0,20, 0,43, 0,57, 0,60, 0,55, 0,47, 0,32, 0,21, 0,12 und 0,03. Der Wert $E = 0{,}60$ nach 35 Min. entspricht einem ε von 1800.

3.2.2. *Thermolyse von* **3e**: 2,3 mg **3e** wurden in 75 ml siedendem Dioxan gelöst und unter Argon unter Rückfluss gekocht. Proben nach 4, 14, 24, 34, 44, 59, 74, 89, 104, 134, 194, 254 und 334 Min. sowie nach 22,5 Std. ergaben die folgendcn E-Werte bei 374 nm: 0,13, 0,28, 0,36, 0,41, 0,46, 0,46, 0,45, 0,45, 0,44, 0,42, 0,39, 0,37, 0,34, 0,23. Der Wert $E = 0{,}46$ nach 44 Min. entspricht einem ε von 2500. Nach 22,5 Std. ($E = 0{,}23$) zeigte das UV.-Spektrum eine von hoher nach kurzer Wellenlänge ansteigende Kurve ohne eigentliche Maxima.

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136. C(10)-Methylation of Steroidal Synthesis Intermediate BCD-Tricyclic 9-En-5-ones[1])

by **John W. Scott**[2]), **Paul Buchschacher, Ludwik Labler, Werner Meier** and **Andor Fürst**

Chemical Research Department, *F. Hoffmann-La Roche and Co., Ltd.*, Basle 4002, Switzerland

(18. XII. 73)

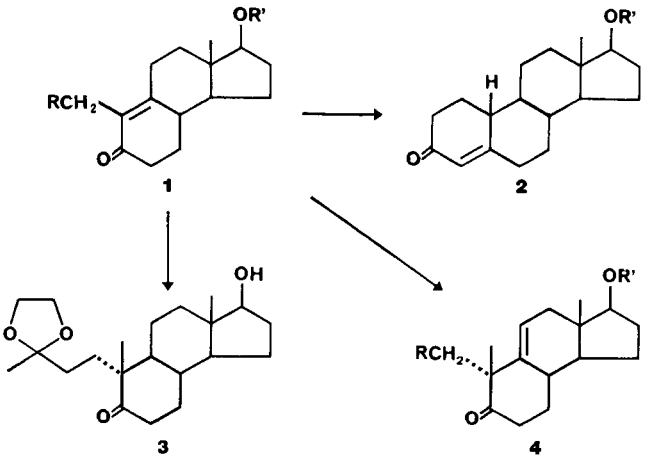
Summary. A literature survey indicated that *stereospecific* non-reductive β-face methylation at C(10) of steroidal synthesis intermediate BCD-tricyclic 9-en-5-ones had never been effected. An attempt to define the factors controlling the β/α product ratio in such alkylations was made. The course of methylation is significantly affected by the temperature. In the best case, methylation of the sodium enolate of 17β-*t*-butoxy-19-(3,5-dimethyl-4-isoxazolyl)-deA-androst-9-en-5-one (**18**) in tetrahydrofuran at $-78°$ gave a β/α product ratio of $>5:1$. The reaction mixture contained no unalkylated or dialkylated materials, indicating that enolate exchange probably did not occur

[1]) Dedicated with affection and esteem to Professor *Pl. A. Plattner* on the occasion of his 70th birthday.

[2]) Correspondence concerning this article should be directed to this author at *Hoffmann-La Roche Inc.*, Nutley, N. J., 07110, USA.

at this temperature. The 10β-methylated product **23**, isolated in 78% yield, was converted to $\Delta^{9(11)}$-dehydrotestosterone (**29**). Compounds **23** and **29** are potential intermediates for the synthesis of 11-oxygenated steroids.

Introduction. – During the last few years, a number of syntheses of 19-nor-steroids (*e.g.* **2**) having, as a key feature, the intermediacy of the deA-androst-9-en-5-ones **1** (R = ring A precursor) have been described [1–9]. With the ready availability

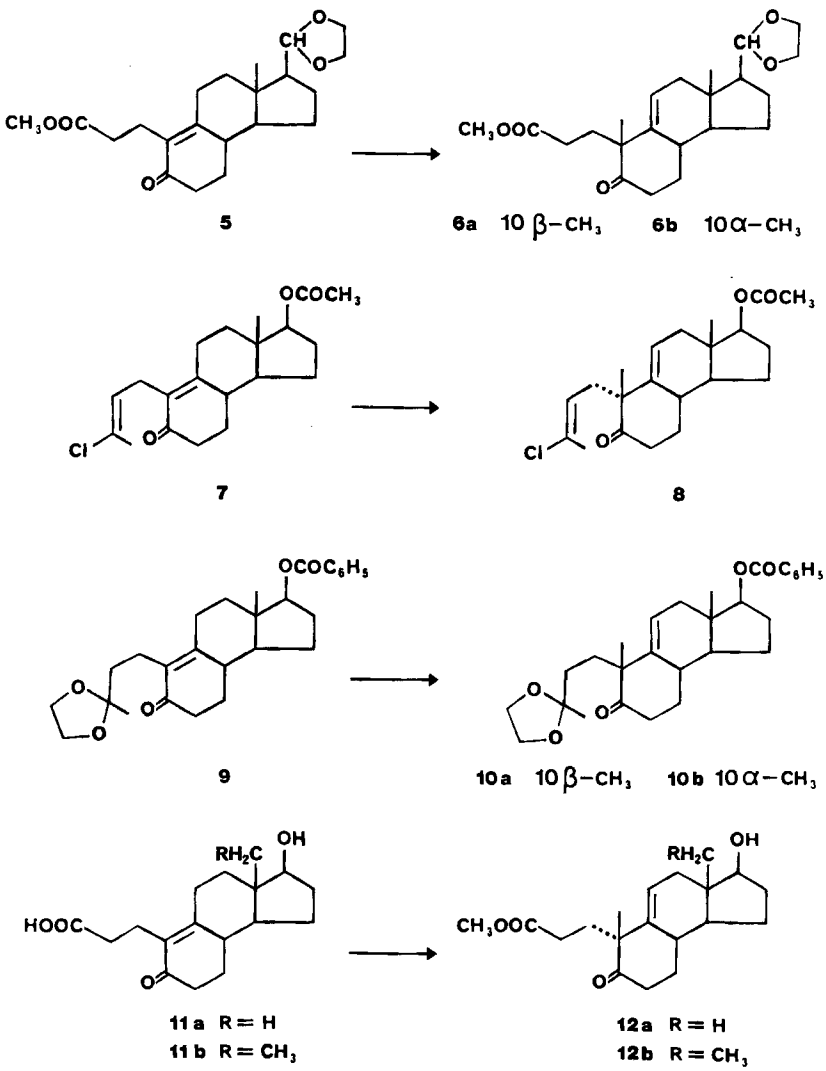


of these compounds, we have turned out attention to their use as starting materials for the preparation of "normal"-steroids (*i.e.*, containing the C(19)-methyl group), including corticoids.

A major problem with the desired conversion of the enones **1** to normal steroids is the stereospecific introduction of the C(19)-methyl group. Conceptually, there are a number of ways in which this could be done. However, only two of these are simple, one-step procedures and thus of practical significance. The first involves reductive methylation of the enone **1**. This reaction, first carried out by *Stork* & *McMurry* [10] [11] on the D-homo analogue of **1** (R' = H, R = $CH_2\overset{\overset{O}{\diagdown}}{\underset{\underset{O}{\diagup}}{C}}CH_3$), gave only β-methylated product (yield = 90%). The reaction has recently been employed by workers at *Roussel-Uclaf* [12] to prepare ketone **3**. Although these authors gave no discussion of the stereochemical outcome to the reaction, it was also very likely highly stereoselective, if not stereospecific.

Reductive methylation is an excellent solution to the problem of introducing C(19). However, for the preparation of corticoids, the additional problem of introducing an oxygen function at C(11) must be solved. In ketones such as **3** there is no handle for this purpose and one would have to rely on a microbiological oxidation. However, methylation of the enone **1** could lead to the $\Delta^{9(11)}$-5-ketone **4**. The latter compound, after conversion into a tetracyclic ketone of type **29**, could then be functionalized at C(11) by means of known methods [13] [14a] [15]. In addition, catalytic hydrogenation of the $\Delta^{9(11)}$-double bond is known [16] to give steroids of natural configuration.

