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Effect of a 17α-(3-Hydroxypropyl)-17β-acetyl Substituent Pattern on the Glucocorticoid and Progestin Receptor Binding of 11β-Arylestra-4,9-dien-3-ones

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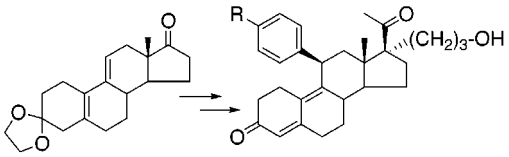
ABSTRACT



Replacing the 17α-acetoxy substituent in an antiprogestational 17β-acetyl-11β-arylestra-4,9-dien-3-one by 3-hydroxypropyl significantly diminished glucocorticoid receptor binding with little effect on progestin receptor binding.

The prototype 11β-aryl antiprogestin, mifepristone (Figure 1), and many of its early analogues bore a 17β-oxy substituent, with mifepristone having a 17β-hydroxyl-17α-propynyl D-ring substitution pattern (for a review, see ref 1). Replacement of these substituents in mifepristone with the progesterone side-chain (17β-acetyl) together with a 17α-acetoxy substituent led to RTI-3021-012[2] (**2**), which is approximately 3 times as potent as mifepristone when given orally to rabbits in the Clauberg antiprogestational assay[3,4] and which has effects similar to those of mifepristone on folliculogenesis in women.[5] Introduction of a 16α-ethyl-17β-acetyl substituent pattern (RTI-3021-022) together with the 11β-[4-(*N*,*N*-dimethylamino)phenyl] substituent of mifepristone resulted in progestational (agonist) activity in the rabbit.[3,4] This compound represented a new class of progestin receptor ligands, which bind to the progesterone receptor in a manner different from that of mifepristone and progester-

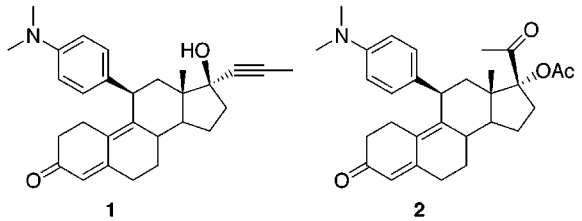


Figure 1. Structures of mifepristone (**1**) and RTI-3021-012 (**2**)

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(1) Teutsch, G.; Philibert, D. *Hum. Reprod.* **1994**, *12*, 31.

(2) RTI-3021-012 has also been given the designations HRP 2000, CBD 2914 and RU 44675.

(3) Cook, C. E.; Lee, Y.-W.; Wani, M. C.; Fail, P. A.; Petrow, V. *Progesterone Antagonists in Reproductive Medicine and Oncology;* Beier, H. M., Spitz, I. M., Eds.; Oxford University Press: New York; *Hum. Reprod.* **1994**, *9*(1), 32.

(4) Cook, C. E.; Wani, M. C.; Lee, Y.-W.; Fail, P. A.; Petrow, V. *Life Sci.* **1993**, *52*(2), 155.

(5) Stratton, P.; Hartog, B.; Hajizadeh, N.; Piquion, J.; Sutherland, D.; Merino, M.; Lee, Y. J.; Nieman, L. K. *Hum. Reprod.* **2000**, *15*(5), 1092.

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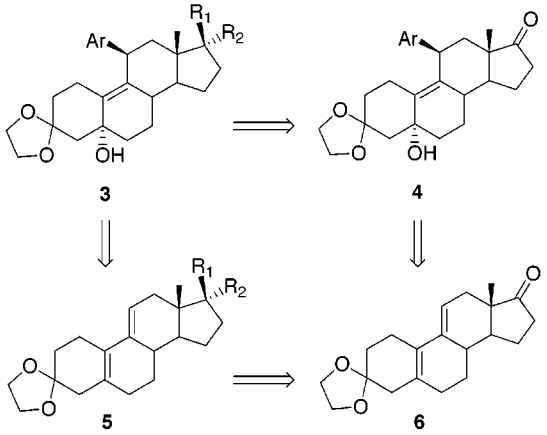
one.[6] Both RTI-3021-012 and -022 exhibited a mode of inhibition of the glucocorticoid receptor action different from that of mifepristone, resulting in lower antiglucocorticoid activity, with the difference being most pronounced for -022.[7]

