Cycloaddition of Nitrosoaromatics with Steroidal Dienes: Unexpected Dependence of the Chemoselectivity on the Aryl Ring Substituent

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Tandem palladium-catalyzed Stille coupling of steroidal alkenyl iodides (17-iodo-androst-16-ene (**1**), 17-iodo-4-methyl-4-aza-androst-16-en-3-one (**4**), and 17-iodo-4-aza-androst-16-en-3-one (**5**)) with vinyltributylstannane and hetero Diels−Alder reaction of the products using nitrosobenzene or some *para*-substituted nitrosoaromatics (*p*-NO_2, *p*-Br, *p*-Me, *p*-OMe) as dienophiles were investigated. Cycloaddition was regioselective in each case, but two stereoisomers were obtained in a 2:1 ratio with unsubstituted pregnadienes as reaction partners. Stereoselectivity was improved by the use of Lewis acid catalysts. The similar reaction of substituted nitrosoaromatics with highly negative Hammett substituent-constants (*p*-OH, *p*-NMe_2) resulted in the spontaneous dehydrogenation of the dihydro-oxazine, which was followed by the formation of rearrangement products. The assignment of stereoisomers was carried out by various NMR techniques including $^1H-^1H$ COSY and NOESY experiments.

Introduction

The replacement of one or more carbon atoms of a steroidal backbone with various heteroatoms or the introduction of a heteroatom (usually nitrogen) to B-, C-, or D-rings often results in molecules with advantageous biological properties. Azasteroids have been tested for their hypocholesterolemic activity and found to be inhibitors of cholesterol biosynthesis.[1−3] Aza- and homoazasteroids have been found to possess antifertility activity[4,5] and are also known as 5α-reductase inhibitors.[6−8] 17α-Aza-D-homo-androstanes have been tested as potential bioregulators on parasites.[9] Recently, steroidal selena, tellura, and thia lactones have been synthesized and were found to have an improved antihypercholesterolemic activity.[10]

The present work was stimulated by the importance of pentacyclic steroids offering novel binding sites and binding distances to the receptors by the introduction of heteroatoms and various functionalities into the E-ring.

As we have shown previously, Pd(0) catalysts can effectively be used for the coupling reaction of steroidal alkenyl iodides with organostannanes [11] or electron-deficient olefins.[12] The iodo-alkenyl derivatives can be prepared easily from the corresponding ketone via the hydrazone[13] and give clean reactions compared to those of the steroidal triflates.[14] Recently we have found that various pentacyclic steroids can be synthesized by a one-pot reaction of a steroidal alkenyl iodide, a dienophile, and vinyltributyltin[15] (or an electron-deficient olefin[16]) in the presence of a homogeneous catalyst containing palladium. In this reaction the diene formed by Stille coupling[17] or Heck reaction[18] undergoes a Diels−Alder reaction in the presence of an olefin or acetylene possessing electron-withdrawing groups. The aim of the present work was the extension of the above-mentioned methodology using nitrosoaromatics as dienophiles.

Results and Discussion

Cycloaddition with Nitrosobenzene as the Dienophile. 17-Iodo-androst-16-ene (**1**) was coupled with vi-

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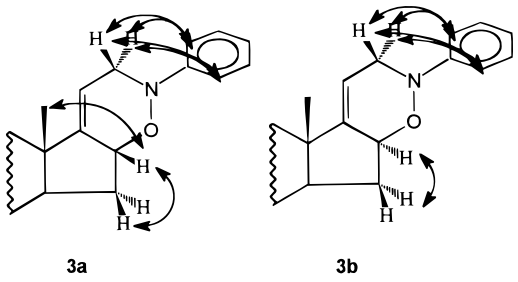
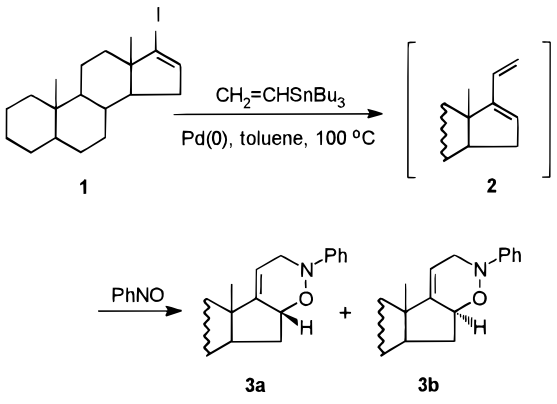


3a **3b**

Figure 1. NOE effects observed during the NMR investigation of **3a** and **3b**

nyltributylstannane in the presence of $Pd(PPh_3)_4$ catalyst yielding the corresponding diene (**2**), which reacts with nitrosobenzene in a one-pot reaction (eq 1). The reaction



(1)

of nitrosobenzene with the steroidal diene is regioselective, affording a 3,6-dihydro-1,2-oxazine E-ring. However, the methodology used for olefins as the dienophiles could not be followed here. Nitrosobenzene could not be added to the reaction mixture before the completion of Stille coupling. The vinylation step was considerably slower, and no more than 50% conversion could be achieved in the presence of this compound. The possible explanation for this is the facile coordination of nitrosobenzene to the palladium, which results in the partial deactivation of the catalyst.