Scheme 1

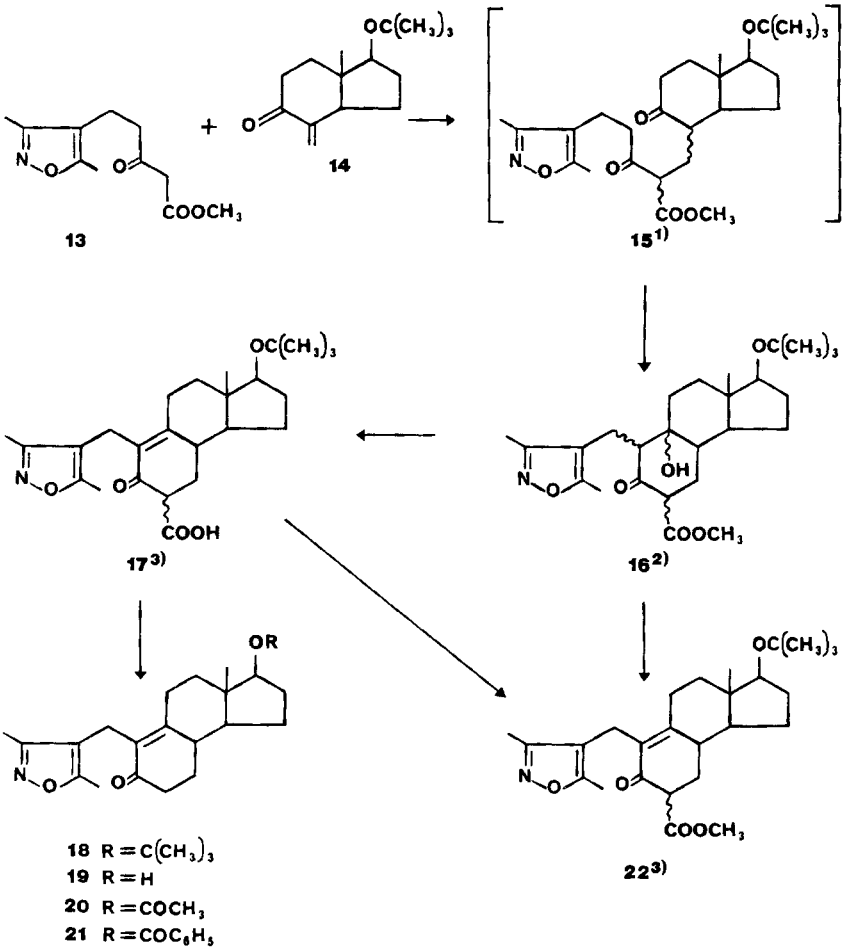


Direct methylation, then, would appear to be a more general method of introducing C(19). This is useful, however, only if methylation occurs exclusively on the β-face of the molecule. There have been several previous attempts to effect this specific alkylation. These are outlined in *Scheme 1*. In the first reported alkylation of a Δ^9-5-one with a 5-membered D-ring[3]), *Barkley et al.* [17] treated the enone **5** with potassium *t*-butoxide in *t*-butanol/benzene, followed by methyl iodide. The product was an oily mixture containing the 10β- and 10α-methylated products **6a**, **b** in a

[3]) There have been a number of studies of similar methylations in cases in which ring D was 6-membered. Since it was reported [17] that methylation was more selective when ring D was 5-, rather than 6-membered, this literature survey includes only the 5-carbon ring D cases.

ratio of *ca.* 2:1. Methylation of enone **7** with methyl iodide and sodium *t*-amylate in toluene was reported in a patent [18] to afford the 10β-methyl ketone **8**. However, neither yield nor any indication as to stereochemical purity was given. *Velluz et al.* [14a] [14b] [19] have methylated the enone **9** using the same base/solvent pair. The 10β-methyl ketone **10a** was isolated as the sole product in 65% yield. In a patent [14c] it is claimed that this methylation method yields only the 10β-methyl product **10a**. Recently, the methylation of enone **9** was reinvestigated in *Stork*'s laboratories [11]. Under a variety of reaction conditions (including those reported in [14c]) methylation of enone **9** gave a *ca.* 3:1 mixture of products **10a** and **10b**, as shown by NMR. Methylation of the acids **11** to the compounds **12**, using an excess of sodium

Scheme 2



[1]) Not isolated.
[2]) Mixture of stereoisomers at C(6) and possibly at C(9) and/or C(10) (steroid numbering).
[3]) Mixture of stereoisomers at C(6) (steroid numbering).

hydride in dimethylformamide and methyl iodide have also been reported. From **11a** *Vida* & *Gut* [20] obtained an oil in 85% yield, which appeared uniform on a thin layer chromatogram. However, no proof of stereospecificity of the reaction was given. According to a patent [21] **12b** was isolated in *ca.* 70% yield from **11b**.

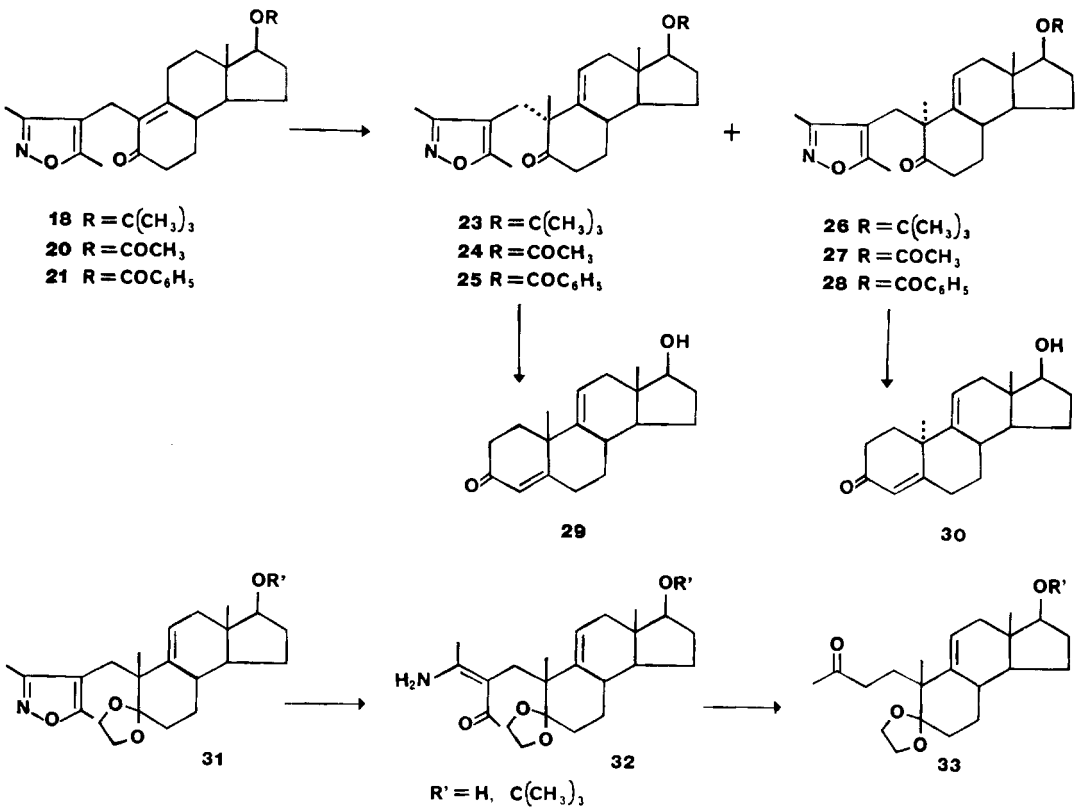
It seemed worthwhile to reinvestigate the problem of angular methylation of the Δ^9-5-ones **1**. We thus decided to study the effect of the reaction conditions on the steric course of such methylations.

Results and Discussion. – We chose to initiate our work with 3,5-dimethylisoxazole-substituted deA-androst-9-en-5-ones **18**, **20** and **21** (*Scheme 2*) for several reasons: our previous experience with these compounds [4], their availability (*vide infra*), and the fact that the products of methylation were expected to be stable, crystalline compounds, which would aid in their isolation and separation. We have previously described [4] a synthesis of compounds **18** and **19**. In *Scheme 2* we present an alternative synthesis of these materials based on the elegant work of *Hajos* & *Parrish* [9]. The β-keto ester **13** was prepared in 45% yield by alkylation of the dianion of methyl acetoacetate [22] with 4-chloromethyl-3,5-dimethylisoxazole [23]. Condensation of this material with the optically-active methylene ketone **14** [24] in the presence of base led, *via* intermediates **15** and **16**, to the acid **17**, which readily decarboxylated on warming to give the tricyclic enone **18** in an overall yield of 65%. *Hajos* & *Parrish* were able to isolate an uncyclized β-keto ester analogous to structure **15**. We have tried to isolate the diketo ester **15** from the addition of **13** to **14**. In our case, however, a mixture of ketols **16** and a by-product, the enone **18**, were obtained. The structure of **16** was confirmed by spectral means and by phosphorous oxychloride dehydration to the same mixture of esters **22** that was obtained by treatment of the acid **17** with diazomethane. Acetylation and benzoylation of **19** (prepared through hydrolysis of **18**) in the usual manner gave esters **20** and **21**.

A description of the methylation of compounds **18**, **20** and **21** is outlined in *Scheme 3*. We first looked at the methylation of these three compounds under standard conditions. The enones were treated with sodium hydride in 1,2-dimethoxyethane (glyme) at reflux and then methylated with methyl iodide at 0°. Work up, followed by reacylation of the crude reaction mixtures from the acetate **20** and the benzoate **21**[4]) gave non-crystalline resins which were analysed by GC. In each case, two major products, in the ratio 2.4:1, were present, along with small amounts of starting material and less-polar, possibly dimethylated products. The mixture from the 17β-*t*-butoxy enone **18** was readily separated into the 10β-methyl ketone **23** (major) and 10α-methyl ketone **26** (minor) by column chromatography. The structures of these compounds were indicated by their spectral characteristics and were confirmed by their conversion to $\Delta^{9(11)}$-dehydrotestosterone (**29**) [25] and 10α-$\Delta^{9(11)}$-dehydrotestosterone (**30**) [26], respectively. These conversions were effected by our previously-described [27] method for the transformation of a 3,5-dimethylisoxazole to the steroid ring A. Thus, the ketones **23** and **26** were separately acetalized to give mixtures of 17β-hydroxy and 17β-*t*-butoxy acetals **31**. These acetals were hydrogenated over Pd/C in ethanolic sodium hydroxide solution. The resulting vinylogous amides **32** were heated at reflux with aqueous base to give the keto acetals **33**. Heating these

[4]) TLC. had shown that 10–20% deacylation had occurred during reaction.

