Synthesis of 17-(2-Methoxy-3-oxazolin-4-yl)-, 17-(3-Oxazolin-4-yl)-, and 17-(2-Oxazolin-4-ylidene)-Substituted Steroids and Their Use as Precursors of Corticosteroids[1]

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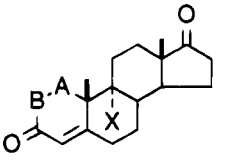
17-(Isocyanotosylmethylene)steroids **4** are useful intermediates in the conversion of 17-oxosteroids into 17-(hydroxyacetyl)steroids. The 21-CH_2OH group is effectively introduced by a base-mediated reaction of compounds **4** with formaldehyde and MeOH to give 17-(2-methoxy-3-oxazolin-4-yl) derivatives **12**, which by acid hydrolysis give 17-(hydroxyacetyl)steroids **10** and **16** in high yields. Partial hydrolysis of the same oxazoline derivatives **12** provides the 17-(hydroxyacetyl) cortico side chain of **13** equipped with a formyl-protected hydroxy group. 3-Oxazolinyl and 2-oxazolinylidene steroid derivatives **19**, **20**, and **21**, without a 2-methoxy substituent, are discussed as alternatives of **12**.

Biodegradation of plant sterols nowadays gives easy access to 17-oxosteroids. Thus C17 side chains of sitosterols—abundantly available from soybean waste—are effectively removed by fermentation processes to provide potentially useful intermediates for the manufacture of drugs.[2] The availability of these intermediates, such as androst-4-ene-3,17-dione (**1**), 9-hydroxyandrost-4-ene-3,17-dione (**2**), and androsta-1,4-diene-3,17-dione (**3**), has triggered the development of several new methods to synthesize pregnane derivatives, in particular corticosteroids.[3] These methods involve the (re)introduction of carbon atoms C20 and C21 in compounds such as **1** to **3**. We have shown recently that 17-(isocyanotosylmethylene)steroids **4**, in this respect, are useful precursors in the synthesis of 20-oxosteroids;[4] compounds **4** are readily available from 17-oxosteroids (*e.g.* **1**–**3**) and tosylmethyl isocyanide (TosMIC).[5] In this paper we describe the introduction of 17-(hydroxyacetyl) side chains—typical of corticosteroids—via the 17-(isocyanotosylmethylene) precursors **4**.

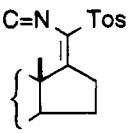
20-Oxopregnanes (**6**, Y = H) have been obtained previously by base-mediated C20 methylation of precursors **4** (via **9**), followed by acid hydrolysis of **5** (Y = H, Scheme 1).[5] Several C21-substituted 20-oxopregnanes (**6**, Y = Me, Cl, Br, MeO, BnO) were obtained in a similar fashion by ethylation, halomethylation, and alkoxymethylation of **4**, respectively.[5] By extrapolation, **hydroxy**methylation of precursors **4** would lead to the important class of **21-hydroxy**-20-oxopregnanes **6**, Y = OH, equipped with the 17-(hydroxyacetyl) side chain of corticosteroids. A direct and short route to **6** via **5** (both with Y = OH) would involve addition of allylic anion **9** (derived from **4** by γ-deprotonation) to formaldehyde. Earlier work, however, has shown that reaction of aldehydes (and ketones) with anions of TosMIC, or monosubstituted TosMIC derivatives comparable to **9**, gives tosyloxazolines or oxazoles (such as **7a** and **8**), instead of the desired β-hydroxy isocyanides of type **5**, Y = OH. Clearly, the addition of anions **9** to carbonyl compounds is accompanied by ring closure (*i.e.* intramolecular α-addition of OH to the isocyano carbon). Indeed, when **4a** was treated with formaldehyde and base, tosyloxazoline **7a** (3:2 mixture of C4′ epimers) was formed in almost quantitative yield, using phase transfer catalysis (PTC) conditions at rt [(benzene/50% NaOH and 10 mol % of benzyltriethylammonium chloride (BTEAC)]. At higher temperatures, the formation of **7** is followed by 1,2-elimination of *p*-toluenesulfinic acid (TosH, salt) to give oxazoles **8**.