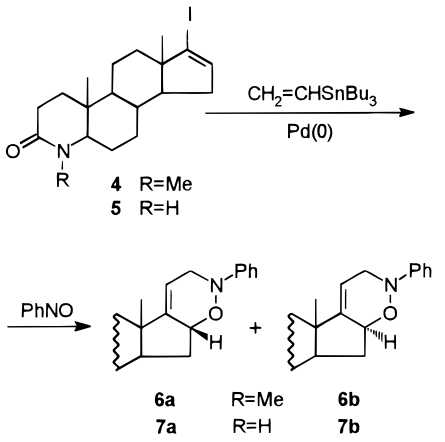
Cycloaddition was completely regioselective; two stereoisomers of the steroidal N,O heterocycles (**3a,b**) were obtained in 85% yield in a tandem reaction in a 2:1 ratio. The structures of the two isomers were determined by NMR including 2D measurements ($^1H-^{13}C$ HETCOR, $^1H-^1H$ COSY) and NOESY. The regioselectivity of the reaction was proved by ^{13}C NMR measurements; the chemical shifts of the 16-C signals of both isomers (at 79.9 and 82.2 ppm, respectively) correspond to carbons next to oxygen. According to the NOESY experiment (Figure 1), saturation of the 16-H signal (5.06 ppm) of **3a** resulted in the increase in the signals at 1.79 ppm (15β-H) and at 0.86 ppm (18-CH_3), which proves the β disposition of 16-H of the major product. Also, the saturation of the 16-H signal (4.74 ppm) of **3b** caused an increase in the signals at 2.1 ppm (15α-H) and 1.3 ppm (14α-H), which corresponds to the 16α-H isomer. The NOE effect observed in the case of both isomers between the 3′ protons (4.04 ppm, 3.60 ppm) and the aromatic protons in the *ortho*-position (7.09 ppm) supports the formation of the regioisomers depicted in eq 1.

The formation of the 16β-H and 16α-H derivatives takes place through transition states in which nitrosobenzene approaches the steroid from the α- and β-side of the steroidal diene, respectively. The latter approach is less favorable because of the β-disposition of 18-CH_3, which results in a more crowded transition state.

The presence of the palladium catalyst did not alter the stereoselectivity of cycloaddition; the same products were obtained in the same ratio when the diene was isolated after the vinylation step and the pure compound was used as the substrate in the Diels−Alder reaction. At the same time the presence of Lewis acids in the cycloaddition step increased the amount of the 16β-H derivative (Table 1) but did not seem to enhance the rate of the reaction. The catalytic activity of Lewis acids in cycloaddition reactions is explained by the fact that these compounds form complexes with the dienophile and so decrease the energy of its LUMO.[19] However, in the case of steroidal dienes, the importance of steric factors seems to outweigh that of electronic ones. Because of the coordination of the Lewis acid to nitrosobenzene, the dienophile becomes bulkier. This hinders not only the less favorable approach from the β-side but also cycloaddition, to some extent.

Separation of the two stereoisomers (**3a,b**) by column chromatography was attempted. Compound **3a** could be isolated with 95% purity when a Lewis acid was used in the cycloaddition step, which led originally to higher selectivity. However, complete separation could not be achieved, because a retro Diels−Alder reaction was observed leading to the formation of diene **2**, especially at elevated retention times (when using less polar solvents as eluents).

As was expected, the structure of the steroidal skeleton did not affect the regio- or stereoselectivity of cycloaddition. The corresponding pentacyclic steroids with 3,6-dihydro-1,2-oxazine E-rings (**6a,b** and **7a,b**) were synthesized with good yields and the same selectivity starting from 17-iodo-4-methyl-4-aza-androst-16-en-3-one (**4**) and 17-iodo-4-aza-androst-16-en-3-one (**5**, eq 2), respectively.



(2)

Cycloaddition of nitrosobenzene with a steroidal diene bearing an electron-withdrawing substituent was also investigated. 21-Methoxycarbonyl-pregna-16,20-diene (**8**) was prepared by the Heck reaction of **1** with methyl

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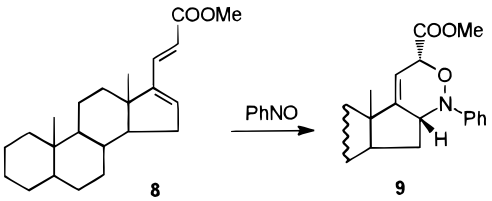
Table 1. Lewis Acid Catalyzed Cycloaddition of 2 with Nitrosobenzene

		product distribution[b] (%)	
Lewis acid	conversion[a] (%)	**3a**	**3b**
	88	68	32
$AlCl_3$	69	75	25
$ZnCl_2$	85	87	13

[a] Reaction time, 5 h. [b]Determined by GC.