These and other[1] indications of the importance of the D-ring substituents in modifying biological activity in the 11β-aryl steroids, the need for separation of glucocorticoid- and progestin-related activities,[1] and the report that a 17β-hydroxy-17α-(3-hydroxypropyl) substitution pattern (such as in ZK 97297) gave a compound with lowered glucocorticoid binding and antiglucocorticoid activity[8] led us to examine the effect of a 17α-(3-hydroxypropyl) group in the 17β-acetyl series of 11β-aryl compounds.

Retrosynthetic analysis (Scheme 1) suggested that the dieneketal **6** was a suitable starting material for making the penultimate intermediate **3**, which is readily converted to the corresponding 4,9-dien-3-one, with the major question being the order of introduction of the substituents. Lengthier routes beginning with estrone or a pregnane derivative were considered but not pursued.

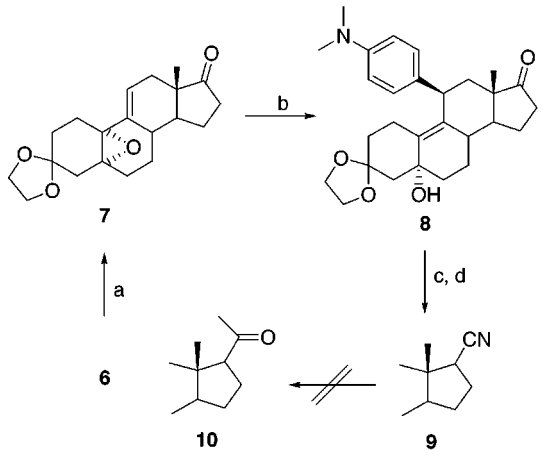
Scheme 1. Strategies for Synthesis of 11β-Aryl 17,17-Disubstituted Compounds



Incorporation of 17-substituents into the 11β-aryl-17-ketone **4** was investigated first (Scheme 2). Ketone **8**, made in the usual way by copper-catalyzed addition of an aryl Grignard reagent to the vinylic epoxide **7**[9] was converted in 69% yield to a 3:2 mixture of 17α- and 17β-cyano derivatives **9**, respectively, by the method of Yoneda et al.[10] Attempts to convert this mixture to the 17-acetyl derivative **10** by reaction with methylmagnesium bromide were not successful.

Believing that the steric crowding caused by the 11β-aryl group and its buttressing effect on the 18-methyl might be

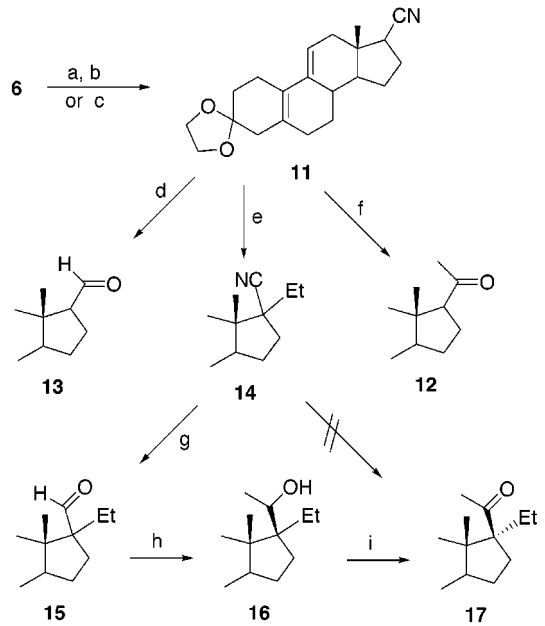
Scheme 2[a]