1 X = H, A-B = CH_2-CH_2

2 X = OH, A-B = CH_2-CH_2

3 X = H, A-B = CH=CH



4

(Tos = 4-$CH_3C_6H_4SO_2$)

4-Tosyl-2-oxazolines 7 *vs* 2-Methoxy-3-oxazolines 12. The structure of the tosyloxazoline moiety of com-

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[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1994.

(1) Chemistry of Sulfonylmethyl Isocyanides. 40. For 39, see: Leusink, F. R.; ten Have, R.; van den Berg, K. J.; van Leusen, A. M. *J. Chem. Soc., Chem. Commun.* **1992**, 1401.

(2) (a) Lenz, G. R. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley Interscience: London, 1983; Vol. 21, p 645. (b) Marsheck, W. J.; Krachy, S.; Muit, R. D. *Appl. Microbiol.* **1972**, *23*, 72. (c) Wovcha, M. G.; Antosz, J. C.; Knigt, L. A.; Komineck, L. A.; Pyke, T. R. *Biochim. Biophys. Acta* **1978**, *539*, 308.

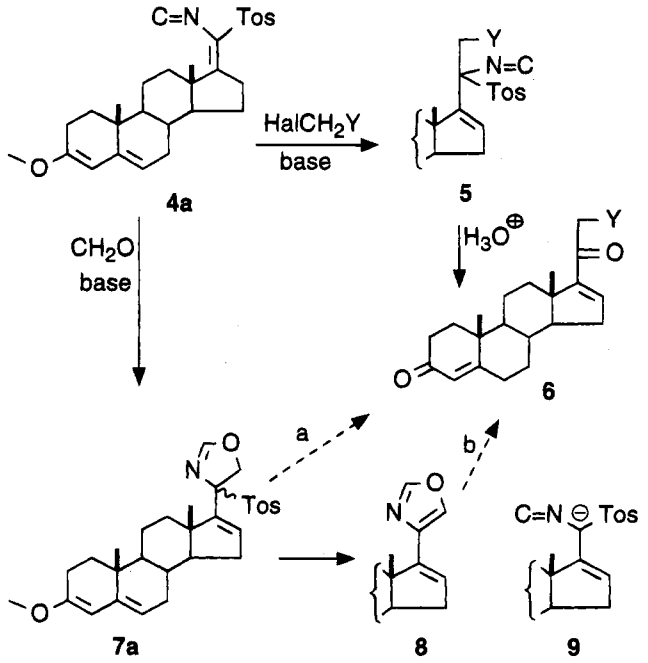
(3) (a) Kubriner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24. (b) Gasc, J. C.; Nédélec, L. *Tetrahedron Lett.* **1971**, 2005. (c) Bull, J. R.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2150. (d) Wroble, R. R.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2939. (e) VanRheenen, V.; Shephard, K. P. *J. Org. Chem.* **1979**, *44*, 1582. (f) Nédélec, L.; Torelli, V.; Hardy, M. *J. Chem. Soc., Chem. Commun.* **1981**, 775. (g) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Nouv. J. Chim.* **1982**, *6*, 295. (h) Redpath, J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75. (i) Danieuwski, A. R.; Wojciechowska, W. *Synthesis* **1984**, 132. (j) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Bull. Soc. Chim. Fr. II* **1987**, 61. (k) Livingston, D. A.; Petre, J. E.; Bergh, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 6449. (l) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1990**, *31*, 1889. (m) Carruthers, N. I.; Garshasb, S.; McPhail A. T. *J. Org. Chem.* **1992**, *57*, 961. (n) Stoelwinder, J.; van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2249.

(4) (a) van Leusen, D.; van Echten, E.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 469. (b) van Leusen, D.; van Leusen, A. M. *Synthesis* **1991**, 531.

(5) van Leusen, D.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 402.