Scheme 3



materials with methanolic hydrochloric acid and then with p-toluenesulfonic acid in benzene (to complete the cleavage of the *t*-butyl ether group) gave the desired steroids. The yields of **29** and **30** (based on **23** and **26**) were 53 and 37%[5]), respectively.

Separation of the reaction mixtures from the methylations of the acetate **20** and the benzoate **21** was not so successful as with the *t*-butyl ethers. In these cases, only the major components **24** and **25** could be isolated in pure form. The structures of these compounds were assigned on the basis of the fact that they were the major products, that they were the first eluted on GC. (as was **23**), and by comparison of their NMR. spectra with that of ketone **23**. In particular, the *AB* signals for the isoxazole-CH_2 protons were instructive. For the 10β-compounds **23**, **24**, and **25**, $\Delta\nu_{AB}$ was only 7.5 Hz, while for the 10α-compound **26**, $\Delta\nu_{AB}$ was 48 Hz.

With the finding that the ratio of products was independent of the C(17) substituent, we turned our attention to a detailed study of the methylation of the 17β-*t*-butoxy enone **18**. This compound was chosen because the products **23** and **26** were easily analysed by GC. The results of a series of orientating experiments are presented in Part A of Table 1. An examination of the data shows that the 10β/10α

[5]) A detailed study of this sequence was not carried out. However, based on our previous experience [27], significantly higher yields should be obtainable.

Table 1. *Methylations of Enone* **18**. A) Orientation Experiments

Expt.	Enolate Preparations[a])	Methylation Conditions[b])	% **18**[c])	% **23**	% **26**	Ratio **23**/**26**
1	Sodium-*t*-Amylate,	100°, 15 min	8.4	54.1	31.2	1.73
2	Toluene, 100°, 2 h	20°, 20 h	11.4	59.3	29.3	2.02
3		0°, 1 h	>90	–	–	–
4	Sodium Hydride, Glyme,	Reflux 10 min	7.2	53.6	31.8	1.69
5	Reflux, 16 h	0°, 1 h	2.1	63.3	26.6	2.38
6		0°, 1 h[b])	8.8	62.7	27.0	2.34
7	Sodium Hydride, Benzene,	Reflux, 2 h	9.2	57.8	33.0	1.75
8	Reflux, 16 h	20°, 23 h	10.9	59.9	29.2	2.05
9	Sodium Hydride, *iso*-Octane,	Reflux, 1 h	18.9	54.4	23.7	2.29
10	Reflux, 24 h	20°, 24 h	1	71	28	2.56
11		0°, 24 h	1	72	27	2.63
12	Lithium Amide, *iso*-Octane, Reflux, 24 h	20°, 24 h	51	30	15	2.00
13	Lithium Hydride, *iso*-Octane, Reflux, 24 h	20°, 24 h	49	36	15	2.40
14	Potassium *t*-Butoxide, *iso*-Octane,	20°, 24 h	4	64	32	2.00
15	Reflux, 22 h	0°, 24 h	3	67	30	2.26
16	Potassium *t*-Butoxide, *t*-Butanol, Reflux, 20 h	25°, 1 h	9	54	34	1.59

Table 1. *Methylations of Enone* **18**. B) Low Temperature Experiments

17	Sodium Hydride,	0°, 1 h	2.1	63.3	26.6	2.38
18	Glyme,	–25°, 6 h	–	66.6	20.2	3.30
19	Reflux, 18 h	–63°, 4 h	–	81.7	18.3	4.46
20		–75°, 6 h	–	81.6	18.4	4.44
21	Sodium Hydride, Glyme/Toluene 1:1, Reflux, 18 h	–75°, 6 h	–	77.5	22.5	3.44
22	Sodium Hydride, Tetrahydrofuran, Reflux, 18 h	–75°, 8 h	–	84.5	15.5	5.46
23	Sodium Hydride, Diglyme, 80°, 18 h	–63°, 6 h	trace	84.4	15.6	5.41
24	Sodium Hydride, Dimethyl-formamide, 80°, 16 h	–63°, 6 h	–	83.0	17.0	4.88

[a]) In reactions involving lithium and sodium hydride, a trace of *t*-butyl alcohol was added to speed enolate formation.

[b]) Methyl iodide was used for all reactions except 6, where methyl chloride was employed.

[c]) Percent yields are relative yields, as determined by GC. In cases where the total is not 100%, the difference represents by-products.

methylation ratio fell within a relatively narrow range, despite the varied reaction conditions. Changes of solvent, cation, or methylating agent had little effect. The only significant change in ratio occurred when the temperature was varied. At lower temperatures, increased β-methylation occurred as can be seen in Part B of Table 1. A major complication in this work was finding suitable solvents. Attempted alkylations in ether, dipropyl ether, formaldehyde diethyl acetal, formaldehyde dimethyl acetal, *iso*-octane and toluene, solvents which gave heterogeneous suspensions of enolate below –50°, led only to recovered enone **18**.

In addition to giving high $10\beta/10\alpha$ ratios, the use of low temperatures in the alkylations yielded another benefit. The crude reaction mixtures contained virtually only the monoalkylated products **23** and **26**. The absence of starting enone **18** and dialkylated products from the mixtures indicated *that anion exchange probably did not occur at these temperatures*. To confirm our GC. results, experiments 20 and 22 (Table 1) were repeated on a preparative scale. The ratio of **23/26** from the glyme experiment (20) was 80.3 : 19.5 by GC. and the 10β-ketone **23** was isolated in 76% yield after chromatography. The ratio of products was not so reproducible when tetrahydrofuran was employed as solvent. In the preparative experiment, the **23/26** ratio was 82.8 :17.8 (GC.) and the ketone **23** was obtained in 78% yield.

We have carried out preliminary attempts to methylate in tetrahydrofuran at –110°. The reaction with methyl iodide was quite slow at this temperature. Besides **23** and **26**, starting material and several as yet unidentified products were present after 24 hours. The ratio of **23/26** was 5.65 : 1.

In order to determine the generality of our findings, we carried out the methylation shown in *Scheme 4*[6]. The 20β-acetoxy enone **36** was prepared by alkylation of **34**[7] with 4-chloromethyl-3,5-dimethylisoxazole [23]. A better yield of **36** was obtained,

Table 2. *Methylation of Enone* **36**

Expt.	Enolate Preparations[a]	Methylation Conditions[b]	% **36**[c]	% **37**	% **38**	Ratio **37/38**
1	Sodium Hydride, Glyme	30°, 6 h	9.5	61.6	26.5	2.32
2	Reflux, 18 h	0°, 6 h	10.3	62.7	23.7	2.64
3		–72°, 6 h	5.9	72.4	20.1	3.60
4	Sodium Hydride, Tetrahydrofuran,	0°, 6 h	19.1	60.2	20.3	2.95
5	Reflux, 18 h	–72°, 6 h	12.3	66.8	15.1	4.42

[a]) A catalytic amount of *t*-butyl alcohol was present during enolate formation in all experiments.

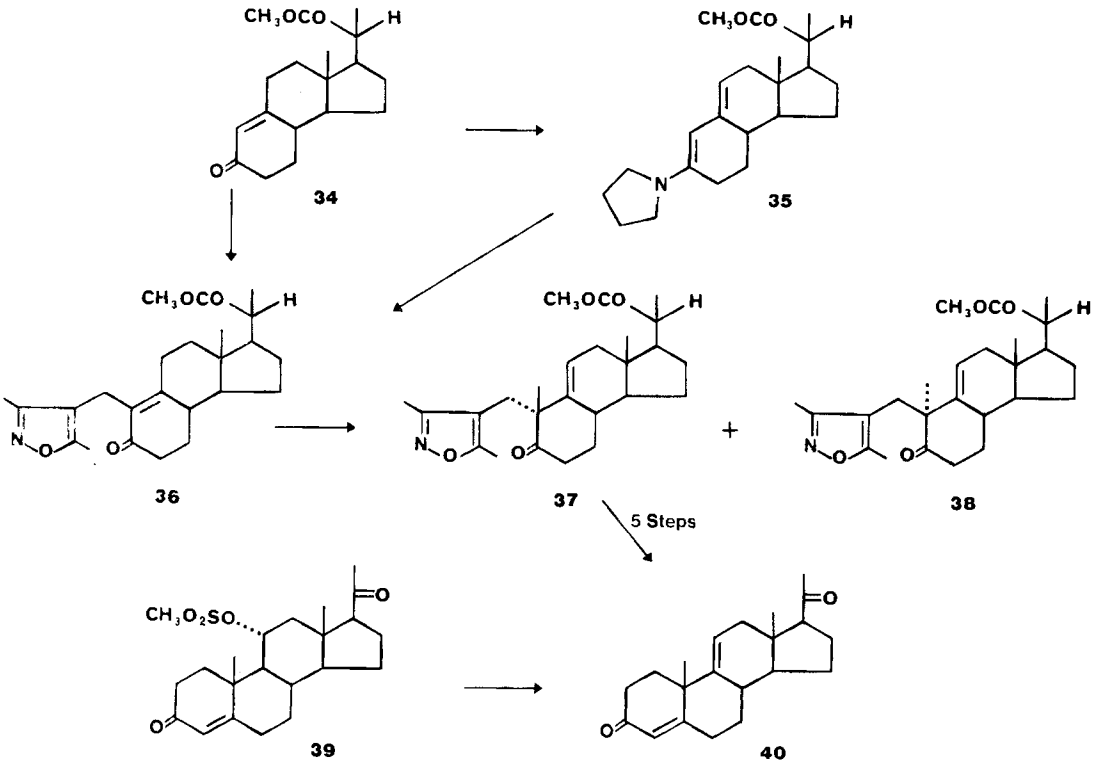
[b]) Methylations were carried out with an excess of methyl iodide. In all experiments the crude methylation products were reacetylated with acetic anhydride in pyridine.