[a] Reagents and conditions: (a) (i) 35% H_2O_2, hexafluoroacetone trihydrate, Na_2HPO_4; (ii) trituration with ether to remove the β-isomer; (b) ArMgBr, CuCl; (c) diethyl cyanophosphonate, tetrahydrofuran (THF), LiCN, *N*,*N*-dimethylformamide (DMF); (d) SmI_2, THF.

affecting reactivity at C-17, we turned our attention to elaboration of the 17-position prior to introduction of the 11β-aryl group (Scheme 3). The 17-cyano derivative **11** was prepared from 17-ketodieneketal **6** by either the method of Yoneda et al.[10] (method A, 79% yield) or the method of Bull

Scheme 3[a]



[a] Reagents and conditions: (a) diethyl cyanophosphonate, THF, LiCN, DMF; (b) SmI_2, THF; (c) *t*-BuOK, dimethoxyethane, *t*-BuOH, tosylmethylisocyanide; (d) (i) diisobutylaluminum hydride, −78 °C; (ii) aq. NH_4Cl; (e) (i) $LiNEt_2$, (−78 °C); (ii) EtI (−78 °C to room temperature); (f) (i) MeMgBr; (ii) aq. NH_4Cl; (g) (i) diisobutylaluminum hydride, −30 °C; (ii) aq. NH_4Cl; (h) MeLi, −78 °C; (i) pyridinium dichromate, CH_2Cl_2.

(6) Wagner, B. L.; Pollio, G.; Leonhardt, S.; Wani, M. C.; Lee, D. Y. W.; Imhof, M. O.; Edwards, D. P.; Cook, C. E.; McDonnell, D. P. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*(16), 8739.

(7) Wagner, B. L.; Pollio, G.; Giangrande, P.; Webster, J. C.; Breslin, M.; Mais, D. E.; Cook, C. E.; Vedeckis, W. V.; Cidlowski, J. A.; McDonnell, D. P. *Endocrinology* **1999**, *140*(3), 1449.

(8) Wehle, H.; Moll, J.; Cato, A. C. B. *Steroids* **1995**, *60*, 368.

(9) Belanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361.

(10) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681.

and Tuinman[11] (method B, 71% yield). In contrast to 11β-aryl-substituted compound **3**, reaction of the 17-cyano group of **11** with methylmagnesium bromide gave methyl ketone **12** in 51% yield. Attempts to alkylate **12** directly by generating the 17-anion with potassium hydride and treating with ethyl iodide in a model reaction failed to give the desired product. Other attempts to generate the desired 17-anion by first forming the 17,20-silyl enol ether foundered on the difficulty of generating this moiety from the 20-ketopregnane molecules.

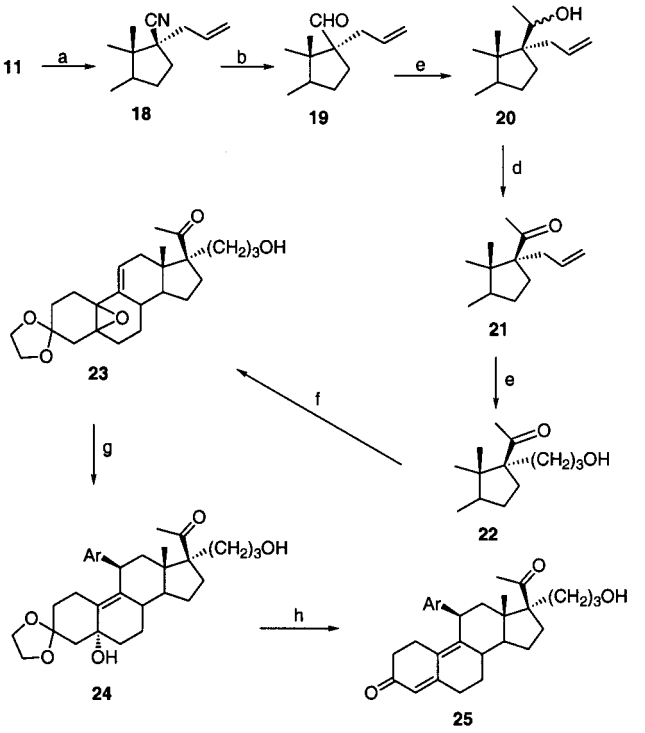
Treatment of nitrile **11** with diisobutylaluminum hydride (DIBAL-H) afforded aldehyde **13** in 62% yield, but efforts to alkylate **13** directly with ethyl iodide under a variety of basic conditions failed to give the desired product. Also, attempts to form the TMS-17(20)-enol ether from **13** with potassium hydride and trimethylsilyl chloride in refluxing THF (2 h) or refluxing dioxane (48 h) gave only recovered starting material. Nor were we able to form an enamine from aldehyde **13** under a variety of conditions. Models indicate that the 5(10),9(11)-diene system results in considerable twist and strain in these molecules, which may contribute to the reduced reactivity at the 17-position.