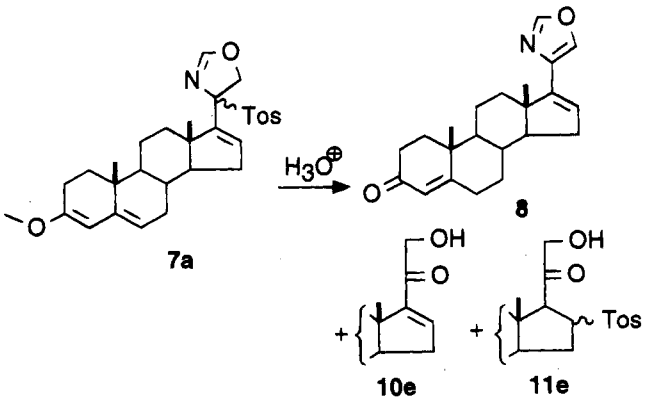
0022-3263/94/1959-5650$04.50/0

Scheme 1. Examples of the Introduction of Various C21 Moieties in 17-(Isocyanotosylmethylene)steroids 4. For Other Steroid Units a–p, see Chart 1



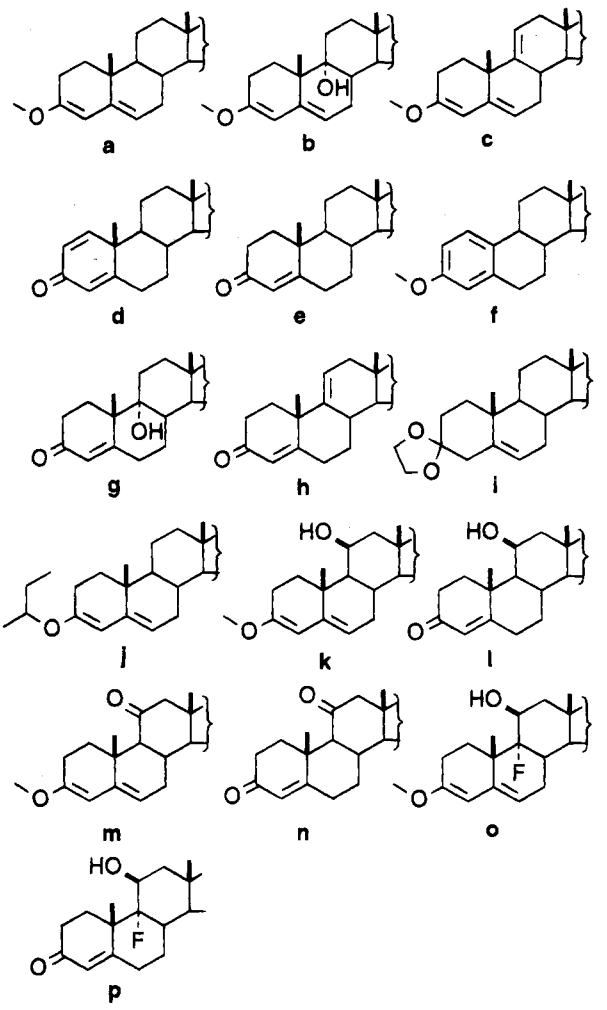
[a] See text. [b] See ref 14.

Scheme 2



pounds **7** is such that (acid) hydrolysis ought to give the desired 17-(hydroxyacetyl) group of **6**, Y = OH, and in fact it does.[6] However, this approach to **6** is of little practical value. Unattractive results were obtained when (impure) **7a** was subjected to acid hydrolysis (4 N H_2SO_4, THF, rt, 17 h, Scheme 2): **7a** was almost quantitatively converted into a mixture of oxazole **8e**,[7,8] the desired 17-(hydroxyacetyl)steroid derivative **10e** (from here on **10** stands for **6** with Y = OH), and compound **11e** (by addition of TosH to the C16,C17 double bond of **10e**),[8] in a ratio of 1:3:6, respectively. Furthermore, tosyloxazoline **7a** is difficult to work with; it is an unstable compound that could not be purified by chromatography or crystallization and that decomposes upon storage even at −20 °C.

Chart 1. Structures of the A, B, and C Ring Moieties of the Steroid Derivatives Described in This Paper



A solution to the above difficulties was offered by the observation that a new product (2-methoxy-3-oxazoline **12a**) was formed when the reaction of **4a** and formaldehyde was carried out in MeOH. Under these conditions (MeOH, K_2CO_3, rt; previously used for the synthesis of tosyloxazolines from TosMIC),[9] we now obtained from **4a** a nearly quantitative mixture of oxazole **8a** and 2-methoxy-3-oxazoline **12a** (7:3, respectively); tosyloxazoline **7a** was not observed.[10] The formation of **12** is explained by the addition–elimination sequence of Scheme 3. 2-Methoxy-3-oxazolines **12** basically are *N,O,O*-orthoformates, which subsequently turned out to be excellent precursors for the synthesis of 17-(hydroxyacetyl)steroids **10** (by acid hydrolysis, Table 1).

