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The remarkable influence of steroid A/B-ring junction on the Wittig olefination reaction of the 11-oxo group: Towards the synthesis of 5α- and 5β-oriented Δ^3-isomers of desogestrel

Sven Ring,* Gisela Weber,* Alexander Hillisch,‡ and Sigfrid Schwarz*

**Division of Research and Development, Jenapharm GmbH & Co.KG; and ‡Institute of Molecular Biotechnology, Jena, Germany*

*The 5α- and 5β-oriented Δ^3-double bond isomers **8, 9** of the widely used progestin desogestrel **(7)** were synthesized. Wittig olefination reaction of the 5α-intermediate **12** showed a dramatically reduced reaction rate compared with the olefination of the 5β-intermediate **13**. Computational studies suggest that different energies of the intermediary 1,2-oxaphosphetanes may, at least partially, have been the reason for this phenomenon.* (*Steroids* **63**:21–27, 1998) *© 1998 by Elsevier Science Inc.*

Keywords: desogestrel isomers; deoxygenation; Wittig olefination; computational studies

Introduction

Recently, we described a novel total synthetic approach to desogestrel **(7)**,[1] a powerful progestin widely used in oral contraception.[2] The procedure which run on a semi-technical scale, involved a reductive deoxygenation of the enone **1** to give compound **4** via the allylic methylether **2** or the thioketal **3** (Scheme 1). A shortcoming of this reaction was that, strongly dependent on various reaction parameters, the Δ^3 - double bond isomers **5** and **6** could be formed as by-products in 3% to more than 15% yield.[1] Thus, contamination, even in traces, of desogestrel **(7)** by the isomers **8, 9** must be strictly precluded by highly efficient purification processes in the course of the synthesis. For the sake of in-process control and quality assurance of the final product **7**, detection of Δ^3 - double bond isomers with a definitively established 5α- or 5β-configuration became essential for all steps following the deoxygenation reaction.

These requisites prompted us to separately synthesize the desogestrel isomers **8** and **9** via the 5α- and 5β-oriented 3,4-unsaturated steroids **5** and **6**. During our investigations, we found that selected compounds of the 5α-series differed markedly by their reaction rates from those of the 5β-series. In particular, rate differences were observed when the isomers **12** and **13** were olefinated by the Wittig reaction to yield the methylene derivatives **14** and **15**. Herein we report our results in this area.

Address reprint requests to Sigfrid Schwarz, Division of Research and Development, Jenapharm GmbH & Co.KG, Otto-Schott-Strasse 15, D-07745 Jena, Germany. E-mail: Sigfrid.Schwarz@Schering.de
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Experimental

General methods

Solvents and chemicals (Merck-Darmstadt, Fluka, Aldrich) were reagent grade and were used without further purification. Chromatography means flash chromatography which was performed on Kieselgel 60 (Merck-Darmstadt, 0.04–0.063 mm). ^{1}H nmr spectra were recorded on a Varian 300. Deuteriochloroform was used as solvent, chemical shifts were reported as δ - values in ppm downfield from tetramethylsilane as internal standard and J were given in Hz. The spectral data were recorded as δ (coupling pattern, J, proton number). Melting points were measured with a Boetius equipment. Optical rotations were taken with a Polamat A (Carl Zeiss Jena), solvent chloroform, c = 1 g/100 mL, t = +20°C. Sonification was performed by a Bandelin "Sonorex Super" DK 514 B at a frequency of 35 kHz.

Computational studies were performed using the semiempirical program VAMP 6.0[3] and the ab initio program Gaussian 94.[4] The calculations were carried out on R8000 and R10000 processors on parallel SiliconGraphics Challenge and PowerChallenge computers. Models were built with the program SYBYL.[5] All molecules were optimized with the semiempirical PM3[6] method in the

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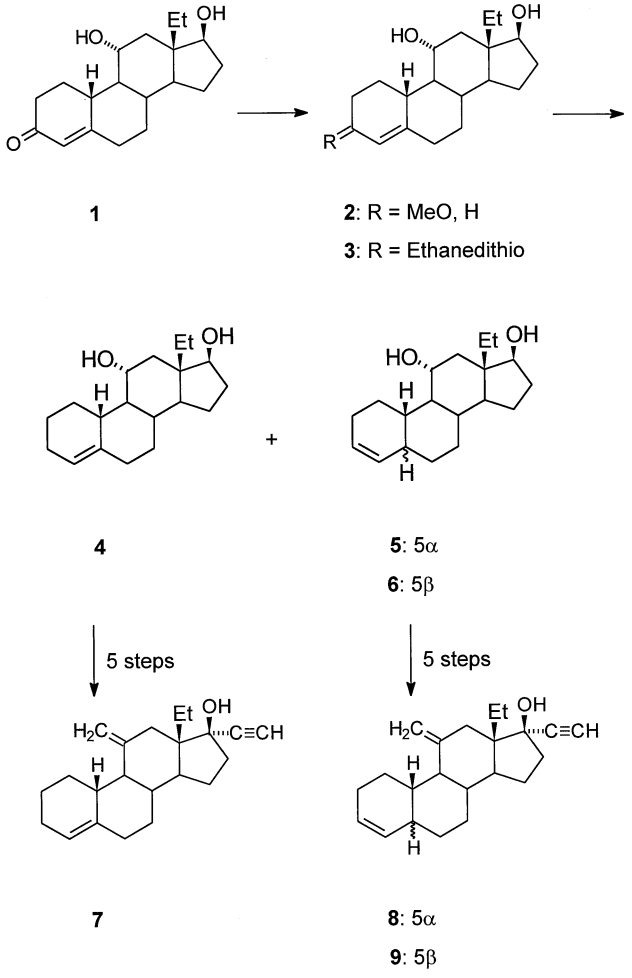