acrylate, as described previously.[12] The rate of cycloaddition of **8** with nitrosobenzene was considerably slower than that of **2** (conversion after 5 h is 30% and 88%, respectively). According to various spectroscopic measurements (MS, GC−MS, ^{1}H NMR) this reaction resulted in the formation of a single isomer of the steroidal oxazine **9** (eq 3). The difference in regioselectivity between the

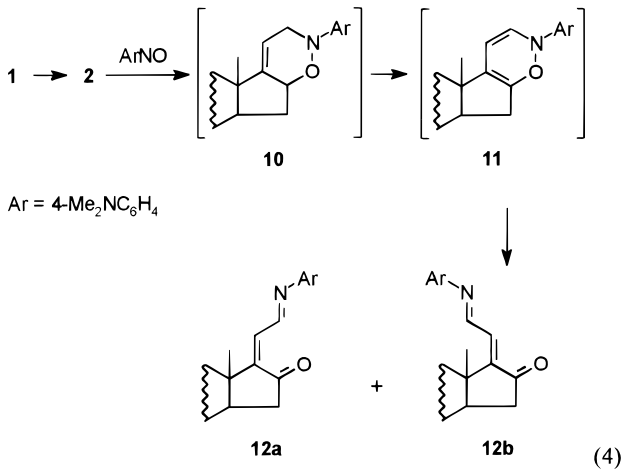


8 **9** (3)

cycloaddition of **8** and that of **2** was proved by ^{1}H NMR and NOE investigations. Chemical shift of 16-H of **9** (4.23 ppm) shows a methine proton next to a nitrogen. (In comparison, the chemical shifts of 16-H of **3a** and **3b** are 5.06 and 4.74 ppm, respectively.) Saturation of the signal at 4.23 ppm resulted in an increase in the signals at 0.95 ppm (18-CH_3) and at 7.42 ppm (aromatic protons in *ortho* positions). The former observation proved the β-disposition of 16-H of **9**, and the latter supported the assumption of the different regioselectivity compared to that of cycloaddition with **2**.

The change in regioselectivity and decrease in reactivity in the case of **8** can be explained according to the frontier orbital theory.[19] The HOMO of **8** is lower in energy than that of diene **2** because of the electron-withdrawing substituent on C-21. So the energy difference between the HOMO of the diene **8** and the LUMO of nitrosobenzene is greater, and consequently cycloaddition is slower. Regioselectivity can be predicted considering the relative sizes of the coefficients of the atomic orbitals at C-16 and C-21. The methoxycarbonyl group reduces the coefficient at C-21, and so orientation of nitrosobenzene is reversed in the transition state compared to that in reaction with diene **2**. These results corresponds well to the data given for the cycloaddition of 1,4-substituted dienes with *p*-chloro-nitrosobenzene by Eisenstein et al.[20] In the case of the steroidal diene, because of the steric hindrance between the phenyl group of nitrosobenzene and the D-ring (and 18-CH_3) of the steroidal skeleton, the approach of the dienophile from the β-side of the steroid is even less favored than in the case of diene **2**, and so cycloaddition is completely stereoselective.

Cycloaddition with 4-Nitroso-*N*,*N*-Dimethylaniline as the Dienophile. Instead of the formation of the awaited cycloaddition products (e.g., **10** with 4-nitroso-dimethylaniline, eq 4) the 16-keto derivatives (**12a,b**) could be produced with 90% isolated yield in 4:1 ratio.



(4)

This can be explained by the spontaneous dehydrogenation of **10**, followed by the rearrangement of the oxazine **11**. Dehydrogenation and rearrangement takes place also in the absence of the Pd catalyst and in inert atmosphere. (However, the mechanism of dehydrogenation is unclear. The diene and the dienophile were used in 1:1 ratio, and almost complete conversion was achieved in each case. No hydrogenation of the steroid or the nitrosoaromatic compound could be observed according to ^{1}H NMR and GC−MS measurements.) 2*H*-1,2-Oxazines have been reported to be unstable compounds. For example, the reaction between 4-nitroso-dimethylaniline and tetracyclone does not give the oxazine but rather the isomeric lactam that is formed via spontaneous decarbonylation and rearrangement of the cycloaddition product.[21]

According to the NMR data (^{1}H and ^{13}C NMR, APT) **12a** and **12b** are the isomers depicted in eq 4. The APT spectrum clearly shows that the carbonyl signals at 206.8 and 205.4 ppm (for **12a** and **12b**, respectively) correspond to keto groups. The presence of three further signals of olefinic carbons (at 153.3, 152.3, and 130.7 ppm for **12a** and at 153.6, 150.5, and 128.4 ppm for **12b**) also supports these structures. The extremely high chemical shift of 21-H of **12a** is due to the deshielding effect of the 16-CO. The position of the aromatic ring was determined by NOE measurements; saturation of 21-H signals of **12a** and **12b** (at 9.35 and 8.61 ppm, respectively) caused an increase in the signals of the corresponding aromatic protons in *ortho* positions (at 7.28 ppm for **12a** and at 7.20 ppm for **12b**).