Conversion of **11** to the desired 17β-acetyl-17α-ethyl model compound **17** was finally accomplished by treatment of nitrile **11** with lithium diethylamide (LDEA) and ethyl iodide to give ethylated derivative **14** as a 4:1 mixture of isomers in 66% yield after purification by chromatography. Treatment of **14** with methylmagnesium bromide failed to give the desired ketone **17**, but reduction of **14** with DIBAL-H afforded aldehyde **15** (60% yield). Reaction of **15** with methyllithium gave alcohol **16** (62% yield), which was oxidized with pyridinium dichromate (PDC) to the 17β-acetyl compound **17** in 86% yield. NOE difference experiments indicated that the stereochemistry at the 17-position of **17** was as shown. Thus the ethylation of **11** proceeded to give mainly the 17α-ethyl compound, although NMR spectra of the product indicated the presence of the 17β-ethyl epimer.

Given the success with the model compound, we attempted introduction of the 17α-(3-hydroxypropyl) moiety by alkylation with THP-protected 3-halopropanols. All attempts with protected bromo- or iodopropanol failed. Cation coordinating agents such as hexamethylphosphoramide (HMPA) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were also added after generation of the anion to increase its nucleophilicity but failed to effect reaction.

Since these studies indicated that alkylation can be achieved only when the electrophile was quite reactive, we tried the alkylation of **11** with highly reactive allyl bromide, which successfully gave the corresponding 17α-allyl product **18** in greater than 75% yield (Scheme 4). The cyanoallyl compound was then reduced with DIBAL-H in toluene at −42 °C to afford the corresponding aldehyde **19** in 75% yield. Treatment of **19** with methyllithium afforded the secondary alcohol **20** almost quantitatively. Oxidation of **20** without purification was carried out with pyridinium dichromate (PDC) to afford the 20-ketone **21** in 40% yield. Further studies using Swern[12] oxidation provided **21** in 70% isolated yield.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) $LiNEt_2$, −78 °C; (ii) allyl bromide, THF; (b) (i) diisobutylaluminum hydride, (toluene, −42 °C; (ii) aq. NH_4Cl; (c) MeLi (−78 °C to room temperature); (d) pyridinium dichromate, CH_2Cl_2; (e) (i) disiamylborane, −5 °C; (ii) NaOH, aq. H_2O_2; (f) 35% H_2O_2, hexafluoroacetone, Na_2HPO_4, CH_2Cl_2; (g) ArMgBr, $CuBr{\cdot}SMe_2$; (h) *p*-toluenesulfonic acid, acetone.