[c]) Percent yields are relative yields, as determined by GC. In cases where the total was not 100%, the difference represents by-products.

[6]) Preliminary experiments in our laboratories indicate that the methylation of Δ^9-5-ketones in which the potential ring A is other than a 3,5-dimethylisoxazole ring are also subject to a significant temperature effect. These studies will be reported in due course.

[7]) The preparation of this crystalline compound (m.p. 71–72.5°, $[\alpha]_D^{25}$ + 10° (c = 2.0, $CHCl_3$)) from pregnenolone will be published later. An oily enone of this structure with unspecified (but probably 20β) configuration has been reported [28].

Scheme 4



however, by alkylation [29] [30] of the dienamine **35**[8]) with the same halide. The methylations of enone **36** (Table 2) were carried out as described in the androstane series. Some cleavage of the acetate group occurred during reaction and so the crude reaction mixture was reacetylated prior to GC. analysis. The presence of recovered enone in the mixture can be ascribed to the use of a portion of the base in acetate cleavage rather than enolate formation. As expected, a significant temperature effect in the β/α product ratio was seen. The ratio of **37**/**38** from the glyme experiment 3 was 72.4:20.1, and **37** was isolated in 55% yield. The 10α-methyl compound **38** could also be isolated and characterized. To confirm the configuration of the introduced methyl group, **37** was converted to the known pregna-4,9(11)-diene-3,20-dione **40** [31–35]. The material was identical in all respects to an authentic sample prepared by heating the mesylate **39** [36] with sodium acetate in acetic acid [37].

The authors wish to express their thanks to Dr. *W. Arnold*, Dr. *L. Chopard*, Dr. *G. Englert*, Dr. *M. Grosjean* and Dr. *W. Vetter* of our Physical Chemistry Department for the spectroscopic determinations and to Dr. *A. Dirscherl* for the microanalyses. In particular, we are indebted to Dr. *M. Vecchi* for innumerable GC. analyses and to Dr. *K. Noack* for preparation of the cryostat, which allowed us to perform the experiment at −110°. One of us (*J.W.S.*) would like to express his gratitude to Dr. *O. Isler*, for his hospitality during the time that much of this work was carried out, and to Dr. *G. Saucy*, for his encouragement.

[8]) Enamine of this gross structure (probably 20β configuration; see previous note) has been alkylated with 1,3-dichloro-2-butene [28].

Experimental Part

General. M.p. were determined on a *Büchi* melting point apparatus and are not corrected. Spectral and gas chromatographic measurements were performed by members of the Physical Chemistry Department of *Hoffmann-La Roche* using the following instruments: NMR., *Varian* A-60 spectrometer with tetramethylsilane as internal standard and, unless otherwise specified, deuteriochloroform as solvent; IR., *Beckmann* IR 9 spectrometer with chloroform as solvent unless otherwise noted; UV., *Cary* Model 14 spectrometer with ethanol as solvent; MS., *AEI* MS 9 spectrometer with a direct inlet system (70 eV); GC., *Perkin-Elmer* 900 gas chromatograph. The phrase 'worked up as usual' indicates extraction or dilution with the indicated solvent, washing, where appropriate, with H_2O, 2 N HCl, saturated $NaHCO_3$, and/or saturated brine, drying (Na_2SO_4), and solvent removal on a rotary evaporator at 30–50°. Chromatography was carried out on *Merck* 0,05–0,2 mm silica gel.

Methyl δ-(3,5-dimethyl-4-isoxazolyl)-β-oxo-valerate (**13**). The procedure used was essentially that of *Weiler* [22]. In a dry flask under N_2, 10.2 g (0.212 mol) of 50% NaH suspension was washed twice with pentane to remove the mineral oil. The NaH was then suspended in 500 ml of tetrahydrofuran (freshly filtered through *Woelm* neutral alumina I). The suspension was cooled in an ice bath as 23.22 g (0.1 mol) of methyl acetoacetate (*Fluka* puriss, redistilled) in 30 ml of tetrahydrofuran was added over 30 min (H_2 evolution). The light brown solution was stirred at 0–5° for another 15 min and then 133 ml of 1.66 M butyl lithium solution in tetrahydrofuran (0.22 mol) was introduced *via* syringe over 5 min. The orange solution was stirred at 0–5° for 10 min and then a solution of 32 g (0.22 mol) of 4-chloromethyl-3,5-dimethylisoxazole [23] in 75 ml of tetrahydrofuran was added over 5 min as much of the orange color faded. The mixture was stirred without cooling for 2 h, cautiously hydrolyzed with 200 ml of 3 N HCl, and worked up as usual with ether to give a light orange oil. The products from two such reactions were combined and distilled through a short-path apparatus to give 51.4 g of light yellow oil. This material was dissolved in 100 ml of ether and cooled to give 37.7 g of the desired ester **13** as a white solid, m.p. 49.5–52.5°. The mother liquors were stripped of solvent, redistilled, and crystallized as above to give another 3.1 g (total 40.8 g = 45.5%) of white solid, m.p. 49–52.5°. The analytical sample was similarly prepared: m.p. 49–52°. – UV.: max 221 (ε 5200) and 250 nm (sh, ε900). – IR.: 1749 (ester C=O), 1721 (ketone C=O) and 1640 cm^{-1} (isoxazole). – NMR.: δ2.21 (*s*, 3H) and 2.33 (*s*, 3H, 2 isoxazole $-CH_3$); 2.70 (*q*, 4H, $-CH_2CH_2-$); 3.43 (*s*, 2H, $-CH_2-$) and 3.60 ppm (*s*, 3H, $COOCH_3$). – MS.: *m/e* 225 (M^+) and 110 (base peak).

$C_{11}H_{15}NO_4$ (225.24) Calc. C 58.66 H 6,71 N 6.23% Found C 58.55 H 6.59 N 6.01%

(+)-17β-t-Butoxy-19-(3,5-dimethyl-4-isoxazolyl)-deA-androst-9-en-5-one (**18**). In a dry flask under N_2, sodium methoxide solution was prepared from 230 mg (10 mmol) of sodium and 75 ml of anhydrous methanol in the usual manner. The solution was stirred for 5 min after reaction had ceased and then 12.4 g (55 mmol) of the β-keto ester **13** was added in one portion. The resulting pale yellow solution was stirred at 20° for 10 min. A solution of 3.94 g of methylene ketone **14** [24] in 15 ml of methanol was added over 45–50 min. This process was repeated twice (total methylene ketone **14** = 11.82 g = 50 mmol). The resulting orangish solution was stirred at 20° for 2 h. It was then diluted with 50 ml of 5 N NaOH solution and stirred at 20° another 16 h. The reddish-brown suspension was stripped of solvent to give a brown paste. This material was suspended in benzene, acidified with 2 N HCl and worked up as usual to give a red-brown resin which was heated at 70°/20 Torr until gas evolution ceased (*ca.* 0.5 h). The products from two such reactions were combined (total 40.8 g) and chromatographed on 2 kg of silica gel. Elution with benzene/ether 92:8 gave 33.3 g of light yellow solid which was triturated with 100 ml of hot ether and cooled to give 25.2 g of granular white solid, sint. 135°, m.p. 141.5–144°. Concentration of the mother liquors gave another 3 g of white solid, m.p. 130–141.5°. The materials were combined and crystallized from 100 ml of methylene chloride/ether to give 24.85 g of the enone **18** as small white prisms, m.p. 142–144.5[9]) $[\alpha]_D^{25}$ + 12.9° (*c* = 1.27, $CHCl_3$). The IR.-, NMR.-, UV.- and mass spectra, as well as the GC. and TLC. behaviour of this material were identical with those of previously prepared samples [4] of enone **18**.

[9]) We previously [4] reported the m.p. of this compound as 125.5–126.5°. The material obtained here is a second crystalline form, identical in all other respects with the lower melting samples.