The formation of the analogous ring-opening products (**13a,b**) was found by using 17-iodo-4-methyl-4-aza-androst-16-en-3-one as the steroidal substrate.

Cycloaddition with Other 4-Substituted Nitrosoaromatics. The above results prompted us to investigate the effect of various *para*-substituents on the Diels−Alder reactions of nitrosoaromatics. The use of most of the dienophiles led to the formation of steroids with a dihydro-oxazine E-ring (Table 2). The ratio of stereoisomers (**a** and **b**) was the same in each case as observed before with nitrosobenzene. No dehydrogenation or formation of ring-opening products was observed in these cases.

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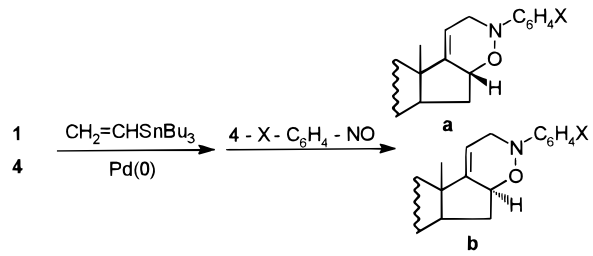
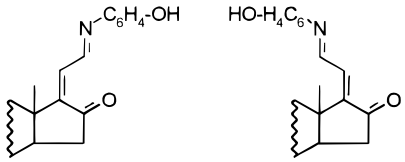
Table 2. Stille Coupling of Steroids 1 and 4 Followed by Cycloaddition with 4-X−C_6H_4-NO



substrate	X	products
1	NO_2	**14a,14b**
4		**15a,15b**
1	Br	**16a,16b**
4		**17a,17b**
1	OCH_3	**18a,18b**
4		**19a,19b**
1	CH_3	**20a,20b**
4		**21a,21b**

4-Nitrosophenol, however, gave rearrangement products (**22a**, **22b**) similar to those of 4-nitroso-dimethylaniline.



Conclusion. The facile synthesis of steroids possessing a dihydro-oxazine E-ring was carried out by tandem palladium-catalyzed Stille coupling and hetero Diels−Alder reaction using nitrosobenzene or some *para*-substituted nitrosoaromatics as dienophiles. However, the similar reaction of substituted nitrosoaromatics with highly negative Hammett substituent-constants (*p*-OH, *p*-NMe_2) results in the spontaneous dehydrogenation of the dihydro-oxazine, which was followed by the formation of rearrangement products. Electronic properties of *para*-substituents of the aromatic ring seem to greatly influence the chemoselectivity of cycloaddition. In addition, the presence of an electron-withdrawing group in the diene leads to reversed regioselectivity.

Experimental Section

All of the homogeneous catalytic experiments were carried out under an argon atmosphere. Solvents were dried over sodium and distilled under argon.

Palladium Catalyst. $Pd(PPh_3)_4$ was prepared as described previously.[22]

Dienophile Reagents. Nitrosobenzene and 4-nitrosophenol were purchased from Aldrich, and 4-nitroso-dimethylaniline[23] and 4-bromo-, 4-methoxy-, 4-methyl-,[24] and 4-nitro-nitrosobenzene[25] were prepared with known methods.

General Procedure for the Synthesis of the Cycloaddition Products. $Pd(PPh_3)_4$ (0.02 mmol) and the steroid (1 mmol) were added to a flask equipped with a reflux condenser and a septum inlet. The flask was flushed with argon and charged with 10 mL of toluene. Then 1.1 mmol of vinyltributyltin was added by means of a hypodermic syringe through the septum inlet. The mixture was stirred at 100 °C. The reaction was followed by GC. After completion of the vinylation, 1 mmol of the dienophile was added under argon without isolation of the diene, and the mixture was stirred further until the cycloaddition was completed. After completion of the reaction (GC, TLC), an aqueous solution of 1.5 mmol of KF was added, and the mixture was stirred overnight. The organic layer was separated and dried over Na_2SO_4. The product was purified after removal of the solvent by column chromatography on silica gel with chloroform/methanol as eluent. The compounds prepared by this procedure are as follows.

(2′-Phenyl)-androstano-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**3a**) and the 16*β* (**3b**) isomers). Anal. Calcd for $C_{27}H_{37}NO$: C, 82.81; H, 9.52; N, 3.58. Found: C, 82.53; H, 9.57; N, 3.60. Yield: 94%.

3a: ^{1}H NMR *δ* 7.28(t, 7.6 Hz, 2H); 7.08(d, 7.6 Hz, 2H); 6.92-(t, 7.6 Hz, 1H); 5.36(m, 1H); 5.07(m, 1H); 4.07(m, 1H); 3.60-(m, 1H); 0.9−2.1(m, 22H); 0.87(s, 3H); 0.79(s, 3H). ^{13}C NMR *δ* 152.4; 150.1; 128.6; 128.6; 121.8; 115.0; 115.0; 108.0; 79.9; 55.2; 53.0; 51.5; 46.9; 43.7; 38.6; 36.9; 36.2; 35.3; 34.2; 31.5; 29.2; 28.8; 26.7; 22.0; 19.8; 17.0; 12.2. MS *m*/*z* 391(5); 376(4); 373-(2); 358(10); 77(20); 43(100).