2-Methoxy-3-oxazolines 12: Synthesis. The yield of methoxyoxazoline **12a** was improved from 30 to 90% by carrying out the PTC reaction of **4a** and formaldehyde (described above) in the presence of 10 equiv of MeOH

(6) Possel, O. Ph.D. Thesis, Groningen University, 1978.

(7) The letter indicator in the compound numbers refers to the A, B, and C rings of the steroid structure, as depicted in Chart 1. Note that this moiety may change during a reaction, for example with H_3O^+ the dienol ether of **a** will hydrolyze to the enone function of **e**.

(8) Probably, **8e** is formed by acid hydrolysis of the dienol ether group of **8a**, already present as impurity in crude **7a**. However, we can not exclude that part of **8e** is formed from **7a** (Scheme 2). TosH would be eliminated in this process, as in the acid hydrolysis of **7a** to **10e**. Attempts to convert compounds of type **11** to **10** by subsequent elimination of TosH have met with little success: ref 11, p 59.

(9) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369.

(10) The enhanced tendency to form oxazole **8a** (instead of tosyloxazoline **7a**) is a result of the use of monosubstituted TosMIC derivatives (such as **9**) and thus of the absence of an (acidic) proton at C4′ in **7a**. This facilitates the 1,2-elimination of TosH from **7a**. Similar observations were made earlier in the synthesis of imidazoles: van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.

Scheme 3

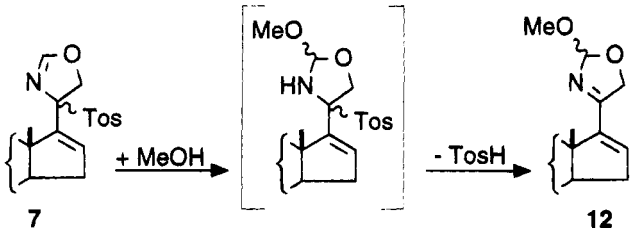
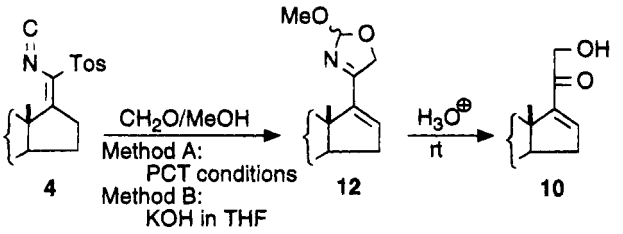


Table 1. 21-Hydroxy-20-oxosteroids 10 Synthesized from 4 via 2-Methoxyoxazolines 12 by Reaction with Formaldehyde and Methanol Followed by Acid Hydrolysis



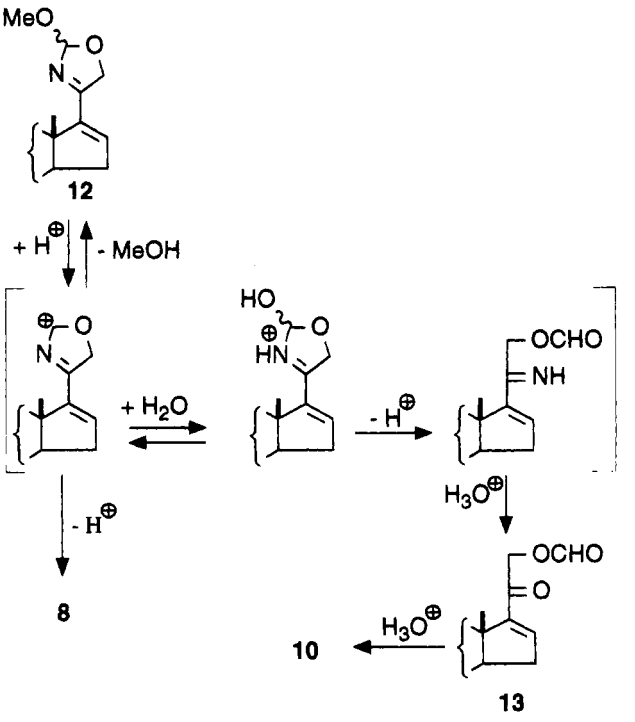
entry	starting compd[a]	oxazolines 12 yield[b] (%)			21-hydroxy 20-ketones 10		
			method A	method B		yield[c] (%)	mp (°C)
1	**4a**	**12a**	90	94	**10e**	90	215–220[d]
2	**4b**	**12b**		84	**10g**	43	220–222[e]
3	**4c**	**12c**	(93)	91	**10h**	93	200–205[f]
4	**4d**	**12d**	(83)	81	**10d**	83	172–174
5	**4f**	**12f**	(92)	90	**10f**	92	144–146
6	**4i**	**12i**		72	**10e**	92	*g*
7	**4j**	**12j**	56		**10e**	73	*g*
8	**4k**	**12k**	(68)		**10l**	68	148–153[h]
9	**4m**	**12m**	(73)		**10n**	73	213–218[i]
10	**4o**	**12o**	(71)		**10p**	71	175–186