Keto ester **22** *and ketols* **16**. In a separate experiment, the keto acid **17** was prepared on the same scale as described above. The benzene solution of this material was not stripped of solvent, but was added to a cold (0–5°) ethereal solution of diazomethane (~100 mmol) [38]. This mixture was stirred at 0–5° for 1 h before the excess diazomethane was destroyed by the addition of 5 ml of acetic acid. The solution was worked up as usual to give 24.9 g of orange resin which was chromatographed on 2 kg of silica gel. Elution with hexane/ether 4:1 gave 5 fractions (total 13.3 g) which were shown by NMR. to be mixtures of C(6)-epimers of **22** in ratios of 3:1 to 2:1 (integration of $COOCH_3$ signals). A middle fraction had the following spectral characteristics: IR.: 1744 (ester C=O), 1670 (C=C—C=O), 1640 (sh, isoxazole) and 1609 cm^{-1} (>C=C<). – NMR.: δ0.90 and 0.92 (2*s*, 3H, 18-CH_3); 1.14 (*s*, 9H, $OC(CH_3)_3$); 2.16 (*s*, 3H, isoxazole-CH_3); 2.29 and 2.32 (2*s*, 3H, isoxazole-CH_3); 3.4 (*m*, 4H, C(17)—H, C(6)—H, and isoxazole-CH_2) and 3.66 and 3.79 ppm (2*s*, ratio 2:1, $COOCH_3$). None of the fractions could be induced to crystallize. A portion of this material was treated with 2 equiv. of sodium methoxide in methanol for 20 h at 20°. The crude product was shown by NMR. to again be a mixture of isomers (ratio 5:2).

In another experiment, 44 mmol of β-keto ester **13** and 40 mmol of methylene ketone **14** were condensed with sodium methoxide as above. The yellow-orange solution was stirred at 20° for 2 h and quenched by the addition of 1 ml of acetic acid. The mixture (pH 5–6) was diluted with brine and worked up with benzene as usual to give a yellow-brown, semi-crystalline resin. This material was dissolved in methylene chloride, treated with active carbon, filtered, stripped of solvent, and crystallized twice from methylene chloride/ether to give ketols **16** as 5.63 g (30.5%) of fine, white needles: m.p. 174–189° with bubbling. – UV.: max 221 nm (ε4600). – IR.: ($CHCl_3$) 3600 and 3422 (hydroxyl), 1745 (ester C=O), 1720 (ketone C=O) and 1638 cm^{-1} (isoxazole). – NMR.: δ0.84 and 0.94 (2*s*, ratio: 1:1, 3H, 18-CH_3); 1.14 (*s*, 9H, $OC(CH_3)_3$); 2.20 (*s*, 3H) and 2.38 (*s*, 3H, 2 isoxazole-CH_3), and 3.73 ppm (*s*, 3H, $COOCH_3$). – MS.: *m/e* 461 (M^+) and 110 (base peak).

$C_{26}H_{39}NO_6$ (461.58) Calc. C 67.65 H 8.52 N 3.03% Found C 67.63 H 8.62 N 2.98%

The mother liquors from the crystallizations of the ketols **16** were stripped of solvent to give an orange resin which was chromatographed on 500 g of silica gel. Elution with benzene and benzene/ether 29:1 gave 387 mg of cloudy yellow oil which was not investigated further. Elution with benzene/ether 29:1 gave 2.61 g of yellowish solid which was crystallized from methylene chloride/ether to give another 1.35 g (7.3%) of ketols **16** as a white powder, m.p. 183–193°, mixture melting point with the sample obtained above 180–191°. Further elution with benzene/ether 19:1 and 9:1 gave two oily fractions (1.88 and 1.45 g). MS. of these materials showed them to contain no material of molecular weight over 225. Elution with benzene/ether 9:1 and 17:3 then gave 5.45 g of cream-white solid. Crystallization of this material from methylene chloride/ether gave 1.83 g (11.9%) of enone **18** as white prisms: m.p. 141–144°; mixture melting point with authentic **18** undepressed; IR., NMR. and MS. were the same as those reported above.

To a solution of 1.384 g (3 mmol) of mixed ketols **16** in 50 ml of pyridine was added 2 ml (*ca.* 22 mmol) of $POCl_3$ and the resulting mixture was heated under N_2 at 90° for 18 h. The red-brown solution was cooled and worked up with benzene as usual to give a brown resin which was filtered through 100 g of silica gel with benzene/ether 9:1. This gave keto ester **22** as 283 mg of pale-yellow, glassy foam which was shown to be identical by IR., NMR. and MS. and TLC. behaviour to the material prepared by esterification of the acid **17**.

17β-Acetoxy-19-(3,5-dimethyl-4-isoxazolyl)-deA-androst-9-en-5-one (**20**) *and 17β-Benzoyloxy-19-(3,5-dimethyl-4-isoxazolyl)-deA-androst-9-en-5-one* (**21**). To a solution of 30 g (78 mmol) of the *t*-butyl enone **18** in 600 ml of benzene was added 15 g of *p*-toluenesulfonic acid monohydrate and the resulting mixture was heated at reflux for 3 h. The dark orange solution was worked up as usual to give crude 17β-hydroxy-19-(3,5-dimethyl-4-isoxazolyl)-deA-androst-9-en-5-one (**19**) as an orange resin. This resin was divided into two equal portions, each of which was taken up in 100 ml of pyridine, degassed, and placed under N_2. To one solution was added 25 ml of acetic anhydride and to the other 25 ml of benzoyl chloride. The solutions were stirred at 25° overnight, stripped of solvent, and worked up as usual with benzene. The crude acetate was filtered through 500 g of silica gel with benzene/ether 9:1. Crystallization of the resultant light yellow resin from isopropyl ether gave 10.9 g (76%) of acetate **20** as a white solid, m.p. 96–98°. A similarly prepared sample was recrystallized from isopropyl ether to give analytically pure material: m.p. 96.5–98.5°; $[\alpha]_D^{25}$ + 3.94° (*c* = 1.523, $CHCl_3$). – IR.: 1733 (ester C=O), 1666 (C=C—C=O), 1650 (sh, isoxazole)

and 1605 cm^{-1} (C=C). – UV.: max 227 (sh, ε11100) and 246 nm (ε14700). – NMR.: δ0.97 (*s*, 3H, angular CH_3); 2.08 (*s*, 3H); 2.18 (*s*, 3H) and 2.32 (*s*, 3H, 2 isoxazole-CH_3 and CH_3CO); 3.41 (*s*, 2H, isoxazole-CH_2) and 4.70 ppm (*t*, 1H, $CHOCOCH_3$). – MS.: *m/e* 371 (M^+).

$C_{22}H_{29}NO_4$ (371.46) Calc. C 71.13 H 7.87 N 3.77% Found C 71.20 H 7.88 N 3.92%

The crude benzoate was chromatographed on 500 g of silica gel. Elution with benzene/ether 19:1 and 9:1 gave a light yellow solid which was crystallized twice from methylene chloride/ether to give 9.1 g (54%) of pure benzoate **21** as small white prisms: sint. 151°, m.p. 154–155.5°; $[\alpha]_D^{25}$ + 65.5° (*c* = 1.624, $CHCl_3$). – IR.: 1712 (ester C=O), 1661 (C=C—C=O), 1600 (C=C) and 1583 and 1492 cm^{-1} (phenyl). – UV.: max 232.5 nm (ε25700). – NMR.: δ1.09 (*s*, 3H, angular CH_3); 2.14 (*s*, 3H) and 2.29 (*s*, 3H, 2 isoxazole-CH_3); 3.39 (*s*, 2H, isoxazole-CH_2); 4.90 (*t*, 1H, $CHOCOC_6H_5$) and 7.5 (*m*, 3H) and 8.0 ppm (*m*, 2H, C_6H_5). – MS.: *m/e* 433 (M^+) and 105 ($C_6H_5C{=}O^+$, base peak).

$C_{27}H_{31}NO_4$ (433.53) Calc. C 74.80 H 7.21 N 3.23% Found C 75.16 H 7.42 N 3.18%

17β-t-Butoxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-androst-9(11)-en-5-one (**23**) *and 17β-t-Butoxy-10-[(3,5-dimethyl-4-isoxazolyl)-methyl]-deA-10α-androst-9(11)-en-5-one* (**26**). A solution of 3.85 g (10 mmol) of enone **18** and 1 drop of *t*-butyl alcohol in 120 ml of dry glyme was degassed and placed under N_2. To the flask was added 480 mg (10 mmol) of 50% NaH in mineral oil and the resulting suspension was heated at a gentle reflux for 18 h. The light brown solution was cooled to 0° as 2.5 ml (*ca.* 40 mmol) of methyl iodide was added *via* syringe over 2 min. The solution was stirred at 0° for 1 h, quenched with water at this temperature, and worked up with benzene as usual. The same experiment was repeated, both crude products combined (**23**/**26** ratio *ca.* 2.4:1 by GC.) and chromatographed on 500 g of silica gel. Elution with hexane/ether 9:1 gave after removal of 2 minor impurities, 4.85 g of 10β-CH_3 ketone **23** as white prisms. Elution with hexane/ether 7:1 then gave the 10α-CH_3 ketone **26** as 2.07 g of white needles.