3b: ^{1}H NMR *δ* 7.28(t, 7.6 Hz, 2H); 7.08(d, 7.6 Hz, 2H); 6.92-(t, 7.6 Hz, 1H); 5.52(m, 1H); 4.72(m, 1H); 4.07(m, 1H); 3.6(m, 1H); 0.9−2.1(m, 22H); 0.95(s, 3H); 0.87(s, 3H). ^{13}C NMR *δ* 152.2; 150.3; 128.6; 128.6; 121.8; 115.0; 115.0; 114.0; 82.2; 55.4; 51.8; 50.9; 47.2; 42.3; 38.4; 36.7; 36.2; 35.3; 33.4; 32.2; 29.3; 28.7; 26.7; 22.6; 20.7; 17.0; 13.5. MS *m*/*z* 391(3); 389(2); 376-(5); 77(20); 43(100).

(2′-Phenyl)-(3-keto-4-methyl-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**6a**) and the 16*β* (**6b**) isomers). Anal. Calcd for $C_{27}H_{36}N_2O_2$: C, 77.10; H, 8.63; N, 6.66. Found: C, 76.94; H, 8.55; N, 6.68. Yield: 96%.

6a: ^{1}H NMR *δ* 7.31(t, 7.6 Hz, 2H); 7.10(d, 7.6 Hz, 2H); 6.95-(t, 7.6 Hz, 1H); 5.41(m, 1H); 5.10(m, 1H); 4.09(m, 1H); 3.64-(m, 1H); 3.03(m, 1H); 2.93(s, 3H); 2.46(m, 2H); 0.9−2.4(m, 15H); 0.93(s, 3H); 0.89(s, 3H).

6b: ^{1}H NMR *δ* 7.31(t, 7.6 Hz, 2H); 7.10(d, 7.6 Hz, 2H); 6.95-(t, 7.6 Hz, 1H); 5.59(m, 1H); 4.77(m, 1H); 4.09(m, 1H); 3.64-(m, 1H); 3.03(m, 1H); 2.93(s, 3H); 2.46(m, 2H); 0.9−2.4(m, 15H); 1.01(s, 3H); 0.93(s, 3H).

(2′-Phenyl)-(3-keto-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**7a**) and the 16*β* (**7b**) isomers). Anal. Calcd for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.55; H, 8.46; N, 6.99. Yield: 91%.

7a: ^{1}H NMR *δ* 7.24(t, 7.6 Hz, 2H); 7.07(d, 7.6 Hz, 2H); 6.92-(t, 7.6 Hz, 1H); 5.68(brs, 1H); 5.37(m, 1H); 5.05(m, 1H); 4.05-(m, 1H); 3.58(m, 1H); 3.05(m, 1H); 2.36(m, 2H); 1.1−2.3(m, 15H); 0.89(s, 3H); 0.81(s, 3H).

7b: ^{1}H NMR *δ* 7.24(t, 7.6 Hz, 2H); 7.07(d, 7.6 Hz, 2H); 6.92-(t, 7.6 Hz, 1H); 5.68(brs, 1H); 5.55(m, 1H); 4.72(m, 1H); 4.05-(m, 1H); 3.58(m, 1H); 3.05(m, 1H); 2.36(m, 2H); 1.1−2.3(m, 15H); 1.02(s, 3H); 0.89(s, 3H).

21-(*N*-(4′-Dimethylamino)-phenyl)-imino-pregn-17(20)-en-16-one (4:1 mixture of the 17.20-*Z* (**12a**) and the 17.20-*E* (**12b**) isomers). Anal. Calcd for $C_{29}H_{40}N_2O$: C, 80.51; H, 9.32; N, 6.47. Found: C, 80.62; H, 9.29; N, 6.51. Yield: 90%.

12a: ^{1}H NMR *δ* 9.35(d, 9.4 Hz, 1H); 7.28(d, 8.9 Hz, 2H); 6.67(d, 8.9 Hz, 2H); 6.39(d, 9.4 Hz, 1H); 2.98(s, 6H); 1.05−2.4-(m, 22H); 0.97(s, 3H); 0.80(s, 3H). ^{13}C NMR *δ* 206.8; 153.3; 152.3; 139.3; 137.5; 130.7; 123.7; 123.7; 112.7; 112.7; 55.1; 53.0; 51.7; 46.7; 44.3; 40.5; 40.5; 39.0; 37.0; 36.3; 35.5; 34.3; 31.5; 29.2; 29.0; 26.5; 22.1; 16.9; 12.5. MS *m*/*z* 432(3); 417(6); 57-(60); 41(100).