Scheme 1 Formation of 3-double bond isomers in the course of the desogestrel synthesis.

VAMP program. The Eigenvector Following optimizer was used for the energy minimizations. Molecules **12, 13** and the corresponding enolate anions: The rotatable bond of the ethyl substituent in position 13 of molecules **12** and **13** was varied in 60° steps to locate the global energy minimum for these structures. All resulting conformers were semiempirically energy optimized. The conformers with the lowest energies were subjected to a Hartree-Fock minimization, applying the 6-31G* basis set. Subsets of molecules **12** and **13** consisting of rings A, B, and C plus the ethyl group at position 13 were also energy minimized, to be comparable to the oxaphosphetane intermediates. The single point energies of the ab initio optimized molecules **12, 13**, and their corresponding enolate anions in DMSO were calculated using the Self-Consistent Isodensity Surface Model within the SCRF method.[4] 1,2-Oxaphosphetane intermediates **18** and **19**: The three rotatable bonds between the phosphorus atom and the phenyl substituents were subjected to a potential energy surface scan. Each torsion angle was varied in steps of 60°. All possible combinations were generated. The resulting conformations were energy minimized using the PM3 Hamiltonian. The conformers with the lowest potential energy were further optimized using the 6-31G* basis set and the Hartree–Fock method. The ring D and the corresponding substituents in **18** and **19** were omitted to enable calculations with larger basis sets. Each energy minimization of the oxaphosphetane intermediate ABC-ring-subsets **18** and **19** took 18 days of CPU time on one R10000 processor.

18a-Homo-5α-estr-3-ene-11α, 17β-diol **(5)** and 18a-homo-5β-estr-3-ene-11α, 17β-diol ***(6)***

Enone **1** (100 g; 328 mmol) was dissolved in acetic acid (7.5 L). Zinc dust (3 kg) was added and the suspension was ultrasonically irradiated for 1 h at 25°C. Work-up by extracting the mixture with toluene followed by rotary evaporation of the solution gave a mixture of compounds **5** and **6** in a ratio of nearly 1:2. Extensive column chromatography (eluent: toluene/ethyl acetate 3:1 v/v) followed by crystallization from ethyl acetate yielded the title compounds **5** (23 g; 24%) and **6** (43 g; 45%) in a 96–99% purity (by gc). **5:** mp. 154–159°C. $[\alpha]_D^{20} = -45°$. ^{1}H nmr: 5.62 (m, H-3), 5.39 (dd, 9.9, 2.1, H-4), 3.75 (t, 8.3, H-17), 3.69 (td, 10.2, 5.0, H-11), 1.06 (t, 7.5, H-18a). ms: m/z 290.22311 (M^+). $C_{19}H_{30}O_2$ (290.45) calculated C 78.57 H 10.41 found C 78.52 H 10.41. **6:** mp. 150–154°C. $[\alpha]_D^{20} = -23°$. ^{1}H nmr: 5.68 (m, H-3), 5.36 (d, 10.0, H-4), 3.75 (t, 8.6, H-17), 3.58 (m, H-11), 1.05 (t, 7.8, H-18a). ms: m/z 272.21438 (M^+-H_2O. $C_{19}H_{30}O_2$ (290.45) calculated C 78.57 H 10.41 found C 78.57 H 10.40.

18a-Homo-5α-estr-3-ene-11,17-dione ***(10)***

To a solution of dihydroxy steroid **5** (20 g; 69 mmol) in triethylamine (126 mL; 904 mmol) and absolute dimethyl sulfoxide (30 mL; 550 mmol) was added dropwise a suspension of pyridine-sulfur trioxide complex (60 g; 376 mmol) in absolute dimethyl sulfoxide (70 mL; 814 mmol) at 25°C. The mixture was stirred for 6 h at 25°C and then diluted with toluene (300 mL) and water (200 mL). The organic phase was separated and the aqueous solution was twice extracted with toluene (100 mL each). Rotary evaporation of the combined extracts and crystallization of the resulting product from methanol gave 14 g of the title compound **10** (70% yield). **10:** mp. 180–184°C. $[\alpha]_D^{20} = +204°$. ^{1}H nmr: 5.64 (m, H-3), 5.43 (d, 9.9, H-4), 2.67 (d, 11.9, H-12), 2.51 (dd, 19.3, 9.3, H-16), 2.28 (d, 11.9, H-12), 2.27 (dd, 19.3, 9.3, H-16), 0.81 (t, 7.5, H-18a). ms: m/z 286.19409 (M^+). $C_{19}H_{26}O_2$ (286.42) calculated C 79.68 H 9.15 found C 79.67 H 9.17.