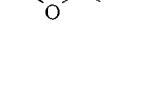
Two crystallizations of **23** from hexane gave the pure material as 3.70 g of small white prisms: m.p. 106–108°; $[\alpha]_D^{25}$ + 17.4° (*c* = 1.08, $CHCl_3$). – IR.: 1705 (ketone C=O) and 1630 cm^{-1} (isoxazole). – UV.: max 205 (ε5560) and 222 nm (ε4710). – NMR.: δ0.72 (*s*, 3H, 18-CH_3); 1.16 (*s*, 9H, $OC(CH_3)_3$); 1.25 (in C_6H_6, δ1.15 ppm) (*s*, 3H, 19-CH_3); 2.18 (*s*, 3H) and 2.30 (*s*, 3H, 2 isoxazole-CH_3); 2.67 (center of *AB*-system, $\Delta\nu_{AB}$ = 7.5 Hz, J_{AB} = 14 Hz, 2H, isoxazole-CH_2); 3.55 (*t*, 1H, C(17)—H) and 5.50 ppm (*t*, 1H, C=CH). – MS.: *m/e* 399 (M^+) and 110 (base peak)[10].

$C_{25}H_{37}NO_3$ (399.55) Calc. C 75.15 H 9.33 N 3.51% Found C 75.08 H 9.41 N 3.35%

Crystallization of the 10α-CH_3 sample from isopropyl ether gave 1.84 g of white rods, sint. 94°, m.p. 103–108°. Recrystallization from ether gave 1.24 g of white prisms, sint. 97°, m.p. 105–118°. Both samples contained solvent of crystallization which was not removed by drying at 25°/0.02 Torr. A similarly prepared sample was crystallized from hexane to give **26** as white needles again containing solvent of crystallization: sint. 100°, m.p. 118–150°, $[\alpha]_D^{25}$ + 61.6° (*c* = 1.454, $CHCl_3$). – IR.: 1710 (ketone C=O) and 1628 cm^{-1} (isoxazole). – UV.: max 206 (ε6230) and 222 nm (ε5770). – NMR.: δ0.82 (*s*, 3H, 18-CH_3); 1.17 (in C_6H_6, δ1.16 ppm) (*s*, 3H, 19-CH_3); 1.20 (*s*, 9H, $OC(CH_3)_3$); 2.15 (*s*, 3H) and 2.28 (*s*, 3H, 2 isoxazole-CH_3); 2.75 (center of *AB*-system, $\Delta\nu_{AB}$ = 48 Hz, J_{AB} = 14.5 Hz, 2H, isoxazole-CH_2); 3.57 (*t*, 1H, C(17)—H) and 5.70 ppm (*t*, 1H, C=CH). – MS.: *m/e* 399.2759 (M^+, $C_{25}H_{37}NO_3$ requires 399.2772), 110[10]) and 86 (M^+ of hexane).

$C_{25}H_{37}NO_3{}^1/_3C_6H_{14}$	Calc.	C 75.72	H 9.81	N 3.27
(428.27)	Found	,, 75.70	,, 9.77	,, 3.34 %

Methylations of enone **18** *at* −75°. A solution of 3.85 g (10 mmol) of enone **18** and 1 drop of *t*-butyl alcohol in 120 ml of dry tetrahydrofuran was degassed and placed under N_2. To the flask was added 480 mg (10 mmol) of 50% NaH in mineral oil and the resulting suspension was heated at a gentle reflux for 18 h. The resulting light brown solution was cooled in a dry ice/acetone bath (bath temp.: −78 to −80°, inside temp.: −73 to −75°) as 2.5 ml (*ca.* 40 mmol) of methyl iodide was added *via* syringe over 2 min. The solution was stirred at −75° for 8 h, quenched with H_2O at this temperature, and worked up with benzene as usual. GC. (3% OV 17; 2 m; 260°) of the resulting

[10]) 

light yellow resin showed 3 peaks: 13.7 min, trace unknown; 14.8 min, 82.2% 10β-CH_3 ketone **23**; 17.9 min, 17.8% 10α-CH_3 ketone **26**. Chromatography of this product mixture on 500 g of silica gel with hexane/ether 9:1 gave after initial elution of the unknown, 3.116 g (78%) of **23** as a cream-white solid. Crystallization from 10–12 ml of hexane gave 2.6 g (65.2%) of **23** as fine white prisms, m.p. 105–107°.

The reaction was run again as above except that glyme was used as solvent and the methylation was carried out at −75° for 6 h. GC. (7% QF 1; 2 m; 280°) again showed 3 peaks: 12.7 min, 0,2% unknown; 14 min, 80.3% 10β-CH_3 ketone **23**; 16.8 min, 19.5% 10α-CH_3 ketone **26**. Chromatography gave 3.049 g (76%) of light yellow solid which was crystallized as above to give 2.59 g (64.8%) of **23** as small white prisms, m.p. 105–107.5°.

17β-Acetoxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-androst-9(11)-en-5-one (**24**). A 3.71 g (10 mmol) sample of acetoxy enone **20** was methylated in glyme at 0° for 1.5 h in the manner described above. The crude product was reacetylated with 3 ml of acetic anhydride and 50 ml of pyridine. Work up as usual gave an orange resin which soon crystallized. GC. (5% SE 30; 3 m; 280°) showed the mixture to contain 3 components: 15.5 min, 60.9% 10β-CH_3 ketone **24**; 17.7 min, 24.8% 10α-CH_3 ketone **27**; 19.8 min, 14.3% enone **20**. The crude product was chromatographed on 500 g of silica gel with hexane/ether 7:3 (1 l fractions). Thirteen fractions containing monomethylated material were obtained. The first 3 of these (0.47 g) were shown to be homogeneous by NMR. The next 3 fractions (1.95 g) which were mostly 10β-CH_3 material, were rechromatographed as above to give another 1.02 g of pure 10β-CH_3 compound. The combined samples were crystallized twice from methylene chloride/isopropyl ether to give **24** as 1,13 g of small white prisms: m.p. 147–148.5°; $[\alpha]_D^{25}$ + 4.4° (c = 1.04, $CHCl_3$). – IR.: 1734 (acetate C=O), 1705 (ketone C=O) and 1628 cm^{-1} (isoxazole). – UV.: max 208 (ε5200) and 218 nm (ε5150). – NMR.: δ0.81 (*s*, 3H 18-CH_3); 1.27 (*s*, 3H, 19-CH_3); 2.10 (*s*, 3H), 2.18 (*s*, 3H) and 2.28 (*s*, 3H, 2 isoxazole-CH_3 and CH_3COO); 2.69 (center of *AB*-system, $\Delta\nu_{AB}$ = 7 Hz, J_{AB} = 14 Hz, 2H, isoxazole-CH_2); 4.77 (*t*, 1H, C(17)—H) and 5.52 ppm (*m*, 1H, C=CH). – MS.: *m/e* 385 (M^+) and 110[10] (base peak).

$C_{23}H_{31}NO_4$ (385.49) Calc. C 71.66 H 8.11 N 3.63% Found C 71.78 H 7.86 N 3.58%

17β-Benzoyloxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-androst-9(11)-en-5-one (**25**). Methylation of the 17β-benzoyloxy enone **21** was carried out as in the previous experiment. The crude product was benzoylated to give a light yellow resin which was shown by GC. (5% OV 210; 2 m; 270°) to contain 3 components: 14.4 min, 6% unknown; 16 min, 66.9% 10β-CH_3 ketone **25**; 17.5 min, 27.1% 10α-CH_3 ketone **28**. The material was chromatographed as above with hexane/ether 2:1. NMR. showed only one fraction (967 mg) to be homogeneous. Two crystallizations of this material from methylene chloride/isopropyl ether gave 586 mg of **25** as white prisms: m.p. 123–125°; $[\alpha]_D^{25}$ + 25.0° (c = 1.12, $CHCl_3$). – UV.: max 227 (ε19200), 272 (ε1200) and 280 nm (ε920). – IR.: (KBr) 1724 (benzoate C=O), 1710 (ketone C=O), 1627 (isoxazole) and 1600, 1584 and 1492 cm^{-1} (aromatic ring). – NMR.: δ0.93 (*s*, 3H, 18-CH_3); 1.27 (*s*, 3H, 19-CH_3); 2.20 (*s*, 3H) and 2.28 (*s*, 3H, 2 isoxazole-CH_3); 2.70 (center of *AB*-system, $\Delta\nu_{AB}$ = 7,5 Hz, J_{AB} = 14 Hz, 2H, isoxazole-CH_2); 5.04 (*t*, 1H, C(17)—H); 5.53 (*m*, 1H, C=CH) and 7.55 (*m*, 3H) and 8.10 ppm (*m*, 2H, C_6H_5). – MS.: *m/e* 447 (M^+), 110[10] (base peak) and 105 ($C_6H_5C{=}O^+$).