[a] For synthesis, see ref 5; for structures see Chart 1 and ref 7. [b] Yields of compounds **12** refer to crude products (see text); when placed in parentheses these are minimum yields based on the overall conversion of **4** to **10**. [c] Yields of purified material based on compounds **4**. [d] Mp lit.[17] 227–232 °C. [e] Mp with dec. [f] Mp lit.[15] 204–209 °C. [g] Identical with **10e** prepared from **12a** (entry 1). [h] Mp lit.[15] 154–156 °C. [i] Mp lit.[15] 223–228 °C.

(Table 1, entry 1, method A). Further improvement was achieved by replacing the PTC method for a reaction with powdered KOH in THF with 10 equiv of MeOH (entry 1, method B). This improvement (94% yield of **12a**) especially relates to the ease of workup, which merely implies filtration and removal of solvents. The synthesis of methoxyoxazolines **12** was applied to several different steroids (Table 1 and Chart 1); the reaction was carried out successfully *inter alia* with steroids bearing unprotected OH groups at C9 (entry 2) or C11 (entries 8 and 10), as well as unprotected C=O groups at C11 (entry 9) and C3 (entry 4).

2-Methoxy-3-oxazolines **12** are obtained as mixtures of two stereoisomers only (C2′ epimers, ratio 4:3), which usually are contaminated with *ca.* 5% of the corresponding oxazoles **8**. Impurities can be removed by crystallization; however, only at the expense of considerable amounts of **12**. It, therefore, is better to postpone purification until after hydrolysis to the 17-(hydroxyacetyl)steroids **10**, as described below. Repeated crystallization of methoxyoxazoline **12a** eventually gave material that proved by single-crystal X-ray analysis to have the *S* configuration at C2′ and a *s-trans* conformation for the C16,N21 moiety.[11]

Scheme 4



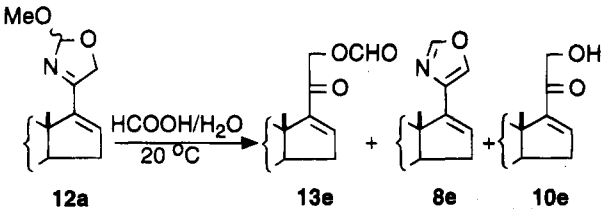
2-Methoxy-3-oxazolines **12** are reasonably stable compounds, which can be stored at −20 °C without decomposition. Compounds **12** have been chromatographed successfully over alumina, unlike tosyloxazolines **7**, which will lose TosH to give oxazoles **8**. Methoxyoxazolines **12** also form oxazoles **8**, by loss of MeOH, albeit under more drastic conditions, for example with strong base (BuLi in THF at rt) or at elevated temperatures (a melt of **12a** at 180 °C was converted quantitatively to oxazole **8a** in 2 min).