18a-Homo-5β-estr-3-ene-11,17-dione ***(11)***

This compound was obtained analogously. Yield: 14 g **11** (70%). **11:** mp. 129–135°C. $[\alpha]_D^{20} = +161°$. ^{1}H nmr: 5.67 (m, H-3), 5.36 (d, 10.1, H-4), 2.67 (d, 12.1, H-12), 2.28 (d, 12.1, H-12), 0.81 (t, 7.1, H-18a). ms: m/z 286.19241 (M^+). $C_{19}H_{26}O_2$ (286.42) calculated C 79.68 H 9.15 found C 79.83 H 9.28.

17,17-(2,2-Dimethyl)propanedioxy-18a-homo-5α-estr-3-en-11-one ***(12)***

A mixture of dioxo steroid **10** (20 g; 70 mmol), (2,2-dimethyl)propane-1,3-diol (40 g; 384 mmol), triethylorthoformate (40 mL; 240 mmol), and p-toluenesulfonic acid monohydrate (1.2 g; 6 mmol) was stirred for 10 h at 40°C. After dilution with toluene (100 mL), the reaction mixture was subsequently washed with saturated aqueous sodium hydrogen carbonate solution (100 mL) and 5 portions of water (50 mL each). The organic phase was dried and rotary evaporated to give ketal **12** which was purified by column chromatography (eluent: toluene) and by crystallization from methanol. Chromatographically recovered dioxo steroid **10** was recycled. Yield in total: 20.3 g **12** (78%). **12:** mp. 167–171°C. $[\alpha]_D^{20} = +112°$. ^{1}H nmr: 5.62 (m, H-3), 5.41 (d, 9.8, H-4), 3.63 (d, 11.0, -OCH_2C-), 3.36 (q, 10.5, -OCH_2C-), 2.78 (d, 11.6, H-12), 2.51 (d, 11.6, H-12), 1.09 (s, -CH_3), 1.01 (t, 7.2, H-18a), 0.72 (s, -CH_3). ms: m/z 372.26779 (M^+). $C_{24}H_{36}O_3$ (372.55) calculated C 77.38 H 9.74 found C 77.37 H 9.85.

17,17-(2,2-Dimethyl)propanedioxy-18a-homo-5β-estr-3-en-11-one ***(13)***

This compound was obtained analogously with the exception that the reaction required 6 hours for a quantitative transformation into ketal **13**. Yield in total: 20.03 g **13** (77%). **13:** mp. 160–164°C. $[\alpha]_D^{20} = +69°$. ^{1}H nmr 5.63 (m, H-3), 5.34 (d, 10.3, H-4), 3.64 (d, 11.0, -OCH_2C-), 3.36 (q, 10.5, -OCH_2C-), 2.76 (d, 12.1, H-12), 2.51 (d, 12.1, H-12), 1.09 (s, -CH_3), 1.01 (t, 7.2, H-18a), 0.72 (s, -CH_3). ms: m/z 372.26730 (M^+). $C_{24}H_{36}O_3$ (372.55) calculated C 77.38 H 9.74 found C 77.35 H 9.65.

17,17-(2,2-Dimethyl)propanedioxy-11-methylene-18a-homo-5α-estr-3-ene ***(14)***

Methylene triphenylphosphorane was generated from methyl triphenylphosphonium iodide (166.2 g; 413 mmol) and sodium hydride (12.4 g, 80% in oil; 413 mmol) in absolute dimethylsulfoxide (300 mL). A solution of ketal **12** (15.38 g; 41 mmol) in toluene (100 ml) was dropped to the ylide and the resulting mixture was allowed to react for 108 h at 80°C with ultrasonical irradiation. After cooling to 25°C, the reaction was quenched by cautious addition of water (20 mL). The mixture was extracted with cyclohexane (3 times 200 mL). The combined organic phases were dried and rotary evaporated to give compound **14** which was purified by column chromatography (eluent: cyclohexane) and by crystallization from acetone. Yield: 9.55 g **14** (62.3%). mp. 144–153°C. $[\alpha]_D^{20} = +66°$. ^{1}H nmr: 5.63 (m, H-3), 5.47 (dd, 9.6, 2.2, H-4), 4.92 (s, $=CH_2$), 4.64 (s, $=CH_2$), 3.60 (d, 11.3, -OCH_2C-), 3.37 (m, -OCH_2C-), 2.45 (d, 12.6, H-12), 2.32 (d, 12.6, H-12), 1.12 (s, -CH_3), 0.99 (t, 7.2, H-18a), 0.72 (s, -CH_3). ms: m/z 370.28720 (M^+). $C_{25}H_{38}O_2$ (370.58) calculated C 81.03 H 10.34 found C 81.18 H 10.40.