$C_{28}H_{33}NO_4$ (447.55) Calc. C 75.14 H 7.43 N 3.13% Found C 74.89 H 7.46 N 3.05%

17β-Hydroxyandrosta-4,9(11)-dien-3-one (**29**). A mixture of 2.4 g (6 mmol) of the 10β-CH_3 ketone **23**, 0.5 g of *p*-toluenesulfonic acid monohydrate, 20 ml of ethylene glycol and 100 ml of benzene was degassed, placed under N_2, and heated at reflux, with azeotropic removal of H_2O, for 20 h. The solution was cooled and worked up as usual to give the crude acetals **31** (10β-CH_3) as a white foam. To a solution of this material in 100 ml of 5% ethanolic KOH was added 500 mg of 5% Pd/C catalyst. The resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 45 min, the uptake of H_2 (180 ml) had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The colorless filtrate was stripped of solvent to a volume of *ca.* 30 ml. To this solution of the vinylogous amides **32** (10β-CH_3) was added 100 ml of 20% KOH solution and the resulting mixture was degassed, placed under N_2, and heated at reflux for 18 h. Work up with benzene as usual gave the keto acetals **33** (10β-CH_3) as a light yellow resin. To a solution of this material in 100 ml of methanol was added 10 ml of 3N HCl. This solution was heated at reflux under N_2 for 3 h, cooled and worked up as usual with benzene. TLC. (benzene/ethyl acetate 1:1) showed the crude product mixture to consist of 2 compounds

in a ratio of *ca.* 2:1. To its solution in 50 ml of benzene was added 0.5 g of *p*-toluenesulfonic acid monohydrate and the mixture was then heated at reflux for 1 h. Another 0.5 g of acid was added and heating was continued for an additional hour. The solution was cooled and worked up as usual to give 1.5 g of red-brown resin. This material was chromatographed on 100 g of silica gel with hexane/ethyl acetate 7:3. The resultant 1.077 g of yellowish solid was crystallized from methylene chloride/isopropyl ether to give 916 mg (53%) of the desired product **29** as clear, slightly yellow prisms: m.p. 152.5–156°, mixture m.p. with an authentic sample [26b] 153–156.5°; $[\alpha]_D^{25}$ + 92.4 (*c* = 1.12, $CHCl_3$)[11]. – UV.: max 238 nm (ε17100).

17β-Hydroxy-10α-androsta-4,9(11)-dien-3-one (**30**). In the manner described above, 1.1 g (2.75 mmol) of the 10α-CH_3 ketone **26** gave 291 mg (37%) of 10α-steroid **30** as pale prisms: m.p. 145.5–149°, mixture m.p. with an authentic sample [26b] 146–150°; $[\alpha]_D^{25}$ – 134.6° (*c* = 0.95, $CHCl_3$). – UV.: max 237 nm (ε14500).

20β-Acetoxy-19-(3,5-dimethyl-4-isoxazoly)-deA-pregn-9-en-5-one (**36**). a) *From* **34**. A solution of 5 g (17.2 mmol) of enone **34**[7]) in 80 ml of dry glyme was degassed and placed under argon. To the solution was added 908 mg (18.9 mmol) of 50% NaH in mineral oil and the resulting suspension was stirred at room temperature for 23 h. A solution of 3.1 g (21.5 mmol) of 4-chloromethyl-3,5-dimethylisoxazole in 20 ml of dry glyme was added dropwise to the orange mixture over 6 h. Stirring was continued for an additional 18 h and then most of the solvent was removed at reduced pressure. The residue was worked up with benzene in the usual manner to give a yellow resin which was dissolved in 30 ml of pyridine and treated with 10 ml of acetic anhydride. The solution was allowed to stand at room temperature for 16 h, poured onto ice and worked up with ether to afford 7.2 g of a yellow oil which was chromatographed on 200 g of silica gel. Elution with hexane/ether 7:3 gave first 1.2 g (24%) of enone **34** and then 3.06 g (44.6%) of **36** as a light yellow solid. Crystallization from ether/isopropyl ether yielded 2.6 g (37%) white prisms, m.p. 129–130° (sint. 126°). A sample for analysis was crystallized from a concentrated etheral solution: m.p. 130–131.5° (sint. 128°); $[\alpha]_D^{25}$ + 44° (*c* = 1.0, $CHCl_3$). – UV.: max 244 nm (ε14700). – IR.: (KBr) 1728 and 1240 (ester C=O), 1660 and 1600 cm^{-1} (C=C–C=O). – NMR.: δ0.80 (*s*, 3H, angular CH_3); 1.18 (*d*, 3H, *J* = 6 Hz, CH–CH_3); 2.02 (*s*, 3H, CH_3COO); 2.13 (*s*, 3H) and 2.28 (*s*, 3H, 2 isoxazole-CH_3); 3.36 (bd *s*, 2H, isoxazole-CH_2) and 4.82 ppm (*m*, 1H, CH–O). – MS.: *m/e* 399 (M^+), 296, 255 and 121.

$C_{24}H_{33}NO_4$ (399.50) Calc. C 72.15 H 8.33 N 3.51% Found C 72.03 H 8.34 N 3.35%

Subsequent fractions eluted with ether yielded 1.7 g (18.7%) of the C(10)-dialkylated product, namely *20β-Acetoxy-1,19-bis-(3,5-dimethyl-4-isoxazolyl)-1,5*-seco-*2,3,4-trinorpregn-9(11)-en-5-one*. Crystallization from ether gave 1.18 g (13%) needles, m.p. 195–196°; $[\alpha]_D^{25}$ + 81° (*c* = 0.1, dioxane). – IR.: (KBr) 1730 and 1249 (ester C=O), 1700 cm^{-1} (C=O). – NMR.: δ0.39 (*s*, 3H, angular CH_3); 1.18 (*d*, 3H, *J* = 6 Hz, CH–CH_3); 2.04 (*s*, 6H), 2.13, 2.18, 2.24 (3*s*, 9H, 4 isoxazole-CH_3 and CH_3COO); 2.81 (bd *m*, 4H, 2 isoxazole-CH_2); 4.80 (*m*, 1H, CH–O) and 5.78 ppm (*m*, 1H, C=CH). – MS.: *m/e* 508 (M^+), 399 and 110.

$C_{30}H_{40}N_2O_5$ (508.64) Calc. C 70.84 H 7.93 N 5.51% Found C 70.88 H 7.89 N 5.47%

b) *via Enamine* **35**. To a solution of 28.8 g (0.1 mol) of enone **34** in 42 ml of methanol, prepared under slight warming, was added 12 ml (0.15 mol) of pyrrolidine in one portion at room temperature. After about 15 seconds the yellow crystalline enamine began to separate. The reaction mixture was allowed to stand at room temperature for 1 h and finally at 0° overnight. The crystals were separated by suction, washed with a little cold methanol and dried at 20°/11 Torr to give 33.3 g (97%) of enamine **35**, m.p. 130–133°. Crystallization from ether gave an analytical sample as yellow needles: m.p. 131–133° (decomp.)[12]. – UV.: max 279 nm (ε24400)[13]. – IR.: (KBr) 2820 (N–C), 1728 and 1246 (ester C=O) and 1622 and 1592 cm^{-1} (C=C–C=C).

$C_{22}H_{33}NO_2$ (343.48) Calc. C 76.92 H 9.68 N 4.08% Found C 76.57 H 9.47 N 4.24%

To a stirred suspension of 31.7 g (92 mmol) of enamine **35** and 15.4 g (92 mmol) of potassium iodide in 180 ml of dry dimethylformamide [29] [30] under argon was added dropwise over 45 min 17.5 g (0.12 mol) of 4-chloromethyl-3,5-dimethylisoxazole. During the addition the temperature

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[11]) Reported [25] for **29**: m.p. 153–154°; $[\alpha]_D^{23}$ + 89° ($CHCl_3$).

[12]) Reported [28] (see footnote 8) m.p. 138°.

[13]) In agreement with the data for enamines of unsaturated steroidal ketones. See [39].

reached 35° and the suspension dissolved to give an orange-brown solution. The stirring was continued for 2 h at room temperature and then for 0.5 h at 40°. A solution of 50 g of sodium acetate in 200 ml of 50% aqueous acetic acid [40] was added and the resulting mixture was heated at reflux for 4 h. After removal of about 180 ml of solvent under reduced pressure, 1500 ml of water was added to the residue and the mixture was worked up with benzene as usual. The residue from solvent removal, which crystallized after a short time, was recrystallized from 100 ml of isopropyl ether to give 21.9 g (59,6%) of monoalkylated product **36**, m.p. 127–131°. The mother liquor was concentrated *in vacuo* and the residue was chromatographed on 540 g of silica gel. Elution with hexane/ether 3:2 gave 2.3 g (8.6%) of enone **34** and then 6.6 g (17%) of crystalline product **36**. Crystallization of this fraction from 60 ml of isopropyl ether gave an additional 5.5 g (14%) of **36** as white needles, m.p. 130.5–132°.

