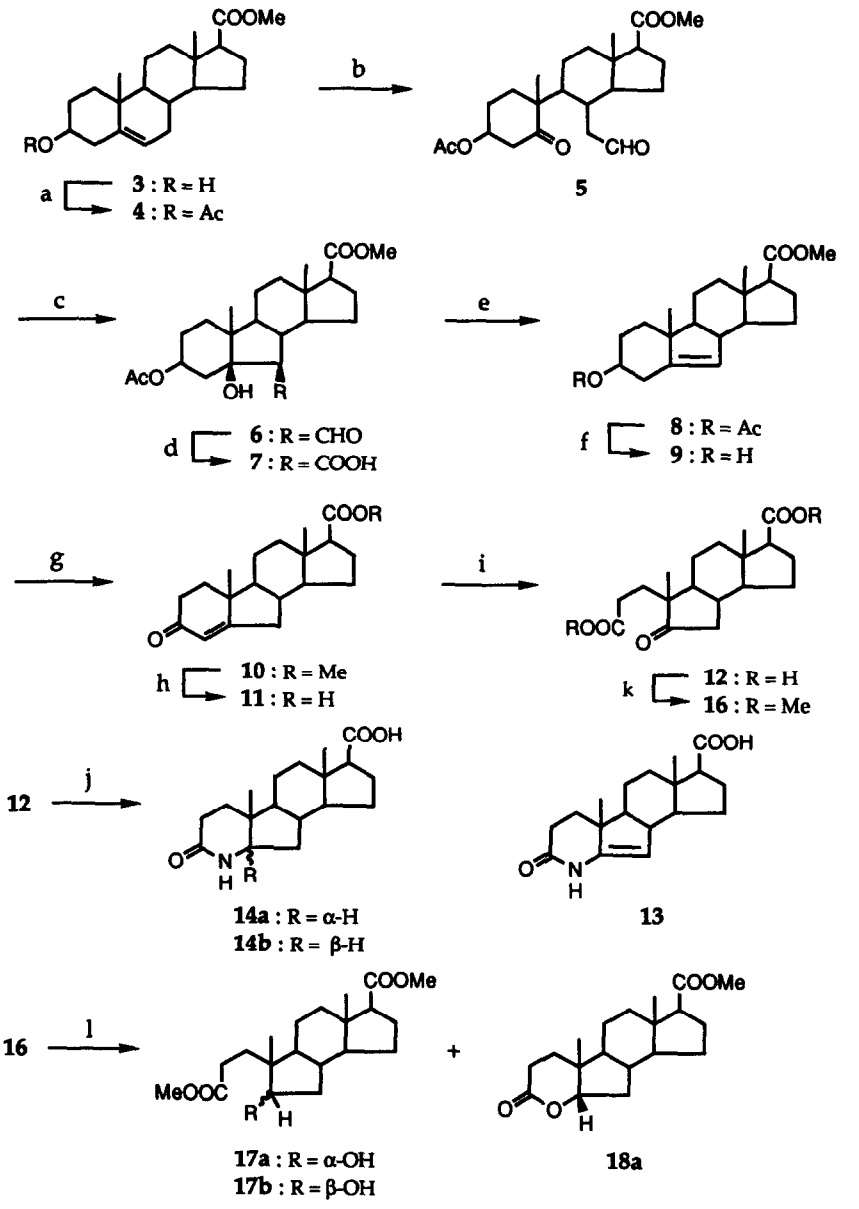
Then, after introducing a nitrogen function onto the B-ring of compound **16**, formation of the A-ring was accomplished. Dicarboxylic acid **12** was esterified to provide **16**. Diester **16** was reduced by $NaBH_4$ in aqueous EtOH, to yield the desired α-alcohol **17a** containing lactone **18a** together with β-alcohol **17b** (major product).[5] A mixture of compounds **17a** and **18a** was converted, on treatment with p-TsOH, to a single product **18a**[6] (4% from **16**). In order to prepare the 5β-azide **26**, lactone **18a** was reduced with $LiAlH_4$ to triol **19a**. Selective silylation of the primary hydroxy group in **19a** gave **20a**[7] (53% from **18a**). The α-alcohol **20a** was mesylated to afford **22**. Treatment of **22** with NaN_3 afforded an azide **23** (19%) with the desired β-configuration at the C-5 position. Desilylation and oxidation of **23** gave dicarboxylic acid **25** (82%). Esterification of **25** gave diester **26** and reduction of **26** afforded directly a B-nor-4-aza-5α-androstane compound **27** (59% from **25**).

Finally, the 17-carbamoyl function was introduced. Treatment of **27** with BCl_3 yielded carboxylic acid **28**.[8] Amidation of **28** with DEPC and benzhydrylamine gave B-nor-4-aza-5α-androstane derivative **1** (30% from **27**).