17,17-(2,2-Dimethyl)propanedioxy-11-methylene-18a-homo-5β-estr-3-ene ***(15)***

Compound **13** (24.48 g; 65 mmol) dissolved in toluene (50 mL) was analogously allowed to react with methylene triphenylphosphorane generated from methyl triphenylphosphonium iodide (84.54 g; 210 mmol) and sodium hydride (5.9 g, 80% in oil; 197 mmol) in absolute dimethylsulfoxide (150 mL). After 1 h the olefination was complete (tlc). Work-up, column chromatography, and crystallization gave 15.8 g of the title compound **15** (65% yield). **15:** mp. 142–146°C. $[\alpha]_D^{20} = +9°$. ^{1}H nmr: 5.61 (m, H-3), 5.35 (d, 10.2, H-4), 4.91 (s, $=CH_2$), 4.75 (s, $=CH_2$), 3.60 (d, 11.4, -OCH_2C-), 3.40 (d, 11.4, -OCH_2C-), 3,34 (m, -OCH_2C-), 2.44 (d, 12.2, H-12), 2.32 (d, 12.2, H-12), 1.12 (s, -CH_3), 0.99 (t, 7.3, H-18a), 0.71 (s, -CH_3). ms: m/z 370.28640 (M^+). $C_{25}H_{38}O_2$ (370.58) calculated C 81.03 H 10.34 found C 81.07 H 10.29.

11-Methylene-18a-homo-5α-estr-3-en-17-one ***(16)***

To a solution of (trimethylsilyl)methyl lithium in *n*-pentane (170 mL; 170 mmol) was added a solution of compound **12** (20 g; 53 mmol) in toluene (120 mL) with stirring at 30°C. The reaction which was complete after 15 min (tlc), was quenched by addition of saturated aqueous ammonium chloride solution with cooling. The organic layer was separated, washed with water until neutral and evaporated. The resulting 11α-(trimethylsilyl)methyl-17,17-(2,2-dimethyl)propanedioxy-18a-homo-5α-estr-3-en-11β-ol was dissolved in acetone, concentrated aqueous hydrochloric acid (1.5 mL) was added, and the mixture was stirred for 1 h at 40°C. Thereafter, the solution was neutralized with saturated aqueous sodium hydrogen carbonate solution and evaporated. The residue obtained was dissolved in toluene, the solution was washed with water and evaporated to give the title compound **16** which was purified by chromatography (eluent: toluene: ethyl acetate 10:1 v/v) and crystallization from methanol. Yield: 10.07 g **16** (66%). **16:** mp. 94–98°C. $[\alpha]_D^{20} = +158°$. ^{1}H nmr: 5.65 (m, H-3), 5.48 (dq, 9.9, 1.9, H-4), 4.89 (s, $=CH_2$), 4.74 (s, $=CH_2$), 2.57 (d, 12.8, H-12), 1.84 (d, 12.8, H-12), 0.76 (t, 7.7, H-18a). ms: m/z 284.21384 (M^+). $C_{20}H_{28}O$ (284.45) calculated C 84.45 H 9.92 found C 84.50 H 9.94.

11-Methylene-18a-homo-5β-estr-3-en-17-one ***(17)***

This compound was obtained analogously. Yield: 11.6 g **17** (76%). **17:** mp. 89–91°C. $[\alpha]_D^{20} = +93°$. ^{1}H nmr: 5.66 (m, H-3), 5.38 (d, 9.8, H-4), 4.88 (d, 1.4, $=CH_2$), 4.85 (d, 1.4, $=CH_2$), 2.56 (d, 12.4, H-12), 2.40 (dd, 19.4, 7.7, H-16) 1.86 (d, 12.6, H-12), 0.75 (t, 7.7, H-18a). ms: m/z 284.21460 (M^+). $C_{20}H_{28}O$ (284.45) calculated C 84.45 H 9.92 found C 84.65 H 9.91.

11-Methylene-5α, 17α-18a-homo-19-nor-pregn-3-en-20-in-17-ol ***(8)***

The protocol described in ref. 1 for the ethinylation of 11-methylene-18a-homo-estr-4-en-17-one was used to give title compound **8** in a 56% yield. **8:** mp. 105–108°C. $[\alpha]_D^{20} = +42°$. ^{1}H nmr: 5.64 (dq, 9.8, 3.0 H-3), 5.48 (dq, 9.8, 2.2, H-4), 4.95 (s, $=CH_2$), 4.68 (s, $=CH_2$), 2.62 (s, -C≡CH), 2.61 (d, 11.9, H-12), 2.28 (d, 11.9, H-12), 1.04 (t, 7.2, H-18a). ms: m/z 310.22909 (M^+). $C_{22}H_{30}O$ (310.48) calculated C 85.11 H 9.74 found C 85.24 H 9.91.