12b: ^{1}H NMR *δ* 8.61(d, 10.1 Hz, 1H); 7.20(d, 9.2 Hz, 2H); 7.01(d, 10.1 Hz, 1H); 6.65(d, 9.2 Hz, 2H); 2.98(s, 6H); 1.05−2.4(m, 22H); 1.00(s, 3H); 0.80(s, 3H). ^{13}C NMR *δ* 205.4; 153.6; 150.5; 139.1; 138.1; 128.4; 122.2; 122.2; 112.9; 112.9; 55.0; 53.2; 51.9; 46.5; 44.6; 40.6; 40.6; 39.0; 36.8; 36.3; 35.5; 34.4; 31.5; 29.3; 29.0; 26.4; 22.3; 16.9; 13.6.

21-(*N*-(4′-Dimethylamino)-phenyl)-imino-4-methyl-4-aza-pregn-17(20)-en-3,16-dione (4:1 mixture of the 17.20-*Z* (**13a**) and the 17.20-*E* (**13b**) isomers). Anal. Calcd for

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$C_{29}H_{39}N_3O_2$: C, 75.45; H, 8.52; N, 9.10. Found: C, 75.73; H, 8.56; N, 9.06. Yield: 91%.

13a: ^{1}H NMR δ 9.37(d, 9.4 Hz, 1H); 7.31(d, 9.1 Hz, 2H); 6.70(d, 9.1 Hz, 2H); 6.38(d, 9.4 Hz, 1H); 3.06(m, 1H); 2.99(s, 6H); 2.93(s, 3H); 2.45(m, 2H); 1.05−2.4(m, 15H); 1.05(s, 3H); 0.94(s, 3H). ^{13}C NMR δ 206.9; 170.7; 152.2; 150.4; 139.5; 137.8; 130.8; 123.4; 123.4; 112.5; 112.5; 65.6; 51.8; 48.7; 44.3; 40.5; 40.5; 39.0; 36.7; 35.1; 33.6; 32.7; 30.1; 29.2; 29.0; 25.2; 20.8; 19.4; 12.4. MS *m/z* 461(2); 341(6); 43(70); 41(100).

13b: ^{1}H NMR δ 8.64(d, 10.2 Hz, 1H); 7.23(d, 9.1 Hz, 2H); 7.03(d, 10.2 Hz, 1H); 6.68(d, 9.1 Hz, 2H); 3.06(m, 1H); 2.97(s, 6H); 2.93(s, 3H); 2.45(m, 2H); 1.05−2.4(m, 15H); 1.05(s, 3H); 0.92(s, 3H). ^{13}C NMR δ 205.5; 170.8; 153.7; 153.5; 139.3; 138.1; 128.5; 122.2; 122.2; 112.7; 112.7; 65.6; 51.9; 48.7; 44.3; 40.6; 40.5; 39.0; 36.6; 35.1; 34.0; 32.9; 29.9; 29.2; 29.1; 25.3; 20.9; 19.4; 13.6.

(2′-(4″-Nitro)-phenyl)-androstano-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**14a**) and the 16*β* (**14b**) isomers). Anal. Calcd for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42. Found: C, 73.98; H, 8.44; N, 6.53. Yield: 82%.

14a: ^{1}H NMR δ 7.63(d, 9 Hz, 2H); 6.98(d, 9 Hz, 2H); 5.40-(m, 1H); 5.07(m, 1H); 4.21(m, 1H); 3.71(m, 1H); 1.0−2.3(m, 22H); 0.91(s, 3H); 0.82(s, 3H).

14b: ^{1}H NMR δ 7.63(d, 9 Hz, 2H); 6.98(d, 9 Hz, 2H); 5.61-(m, 1H); 4.66(m, 1H); 4.21(m, 1H); 3.71(m, 1H); 1.0−2.3(m, 22H); 0.99(s, 3H); 0.91(s, 3H).

(2′-(4″-Nitro)-phenyl)-(3-keto-4-methyl-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**15a**) and the 16*β* (**15b**) isomers). Anal. Calcd for $C_{27}H_{35}N_3O_4$: C, 69.65; H, 7.58; N, 9.03. Found: C, 69.87; H, 7.56; N, 9.08. Yield: 85%.

15a: ^{1}H NMR δ 7.61(d, 9 Hz, 2H); 6.97(d, 9 Hz, 2H); 5.39(m, 1H); 5.05(m, 1H); 4.21(m, 1H); 3.70(m, 1H); 3.05(m, 1H); 2.88-(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.90(s, 3H); 0.85(s, 3H).

15b: ^{1}H NMR δ 7.61(d, 9 Hz, 2H); 6.97(d, 9 Hz, 2H); 5.59(m, 1H); 4.65(m, 1H); 4.21(m, 1H); 3.70(m, 1H); 3.05(m, 1H); 2.88-(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 1.02(s, 3H); 0.90(s, 3H).