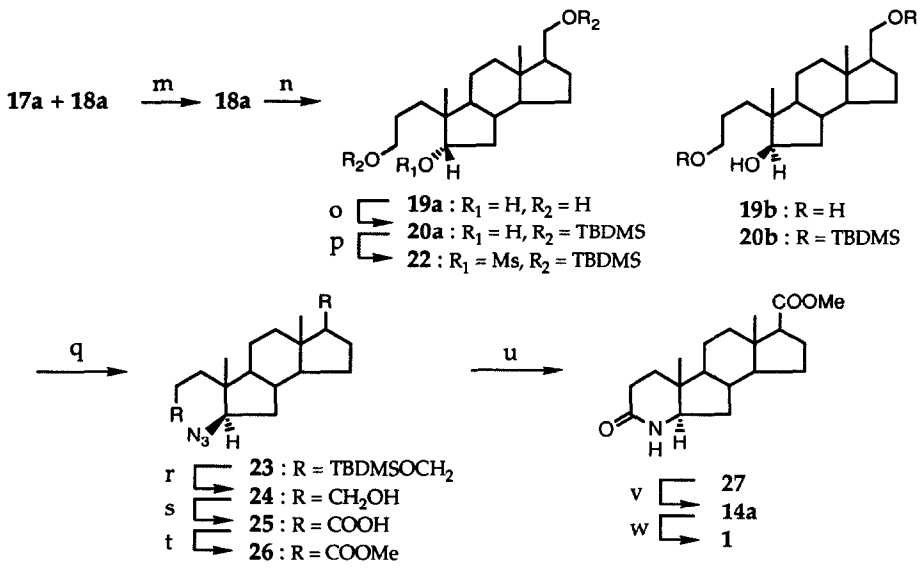
The *in vitro* inhibition of rat 5α-reductase was determined by using the standard method.[9] The compound **1** had a 63% inhibition rate at 10^{-8}M concentration. It was more potent than MK-906 (28% inhibition).

In conclusion, the compound **1**, which has a new B-nor-4-aza-5α-androstane structure, was synthesized, and it showed fairly potent inhibition activity against 5α-reductase.

Scheme 1



Reagents : (a) Ac_2O, pyridine, r.t.→70°C ; (b) O_3, CH_2Cl_2-MeOH, -78°C then Zn, AcOH ; (c) alumina (grade 3), benzene, r.t. ; (d) Jones reagent, acetone, 0°C ; (e) Ac_2O, triacetin, reflux ; (f) K_2CO_3, MeOH, 60°C ; (g) Al(*i*-PrO)$_3$, cyclohexanone, toluene, reflux ; (h) KOH, MeOH-H_2O, reflux ; (i) $KMnO_4$, $NaIO_4$, Na_2CO_3, *t*-BuOH-H_2O, reflux ; (j) formamide, formic acid, 180°C ; (k) CH_2N_2, EtOAc, r.t. ; (l) $NaBH_4$, EtOH-H_2O, r.t.



Reagents : (m) *p*-toluenesulfonic acid, benzene, reflux ; (n) $LiAlH_4$, Et_2O-THF, 0°C→r.t. ; (o) *t*-$BuMe_2SiCl$, imidazole, DMF, r.t. ; (p) MsCl, Et_3N, CH_2Cl_2, r.t. ; (q) NaN_3, DMF, 110°C ; (r) AcOH, THF-H_2O, r.t.→50°C ; (s) Jones reagent, acetone, r.t. ; (t) CH_2N_2, $CHCl_3$-MeOH, r.t. ; (u) H_2, PtO_2, Molecular Sieves 3A, MeOH, r.t. ; (v) BCl_3, CH_2Cl_2, r.t. ; (w) benzhydrylamine, DEPC, Et_3N, r.t.

References and Notes

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4) a) Tanabe, K. ; Morisawa, Y. *Chem. Pharm. Bull.*, **1963**, *11*, 536.
b) Tanabe, K. ; Hayashi, R. ; Takasaki, R. *Chem. Pharm. Bull.*, **1961**, *9*, 12.
5) Yield of **17b** was 43%. The formation ratio of **17a**, **17b**, and **18a** = 20, 9, and 71 based on ^{1}H-NMR.
6) Stereochemistry at the C-5 position in **18a** was assigned based on the NOE experiment. The NOE was observed between 5β-H and 19-methyl group in **18a**.
7) The undesired isomer **17b** was also converted to the desired **20a** : By using a similar sequence of reactions to that described for the synthesis of **20a** from **18a**, **17b** gave **20b**. Oxidation and then reduction of **20b** gave **20a** (35%) along with **20b** (64%).
8) The lactam ring of **27** was labile to the general hydrolysis condition used for the hydrolysis of 17-ester.
9) The biological test method is described in reference 3.

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