11-Methylene-5β, 17α-18a-homo-19-nor-pregn-3-en-20-in-17-ol ***(9)***

The protocol described in ref. 1 for the ethinylation of 11-methylene-18a-homo-estr-4-en-17-one was used to give title compound **9** in a 79% yield. **9:** mp. 98–99°C. $[\alpha]_D^{20} = -31°$. ^{1}H nmr: 5.68 (dq, 9.8, 3.2 H-3), 5.38 (d, 9.8, H-4), 4.94 (d, 1.5, $=CH_2$), 4.79 (s, $=CH_2$), 2.63 (s, -C≡CH), 2.60 (d, 12.4, H-12), 2.27 (d, 12.6, H-12), 1.42 (q, 7.3, H-18), 1.03 (t, 7.3, H-18a). ms: m/z 310.23098 (M^+). $C_{22}H_{30}O$ (310.48) calculated C 85.11 H 9.74 found C 85.21 H 9.68.

Results

Initially, we focused on an effective large-scale preparation of 5α-compound **5** and 5β-compound **6** from the hydroxy enone **1.** Among methods which have been used to prepare steroid 3-olefins from 4-en-3-oxo steroids are Wolff–Kishner reductions and the reduction with zinc in acetic acid. Wolff–Kishner reduction of cholest-4-en-3-one, using hydrazine with sodium ethoxide in ethanol or with potassium hydroxide in diethylene glycol reportedly gave a mixture of 5α- and 5β-cholest-3-enes appreciably contaminated with cholest-4-ene. Isolation of the Δ^3-double bond isomers was accomplished by a laborious bromination, chromatography, and debromination procedure.[7] Due to these disadvantages, the reduction of compound 1 using zinc in acetic acid[8] was considered to be the method of choice, though a high excess of zinc is needed which may be a drawback when working on a larger scale (stirring problems and production of a highly pyrophorous zinc waste). Nevertheless, high yields of pure 3-ene steroids have been reported with different 4-en-3-oxo steroids.[8,9] To this end, we treated compound **1** with a thirtyfold excess of zinc (by weight) in acetic acid for

1 hour at 30°C (Scheme 2). The processing clearly benefited from sonification.[9] After work-up the product was shown by glc to be a mixture consisting of **5** (30.5%), **6** (64.5%), **4** (3%), and three less polar species (in total 2%; probably acetates). The mixture was separated by chromatography on silica gel affording **5** (24% yield) and **6** (45% yield). The C-5 stereochemistry of both products was established retrospectively, but rigorously, by x-ray diffraction analysis (vide infra).

Continuing in line with our previously reported desogestrel synthesis,[1] compounds **5** and **6** were oxidized by the Parikh–Doering procedure[10] (Scheme 2) to give the diketones **10** and **11** (70% yield each) which were allowed to react with 2,2-dimethylpropane-1,3-diol, triethylorthoformate and a catalytic amount of *p*-toluenesulfonic acid. Within 6 h, the 5β-compound **11** was transformed quantitatively into the 17-ketal **13** (77% isolated yield), whereas, under the same reaction conditions, the 5α-compound **10** showed a merely 65% formation of ketal **12** after 10 h. A 78% isolated yield of ketal **12** was obtained after repeated ketalization of recycled starting material. A different behaviour of the diketones **10** and **11** with respect to the regiospecificity of ketal formation was not observed.