(2′-(4″-Bromo)-phenyl)-androstano-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**16a**) and the 16*β* (**16b**) isomers). Anal. Calcd for $C_{27}H_{36}NOBr$: C, 68.93; H, 7.71; N, 2.98. Found: C, 68.81; H, 7.69; N, 2.99. Yield: 93%.

16a: ^{1}H NMR δ 7.35(d, 9 Hz, 2H); 6.95(d, 9 Hz, 2H); 5.38-(m, 1H); 5.05(m, 1H); 4.05(m, 1H); 3.55(m, 1H); 0.9−2.0(m, 22H); 0.82(s, 3H); 0.75(s, 3H). ^{13}C NMR δ 152.6; 149.4; 132.0; 132.0; 123.9; 116.7; 116.7; 108.0; 79.9; 55.1; 53.1; 51.3; 47.0; 43.7; 42.4; 38.6; 36.4; 35.3; 34.2; 31.5; 29.0; 29.0; 26.7; 22.1; 19.9; 17.0; 12.2.

16b: ^{1}H NMR δ 7.35(d, 9 Hz, 2H); 6.95(d, 9 Hz, 2H); 5.55-(m, 1H); 4.72(m, 1H); 4.05(m, 1H); 3.55(m, 1H); 0.9−2.0(m, 22H); 0.90(s, 3H); 0.82(s, 3H). ^{13}C NMR δ 152.4; 149.4; 131.6; 131.6; 123.9; 116.6; 116.6; 113.9; 82.4; 55.4; 51.6; 50.7; 47.2; 43.6; 41.5; 38.4; 36.6; 35.3; 33.5; 32.2; 29.2; 28.9; 27.2; 22.9; 20.8; 17.0; 13.6.

(2′-(4″-Bromo)-phenyl)-(3-keto-4-methyl-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**17a**) and the 16*β* (**17b**) isomers). Anal. Calcd for $C_{27}H_{35}N_2O_2Br$: C, 64.93; H, 7.06; N, 5.61. Found: C, 64.71; H, 7.09; N, 5.62. Yield: 94%.

17a: ^{1}H NMR δ 7.35(d, 9 Hz, 2H); 6.95(d, 9 Hz, 2H); 5.39(m, 1H); 5.05(m, 1H); 4.07(m, 1H); 3.58(m, 1H); 3.05(m, 1H); 2.90-(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.90(s, 3H); 0.85(s, 3H).

17b: ^{1}H NMR δ 7.35(d, 9 Hz, 2H); 6.95(d, 9 Hz, 2H); 5.55(m, 1H); 4.72(m, 1H); 4.07(m, 1H); 3.58(m, 1H); 3.05(m, 1H); 2.90-(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.95(s, 3H); 0.90(s, 3H).

(2′-(4″-Methoxy)-phenyl)-androstano-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**18a**) and the 16*β* (**18b**) isomers). Anal. Calcd for $C_{28}H_{39}NO_2$: C, 79.77; H, 9.32; N, 3.32. Found: C, 80.06; H, 9.35; N, 3.33. Yield: 84%.

18a: ^{1}H NMR δ 7.09(d, 9 Hz, 2H); 6.82(d, 9 Hz, 2H); 5.35-(m, 1H); 5.08(m, 1H); 3.95(m, 1H); 3.75(s, 3H); 3.58(m, 1H); 1.0−2.2(m, 22H); 0.80(s, 3H); 0.75(s, 3H).

18b: ^{1}H NMR δ 7.09(d, 9 Hz, 2H); 6.82(d, 9 Hz, 2H); 5.53-(m, 1H); 4.72(m, 1H); 3.95(m, 1H); 3.75(s, 3H); 3.58(m, 1H); 1.0−2.2(m, 22H); 0.95(s, 3H); 0.80(s, 3H).

(2′-(4″-Methoxy)-phenyl)-(3-keto-4-methyl-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**19a**) and the 16*β* (**19b**) isomers). Anal. Calcd for $C_{28}H_{38}N_2O_3$: C, 74.63; H, 8.50; N, 6.22. Found: C, 74.52; H, 8.56; N, 6.27. Yield: 87%.

19a: ^{1}H NMR δ 7.09(d, 9 Hz, 2H); 6.82(d, 9 Hz, 2H); 5.36-(m, 1H); 5.09(m, 1H); 3.96(m, 1H); 3.76(s, 3H); 3.59(m, 1H); 3.05(m, 1H); 2.90(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.90-(s, 3H); 0.85(s, 3H).

19b: ^{1}H NMR δ 7.09(d, 9 Hz, 2H); 6.82(d, 9 Hz, 2H); 5.53-(m, 1H); 4.72(m, 1H); 3.96(m, 1H); 3.76(s, 3H); 3.59(m, 1H); 3.05(m, 1H); 2.90(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 1.02-(s, 3H); 0.90(s, 3H).

(2′-(4″-Methyl)-phenyl)-androstano-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**20a**) and the 16*β* (**20b**) isomers). Anal. Calcd for $C_{28}H_{39}NO$: C, 82.91; H, 9.69; N, 3.45. Found: C, 83.13; H, 9.59; N, 3.46. Yield: 86%.