The terminal olefin of **21** was converted to the primary alcohol by hydroboration−oxidation with disiamylborane followed by basic hydrogen peroxide. Anti-Markovnikoff addition, as expected, led to primary alcohol **22** in 62% yield. Epoxidation of diene ketal **22** with *m*-chloroperbenzoic acid (MCPBA) afforded the 5(10)-epoxide **23** as a mixture of isomers in 89% yield. Use of 50% hydrogen peroxide and hexafluoroacetone in the presence of a small amount of disodium phosphate gave a 98% crude yield of epoxides containing about 60% of the desired 5(10)α-epoxide by NMR analysis (comparison of integration of the 11-proton). Copper-catalyzed reaction[9] of **23** with the Grignard reagents prepared from *p*-*N*,*N*-dimethylaminobromobenzene, the ethylene ketal of *p*-acetylbromobenzene, and *p*-thiomethylbromobenzene led to the corresponding 11β-aryl intermediates **24a** through **24c**, albeit in low yields (16%, 15%, and 17%, respectively). These were deketalized and dehydrated

(11) Bull, J. R.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2151.

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by treating with *p*-toluenesulfonic acid in acetone to give the final compounds **25a**, **25b**, and **25c**.

The NMR spectra of the progression of compounds from **18** through **22** (Scheme 4) are consistent with the finding above that the alkylation of the cyano compound **11** yields predominantly the α-substituted-β-cyano product. The position of the C-18 resonance shifted markedly as the 17-substituent of the allyl compounds was changed from cyano (δ 1.07 ppm) to formyl (δ 0.75) to ketone (δ 0.65), consistent with these substituents being in the β-position. However, little further change (δ 0.63) occurred on hydroxylation of the allyl group to **22**, consistent with the allyl group being an α-substituent.

Relative receptor binding activities (RBA) for compounds **25a**, **25b**, and **25c** are shown in Table 1. Replacement of the 17α-acetoxy group in RTI-3021-012 with 17α-(3-hydroxypropyl) (**25a**) did indeed reduce the RBA for the glucocorticoid receptor (GR) by a factor of 4. There was much less effect on the progestin receptor (PR) RBA, so the PR/GR ratio was more than tripled. Marked reduction of glucocorticoid receptor binding was observed by substitution of an 11β-(p-acetyl)phenyl moiety (**25b**) for dimethylaminophenyl, and this change also improved the progestin receptor binding. An 11β-(*p*-methylthio)phenyl analogue (**25c**) was intermediate in the ratio of relative binding to the two receptors. Despite the relatively high binding affinity for the progestin receptor, none of the three new compounds showed oral antiprogestational activity in the rabbit (anti-Clauberg assay) at total doses of up to 8 mg (at which dose the standard, RTI-3021-012, was more than 50% effective). Whether this is due to their pharmacokinetic properties or to their interaction with the receptor remains to be determined.

Table 1

compounds		relative binding affinity		
no.	RTI no.	r-PR[a]	r-GR[b]	PR/GR ratio
1	3021-012	134	86	1.6
25a	6413-003	118	20	5.8
25b	6413-018	144	5	29
25c	6413-033	106	10	11

[a] Progestin receptor from rabbit. The radioligand was tritium-labeled progesterone and progesterone was used as the standard (RBA = 100). Incubation was for 16 h at 4 °C. See ref 13 for details of the method. [b] Glucocorticoid receptor from rabbit thymus. The radio-ligand was tritium-labeled dexamethasone, and dexamethasone was used as the standard (RBA = 100). Incubation was for 16 h at 4 °C (general methodology of ref 13).

In conclusion, replacement of 17α-acetoxy by 17α-(3-hydroxypropyl) in the potent antiprogestin RTI-3012-012 has been accomplished through stepwise construction of the 17-substituents. The resulting compounds exhibit reduced glucocorticoid binding, with enhanced progestin/glucocorticoid binding ratios. Although they retain good progestin receptor binding, they were not orally active as antiprogestins in the rabbit at the doses tested, in contrast to the strong antiprogestational activity of RTI-3021-012.

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Supporting Information Available: Procedures for the preparation of compounds in this paper and their characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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