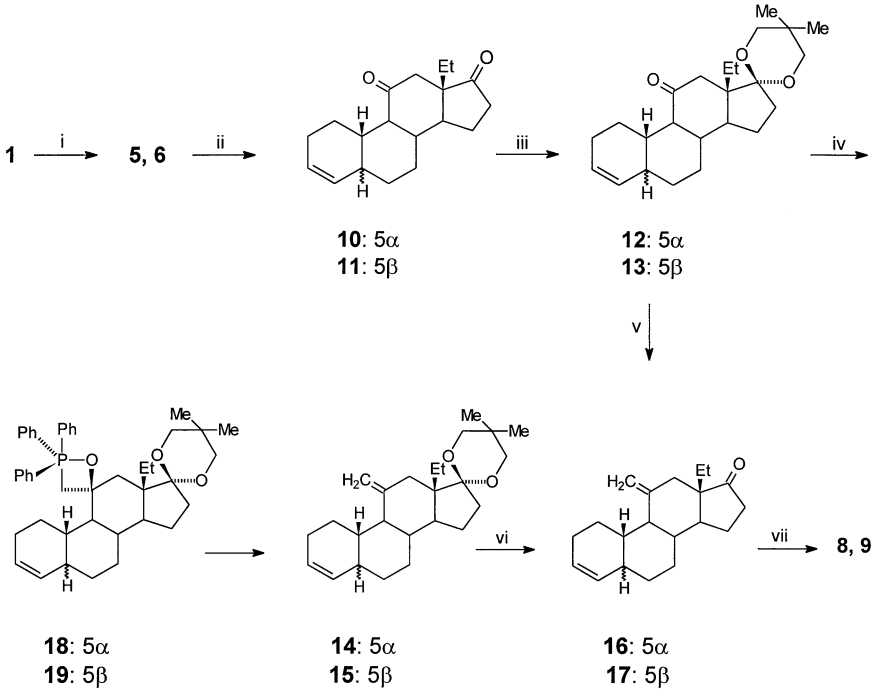
The following Wittig olefination reaction with oxo ketals **12** and **13** (Scheme 2) was performed in the presence of ultrasound.[1] In spite of this accelerating modification the reaction rates of 5α- ketal **12** and 5β-ketal **13** proved to be dramatically different. When the 5β-ketal **13** was treated with 3.15 equiv. methylene triphenylphosphorane in dimethylsulfoxide at 80°C, a quantitative transformation into the corresponding 11-methylene steroid **15** occurred after 1 h (65% yield upon isolation and crystallization). However, using 5α-ketal **12**, a quantitative transformation into the methylene steroid **14** required 10 equiv. of ylide and a reaction time of 108 h (61% yield upon isolation and crystallization).

In continuation, the olefinated ketals **14** and **15** obtained by the Wittig reaction were deprotected using *p*-toluenesulfonic acid in acetone to give the ketones **16** and **17** (Scheme 2). More conveniently, the bulk of **16** and **17** was obtained by the Peterson olefination reaction of compounds **12** and **13**. As final steps of the title synthesis the ketones **16** and **17** were subjected to ethinylation by lithium acetylide/ethylenediamine following the protocol described earlier[1] (Scheme 2). In this way, compounds **8** and **9** were obtained in a 56% and 79% yield respectively.

The A/B ring junctions belonging to the compounds described in this paper have been elucidated by x-ray analysis. For crystallographic reasons the final intermediates **16** and **17** were selected for the measurements. Compound **16** showed a 5α-configuration (Fig. 1) and compound **17** proved to be 5β-oriented (Fig. 2). These results retrospectively allowed to define the A/B ring junctions belonging to series **5, 10, 12, 14, 16, 8** on the one hand and **6, 11, 13, 15, 17, 9** on the other hand.

Discussion

The reason for the dramatic difference between the 11-oxo steroids **12** and **13** to undergo olefination with methylene triphenylphosphorane was not obvious. In principle, the low reactivity of compound **12** towards the Wittig reagent may



Scheme 2 Formation of title compounds **8, 9** from hydroxy enone 1. i: Zn, AcOH, chromatography; ii: DMSO, NEt_3, Py-SO_3; iii: (2,2-dimethyl)propane-1,3-diol, triethylorthoformate, TsOH; iv: $Ph_3P^{(+)}Me\ I^{(-)}$, NaH, DMSO, PhMe,)))); v: 1. Me_3SiCH_2-Li, n-pentane, 2. HCl, acetone, H_2O, 40°C; vi: : p-TsOH, acetone; vii: ethine, Li, ethylenediamine, THF.

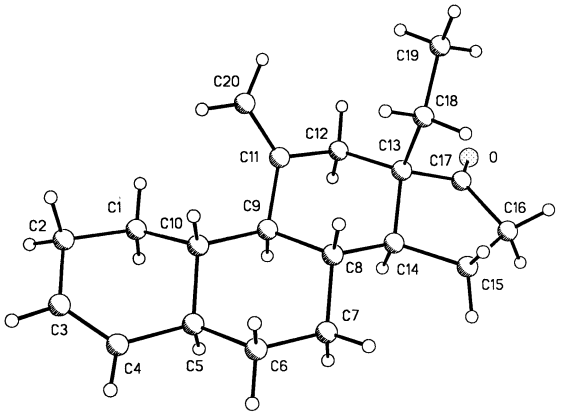


Figure 1 Crystal structure of 11-methylene-18a-homo-5α-estr-3-en-17-one **(16)** (crystallographic numbering).

have been due to steric shielding of the 11-oxo group from the α- as well as from the β-side of the steroid molecule. However, steric hindrance was considered unlikely, since ring C of both the compounds **12** and **13** should be equally accessible from the β-side. In the case of an α-approach ring C of compound **13** would be expected to be the more hindered.[11] Indeed, when the oxo steroids **12** and **13** were subjected to the Peterson olefination reaction[12] (Scheme 2), they reacted equally fast: conversion into the two isomeric methylene ketones **16** and **17** via the corresponding 11-(trimethylsilyl)methyl carbinols was complete after 15 min at 30°C (nearly quantitative yield each). Semiempirical PM3 calculations also suggested no energetical preference of the intermediary 5α- over the 5β-11-(trimethylsilyl)methyl carbinols. The energy difference between these two reaction intermediates is the same as calculated for **12** and **13** (see Table 1). This indicates that the 11-oxo group of **12** and **13** is comparably accessible for the reaction with trimethylsilylmethyl-lithium. Thus, we concluded that the retarded Wittig reaction of compound **12** was not caused by steric hindrance of the 11-oxo group.