20a: ^{1}H NMR δ 7.06(d, 8.5 Hz, 2H); 6.95(d, 8.5 Hz, 2H); 5.35(m, 1H); 5.05(m, 1H); 4.00(m, 1H); 3.58(m, 1H); 2.25(s, 3H); 1.0−2.2(m, 22H); 0.80(s, 3H); 0.75(s, 3H).

20b: ^{1}H NMR δ 7.06(d, 8.5 Hz, 2H); 6.95(d, 8.5 Hz, 2H); 5.52(m, 1H); 4.71(m, 1H); 4.00(m, 1H); 3.58(m, 1H); 2.25(s, 3H); 1.0−2.2(m, 22H); 0.90(s, 3H); 0.80(s, 3H).

(2′-(4″-Methyl)-phenyl)-(3-keto-4-methyl-4-aza-androstano)-[16,17-*e*]-3′,6′-dihydro-1′,2′-oxazine (2:1 mixture of the 16α (**21a**) and the 16*β* (**21b**) isomers). Anal. Calcd for $C_{28}H_{38}N_2O_2$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.15; H, 8.79; N, 6.42. Yield: 89%.

21a: ^{1}H NMR δ 7.06(d, 8.5 Hz, 2H); 6.95(d, 8.5 Hz, 2H); 5.36(m, 1H); 5.06(m, 1H); 4.01(m, 1H); 3.59(m, 1H); 2.25(s, 3H); 3.05(m, 1H); 2.90(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.94-(s, 3H); 0.91(s, 3H).

21b: ^{1}H NMR δ 7.06(d, 8.5 Hz, 2H); 6.95(d, 8.5 Hz, 2H); 5.52(m, 1H); 4.72(m, 1H); 4.01(m, 1H); 3.59(m, 1H); 2.25(s, 3H); 3.05(m, 1H); 2.90(s, 3H); 2.45(m, 2H); 1.0−2.2(m, 15H); 0.97-(s, 3H); 0.94(s, 3H).

21-(*N*-(4′-Hydroxy)-phenyl)-imino-pregn-17(20)-en-16-one (3.5:1 mixture of the 17.20-*Z* (**22a**) and the 17.20-*E* (**22b**) isomers). Anal. Calcd for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.70; N, 3.45. Found: C, 80.23; H, 8.58; N, 3.44. Yield: 91%.

22a: ^{1}H NMR δ 9.14(d, 9.3 Hz, 1H); 7.09(d, 8.8 Hz, 2H); 6.78(d, 8.8 Hz, 2H); 6.25(d, 9.3 Hz, 1H); 1.05−2.4(m, 22H); 0.95(s, 3H); 0.78(s, 3H). ^{13}C NMR δ 207.0; 156.5; 155.2; 147.5; 133.6; 131.5; 127.2; 127.2; 120.3; 120.3; 58.9; 53.2; 51.3; 45.0; 42.9; 42.5; 40.9; 37.5; 36.8; 35.5; 31.7; 30.9; 29.5; 26.4; 22.9; 17.6; 16.1.

22b: ^{1}H NMR δ 8.64(d, 10.0 Hz, 1H); 7.20(d, 8.6 Hz, 2H); 6.77(d, 8.6 Hz, 2H); 6.65(d, 10.0 Hz, 1H); 1.05−2.4(m, 22H); 1.09(s, 3H); 0.78(s, 3H). ^{13}C NMR δ 205.5; 154.1; 151.9; 147.3; 133.4; 129.2; 127.6; 127.6; 119.5; 119.5; 58.6; 53.7; 51.0; 46.1; 43.2; 42.1; 40.5; 37.7; 36.2; 35.1; 32.1; 31.1; 28.7; 26.7; 23.2; 17.6; 15.9.

Synthesis of (2′-Phenyl-6′-methoxycarbonyl)-androstano-[16α,17-*c*]-3′,6′-dihydro-1′,2′-oxazine (9). A mixture of **1** (1 mmol), methyl acrylate (2 mmol), $Pd(OAc)_2$ (0.02 mmol), and Et_3N (3 mmol) were reacted in DMF under argon at 60 °C. The reaction was monitored by GC. After completion of the reaction, 1 mmol of nitrosobenzene was added without isolation of the diene, and the mixture was stirred further until the cycloaddition was completed. Then the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$, washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. The product was purified by chromatography on silica gel (eluent, hexane/ethyl acetate 70/30). Anal. Calcd for $C_{29}H_{39}NO_3$: C, 77.47; H, 8.74; N, 3.12. Found: C, 77.63; H, 8.76; N, 3.11. Yield: 28%. ^{1}H NMR δ 7.1(m, 5H); 5.57(m, 1H); 4.86(m, 1H); 4.23(m, 1H); 3.83(s, 3H); 1.04−2.4-(m, 22H); 0.95(s, 3H); 0.79(s, 3H); MS *m/z* 449(1); 431(3); 416-(8); 77(10); 43(100).

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