20β-Acetoxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-pregn-9(11)-en-5-one (**37**) *and 20β-Acetoxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-10α-pregn-9(11)-en-5-one* (**38**). A solution of 3.99 g (10 mmol) enone **36** in 120 ml of dry glyme was degassed and placed under argon. To the solution was added 530 mg (11 mmol) of 50% sodium hydride in mineral oil and the resulting suspension was heated at reflux for 18 h. The light brown solution was cooled in a dry ice/acetone bath to an inside temperature of −72° as 2.5 ml (*ca.* 40 mmol) of methyl iodide was added over 2 min. The solution was stirred at −75° for 6.5 h, quenched with 20 ml of water at this temperature and worked up with benzene as usual. The residual yellow oil from solvent removal was dissolved in 25 ml of pyridine, treated with 13 ml of acetic anhydride and kept at room temperature for 16 h. The reaction mixture was poured onto ice-water and worked up with ether as usual. GC. (5% OV 210; 2 m, 235°) of the resulting yellow resin showed 3 peaks: 15.9 min, 72.4% 10β-CH_3 ketone **37**; 18.7 min, 20.1% 10α-CH_3 ketone **38**; 24.8 min, 5.9% starting material **36**. The resin was chromatographed on 500 g of silica gel. Elution with hexane/ether 7:3 gave first 2.3 g (55%) of pure 10β-CH_3 ketone **37**, m.p. 136–137.5°. A sample for analysis was crystallized from methylene chloride/ether: m.p. 136–137.5°; $[\alpha]_D^{25}$ + 31° (*c* = 1.0, $CHCl_3$). – IR.: (KBr) 1729 and 1253 (ester C=O) and 1705 cm^{-1} (C=O). – NMR.: δ0.62 (*s*, 3H, angular CH_3); 1.24 (*s*, 3H, angular CH_3); 1.11 (part of a *d*, the second overlapped by the 1.24 ppm signal, CH—CH_3); 2.02 (*s*, 3H, CH_3COO); 2.15 (*s*, 3H) and 2.26 (*s*, 3H, 2 isoxazole-CH_3); 2.67 (center of *AB*-system, $\Delta\nu_{AB}$ = 9 Hz, J_{AB} = 13 Hz, 2H, isoxazole-CH_2); 4.86 (bd *m*, 1H, CH—O) and 5.45 ppm (*m*, 1H, —CH=C). – MS.: *m/e* 413 (*M*+), 304, 244 and 110[10]).

$C_{25}H_{35}NO_4$ (413.56) Calc. C 72.61 H 8.53 N 3.39% Found C 72.72 H 8.66 N 3.30%

Further fractions eluted with hexane/ether 7:3 contained a mixture of both methyl derivatives **37** and **38** and then pure 10α-CH_3 ketone **38**, from which 0.6 g (14.5%) of material, m.p. 165–180°, could be separated. Two crystallizations from methylene chloride/ether gave 0.236 g (5.6%) of pure **38** as white needles: m.p. 186–188°; $[\alpha]_D^{25}$ + 82° (*c* = 1.0, $CHCl_3$). – IR.: 1724 and 1259 (ester C=O) and 1709 cm^{-1} (C=O). – NMR.: δ0.69 (*s*, 3H, angular CH_3); 1.16 (*s*, 3H, angular CH_3); 1.18 (*d*, 3H, *J* = 7 Hz, CH—CH_3); 2.05 (*s*, 3H, CH_3COO), 2.10 (*s*, 3H) and 2.22 (*s*, 3H, 2 isoxazole-CH_3), 2.68 (center of *AB*-system, $\Delta\nu_{AB}$ = 40 Hz, J_{AB} = 14 Hz, 2H, isoxazole-CH_2); 4.85 (bd *m*, 1H, CH—O) and 5.62 ppm (*m*, 1H, —CH=C). – MS.: *m/e* 413 (*M*+), 304, 244 and 110[10]).

$C_{25}H_{35}NO_4$ (413.56) Calc. C 72.61 H 8.53 N 3.39% Found C 72.44 H 8.73 N 3.30%

Pregna-4,9(11)-diene-3,20-dione (**40**). a) *From 20β-Acetoxy-10-[(3,5-dimethyl-4-isoxazolyl)methyl]-deA-pregn-9(11)-en-5-one* (**37**). A mixture of 2.48 g (6 mmol) of the ketone **37**, 0.5 g of *p*-toluenesulfonic acid monohydrate, 20 ml of ethylene glycol, and 100 ml of benzene was placed under nitrogen and heated at reflux, with azeotropic removal of water, for 23 h. The reaction mixture was cooled and worked up as usual to give 3.1 g of a white foam which was taken up in 100 ml of 5% ethanolic KOH. To this solution was added 0.5 g of 5% Pd/C catalyst and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 100 min the uptake of hydrogen (165 ml) had ceased. The catalyst was removed by filtration and washed with ethanol and the filtrate was evaporated to *ca.* 30 ml. To this solution was added 100 ml of 20% aqueous KOH solution and the mixture was heated at reflux for 18 h under argon. The reaction mixture was cooled, diluted with water and worked up as usual with benzene and ether to yield 2.6 g of a yellow resin. To a solution of this product in 75 ml of butanol was added 25 ml of 25% HCl and the resulting mixture was heated at reflux under argon for 4 h. Most of the solvents were removed under reduced pressure and the residue was worked up with ether as usual to give 1.95 g

of an orange resin. Its solution in 15 ml of pyridine was added at 0° to a stirred mixture of 100 ml of pyridine and 2.0 g of chromium trioxide [41]. After 5 min, the cooling bath was removed and the stirring was continued at room temperature for 24 h. The mixture was poured into 500 ml of saturated aqueous $NaHCO_3$ and worked up with ether as usual to give 1.81 g of a yellow semi-crystalline product, which was chromatographed on 100 g of silica gel prepared with hexane/ether 9:1. Elution with hexane/ether 3:2 gave 1.17 g (62.7%) of a white solid, m.p. 120–122°. Crystallization from methylene chloride/hexane afforded 1.02 g (54.6%) of white prisms, m.p. 121–122°. An analytical sample was obtained by further crystallization from methylene chloride/ether: m.p. 121–122.5°[14]) [15]); $[\alpha]_D^{25}$ + 172° (*c* = 1.0, $CHCl_3$)[15]). – UV.: max 239 nm (ε17300)[15]). – IR.: 1705 (CO), 1665 and 1615 cm^{-1} (C=OC–C=O)[15])[16]). – NMR.: δ0.62 (*s*, 3H, 18-CH_3); 1.33 (*s*, 3H, 19-CH_3); 2.12 (*s*, 3H, $COCH_3$); 5.53 (*t*, 1H, *J* = 3 Hz, C(11)–H) and 5.73 ppm (*d*, 1H, C(4)–H)[15]). – MS.: *m/e* 312 (M^+), 297 and 227.

$C_{21}H_{28}O_2$ (312.43) Calc. C 80.73 H 9.03 Found C 80.50 H 9.08%

b) *From 11α-Methansulfonyloxy-pregn-4-ene-3,20-dione* (**39**). A 3.0 g (7.33 mmol) sample of the mesylate **39**[17]) [36] was added to a stirred boiling solution of 4.0 g of anhydrous sodium acetate in 40 ml of glacial acetic acid [37] and heating was continued an additional 30 min. The reaction mixture was cooled to 0° and diluted with 150 ml of cold water. The solid was collected by suction, washed with water and dissolved in ether. The etheral solution was worked up as usual to give 2.14 g of yellow crystalline residue which was chromatographed on 100 g of silica gel.

Elution with hexane/ether 3:2 afforded first 99 mg of a crystalline product, m.p. 171–173° (sint. 165°) which, after crystallization from methylene chloride/hexane, yielded 77 mg (3.3%) of *pregna-4,11-diene-3,20-dione*: m.p. 173–174°[18]); $[\alpha]_D^{25}$ + 184° (*c* = 0.56, acetone)[18]). – UV.: max 239 nm (ε17000)[18]). – IR.: (KBr) 1695 (CO), 1676 and 1616 cm^{-1} (C=C–C=O). – NMR.: δ0.75 (*s*, 3H, 18-CH_3); 1.13 (*s*, 3H, 19-CH_3); 2.18 (*s*, 3H, $COCH_3$) and 5.55 and 6.25 (*AB*-system, 2H, *J* = 10 Hz, C(11)- and C(12)–H) and 5.78 ppm (*d*, 1H, C(4)–H). – MS.: *m/e* 312 (M^+), 297 and 145. $C_{21}H_{28}O_2$ (312.43) Calc. C 80.73 H 9.03% Found C 80.57 H 9.16%

Further fractions eluted with hexane/ether 3:2 contained a total of 0.76 g of a crystalline mixture of products which was not separated. The last eluates furnished 1.19 g of colorless crystalline material, m.p. 120–122°, which after recrystallization from methylene chloride/ether gave 912 mg (40%) of *pregn-4,9(11)-diene-3,20-dione* (**40**): m.p. 121–122.5°; $[\alpha]_D^{25}$ + 172° (*c* = 1.0, $CHCl_3$). – UV.: max 239 nm (ε17500). – IR.: ($CHCl_3$) 1705 (CO), 1665 and 1615 cm^{-1} (C=C–C=O).

$C_{21}H_{28}O_2$ (312.43) Calc. C 80.73 H 9.03% Found C 80.49 H 9.05%

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[14]) Undepressed on admixture with a specimen prepared under b).

[15]) Reported: m.p. 118–119° [31], 120–122° [32] [33], 127–128° [34]; $[\alpha]_D$: + 171° [34], + 174° ($CHCl_3$) [35]; UV.: max 239 [35]; 240 nm ε = 16600 [34]; 240 nm ε = 15900 [31]; IR.: 1700 and 1666 cm^{-1} (C=O) [34]; NMR.: *cf.* [31].

[16]) Identical with the IR.-spectrum of the specimen prepared under b).

[17]) Kindly supplied by Dr. *E. Widmer*.

[18]) Reported: m.p.: 169–171° [42], 175–177° [33], 177–179° [43]; $[\alpha]_D$: + 180° [33], +182° (acetone) [43]; UV.: max 239 nm (ε16000) [42].

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