Next, we focused on the preferred ylide mediated 11-oxo group enolization of compound **12** versus compound **13**. Several unsuccessful attempts have been reported to attack the 11-oxo group of 5α-pregnane derivatives with nuleophiles[13,14,15] which, in one analogous case, was suggested to be due to exclusive enolization of the 11-oxo group. On the other hand, a structurally comparable compound, showing a 5β-configuration, was much less prone to enolization using the same reaction conditions.[16] However, since effective nucleophilic reactions with 11-oxo steroids have also been shown not to be influenced by their A/B-ring core,[17] detailed structural factors involved in more or less smooth enolization of 11-oxo groups remain undefined as yet. To investigate the tendency of enolization of compounds **12** and **13** the potential energies of the keto and the enolate anion forms were calculated and compared. The semiempirically determined starting geometries were minimized using the ab initio HF 6-31G* method. The single point energies of the resulting minimum structures were computed in DMSO as solvent.[4] The energy difference between the two keto forms **12** and **13** (−1.35 kcal/mol in vacuo, −1.32 kcal/mol in DMSO) and the enolate anion forms (−2.08 kcal/mol in vacuo, −2.11 kcal/mol in DMSO) was −0.73 kcal/mol in vacuo, respectively −0.79 kcal/mol in DMSO (see Table 2). The energetic preference of the 5β-enolate anion of approximately 0.8 kcal/mol over the 5α-enolate anion is considered not to be sufficient to explain the big difference in the reaction time solely.

A higher energetic burden in the formation of the 5α-oriented oxaphosphetane Wittig reaction intermediate versus the corresponding 5β-species might be another explanation for the different olefination reaction rates. It was found by the low-temperature nmr studies of Vedejs et al. that pentacoordinate 1,2-oxaphosphetanes were in situ intermediates in the Wittig olefination reaction which decomposed to give the corresponding olefins.[18] Reactions at C-11 of estrane and 18a-homo estrane derivatives which were passing a four-membered transition state were shown to proceed almost exclusively from the rear side of the molecule.[19,1] Hence, in our case, oxaphosphetanes resulting from methylene triphenylphosphorane attack at the 11-oxo groups of compounds **12, 13** were suggested to have structures **18** and **19** (Scheme 2). Ab initio molecular orbital

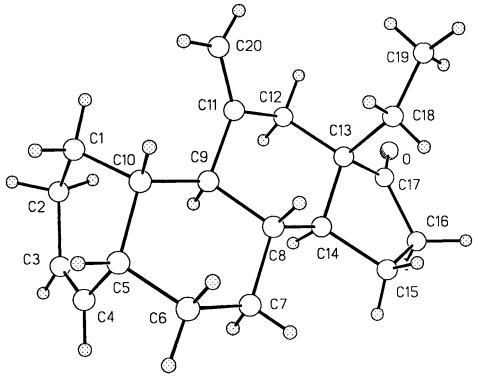


Figure 2 Crystal structure of 11-methylene-18a-homo-5β-estr-3-en-17-one **(17)** (crystallographic numbering).

Table 1 Energies of **12, 13, 18**, and **19** Calculated with ab initio and Semiempirical Methods

Compound	E [kcal/mol] HF 6-31G*	E [kcal/mol] PM3
12	−435957.75	−146.38
13	−435956.33	−145.28
18	−1107419.33	−35.97
19	−1107419.42	−36.11

Table 2 Ab initio Calculated Potential Energies of the Keto and Enolate Anion Forms of Compounds **12** and **13**

Compound	E [kcal/mol] in vacuo	E [kcal/mol] in DMSO
12	−724388.03	−724391.52
13	−724386.68	−724390.20
12 enolate anion	−723995.20	−724025.65
13 enolate anion	−723993.12	−724023.54

calculations were carried out to investigate this explanation for the differing reaction times. The potential energies for the educts **12/13** and the intermediates **18/19** in the Wittig olefination were calculated. The energy difference between molecules **12/13** (−1.42 kcal/mol) and the 5α-/5β-intermediates **18/19** (+0.09 kcal/mol) was −1.51 kcal/mol (see Table 1). This indicates an energetic preference of 1.51 kcal/mol of the 5β-oxaphosphetane intermediate over the corresponding 5α-intermediate. Steric repulsion between the axial proton at C-2 of ring A and one of the phosphorus-bound phenyl group of oxaphosphetane **18** led to a slightly different and energetically less favorable position of the four-ring system and the phenyl substituents compared to the 5β-fused oxaphosphetane **19** (see Fig. 1). Since the 5α-oriented 1,2-oxaphosphetane intermediate **18** adopted a less favorable conformation, a steric hindrance in the formation of the 5α-intermediate **18** vs. the corresponding 5β-intermediate **19** seemed to be possible. But care should be taken with the interpretation of the calculations, since not the whole potential energy surface, resulting from the three rotatable bonds at the phenyl substituents, could be calculated with ab initio methods. Even the smallest 1,2-oxaphosphetane-intermediate fragments, consisting of at least 78 atoms (37 non-hydrogen and 41 hydrogen atoms), are too big to be applicable to ab initio conformational searches. To ensure a sufficient sampling of conformational space, instead a semiempirical conformational search was performed. The energetically most favorable conformations from this systematic conformational search were further investigated by ab initio methods. Since ring D and the corresponding substituents were the same in molecules **18** and **19** and not in direct contact to the phenyl substituents, these molecule parts were omitted from the ab initio calculations. These HF/6-31G* calculations were only feasible by reducing the number of atoms in the system and calculating a subset of the molecules, consisting of rings A, B, C and the ethyl group. Neither the conformations nor the energy differences of the ab initio calculations (−1.51 kcal/mol) differed greatly from the PM3 calculations (−1.24 kcal/mol). This suggests that the PM3 results are approximately comparable to the ab initio calculations and that the semiempirical systematic conformational search resulted in relevant energy minimum structures for the intermediates. The potential energy values for **12, 13, 18** and **19**, as printed out by Gaussian 94[4] and VAMP[3], are shown in Table 1. The values listed for the HF 6-31G* method have been calculated for the ABC-ring subsets. A superposition of the lowest energy conformers of the ABC-ring subsets of compounds **18** (black) and **19** (grey) is depicted in Fig. 3. The molecules were fitted at the 10 carbon atoms in the B and C ring.

As a summing-up, our efforts to find out why the 11-oxo steroids **12** and **13** showed such dramatic differences in the Wittig olefination reaction rates, gave an incompletely satisfying answer only. Attempts to get insight into this phenomenon by computational studies suggested that different enolization or enolate formation rates of the 11-oxo groups in question were obviously less important. Ab initio molecular orbital calculations showed that an unfavorable geometry of the 1,2-oxaphosphetane intermediate **18** may have participated in the slower olefination reaction of oxo steroid **12** in comparison to oxo steroid **13**. However, whether the calculated energy difference between molecules **12/13** and **18/19** of 1.51 kcal/mol may be the sole, reasonable explanation for the dramatic reaction rate difference, remains questionable. Hence, further studies have to be done in this field.

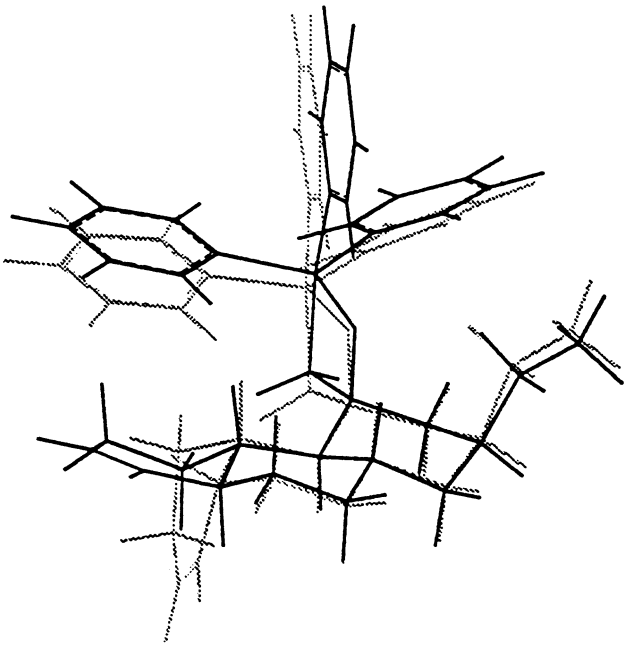


Figure 3 Superposition of energy minimum structures of **18** and **19**.

In conclusion, we have been studying the synthesis of the 5α- and 5β-oriented 3-unsaturated analogs **8, 9** of the progestin desogestrel **(7)**. The Wittig olefination reaction of the intermediates **12** and **13** showed a dramatically reduced reaction rate of the 5α-isomer **12** versus the 5β-isomer **13**. Computational studies suggest that different energies of the 1,2-oxaphosphetane intermediates may, at least partially, have been the reason for this phenomenon. The structural assignment of the 5α- and the 5β-oriented compounds was performed on the basis of x-ray analysis.

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