2-Methoxy-3-oxazolines 12: Hydrolysis. Complete hydrolysis of methoxyoxazolines **12** gives 21-hydroxy-20-oxosteroids **10** (Table 1). Scheme 4 provides a rationale for the hydrolytic processes. The hydrolysis to **10** is carried out effectively at rt with 2 to 4 N H_2SO_4 in THF (16–18 h). Under these conditions the conversions of **12** to **10** are essentially quantitative, with the exception of entry 2 (probably as a result of the acid sensitive tertiary 9α-hydroxy group of **12b**). The lower yields of **10** (based on **4**) of entries 7–10 are due to the first reaction step to **12**. Two potential side products of the hydrolysis to **10** have been identified. One is oxazole **8**, the same compound that is formed by elimination of TosH from tosyloxazoline **7** or MeOH from methoxyoxazoline **12**, as discussed above. Apparently, elimination of MeOH from **12** may be induced by acid also (see Scheme 4). The acid-induced elimination of MeOH becomes prominent when little or no water is present. For example, oxazole **8e** was formed quantitatively from **12a**[7] with dry HCl in THF (compare Table 2). A second potential impurity, formed on hydrolysis to **10**, is formate **13**, which results from incomplete hydrolysis of **12** (Scheme 4).

For practical purposes the hydrolysis to 21-hydroxy-20-oxosteroids **10** is best carried out with crude methoxyoxazolines **12**, as was explained above. Therefore, only the yields of hydroxy ketones **10** (based on **4**, Table 1) relate to isolated and purified materials. The yields

(11) van Leusen, D. Ph.D. Thesis, Groningen University, 1990, p 84.

Table 2. Hydrolysis of Methoxyoxazoline 12a (0.1 mmol) in Aqueous Formic Acid under Various Conditions at rt



					products and yields[a] (%)		
entry	time	HCOOH (mL)	H_2O (mL)	acetone (mL)	formate **13e**	oxazole **8e**	hydroxy ketone **10e**
1	60h	0.99	0.01		50	50	
2	1 h	0.8	0.2		75	25	
3	17 h	0.7	0.3		50	7	41
4	90 min	0.7	0.3		88	7	5
5	20 min	0.7	0.3		70	6	
6	90 min	0.6	0.4		90	3	7
7	45 min	0.6	0.4		90	3	4
8	20 min	0.6	0.4		72	3	
9	5 h	0.5	0.5	4	68	20	12
10	17 h	0.5	0.5	4	60	20	20

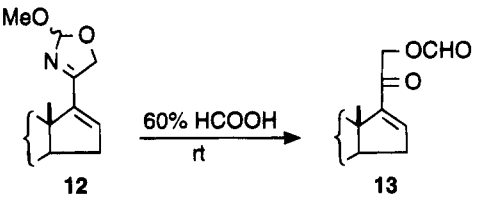
[a] Yields determined by ^1H NMR analysis of crude reaction mixtures, consisting of **13e**, **10e**, **8e**, and an unidentified product (probably an intermediate of the hydrolysis) by integration of characteristic signals at δ 7.64 of **8e**, 4.45 of **10e**, 8.17 of **13e**, and taking the signal of C4-*H* between 5.6 and 5.72, present in all four products, as 100%.

of oxazolines **12** refer to crude materials containing 3–10% of oxazoles **8**.

The C21 formates **13**—intermediates in the hydrolysis to **10**—are of interest in their own right. These 17-(hydroxyacetyl)steroids, with a formyl-protected OH, may serve as alternatives for the usual C21 acetates.[12] Besides, incomplete hydrolysis of methoxyoxazolines **12** offers a new method of synthesizing such formyl-protected 21-hydroxysteroids **13** in a direct manner, without the necessity to prepare unprotected 21-hydroxy-20-oxosteroids first.[13] We, therefore, have adjusted the hydrolysis conditions of **10** so as to obtain formates **13** as main products. The best results were obtained by using 60% aqueous formic acid for 45 min at rt. Thus, purified methoxyoxazoline **12a** (free of oxazole **8a**) gave formate **13e** together with hydroxy ketone **10e** and oxazole **8e** in 90% yield and a ratio of 90:4:3 (Table 2, entry 7).[7] With 80% aqueous formic acid, for example, **13e** and **8e** were obtained in a 75:25 ratio (entry 2). Analogous formates are collected in Table 3.

Further Extensions. We have shown previously that the C17,C20 double bond of **4a** can be reduced almost quantitatively to give 17β-(isocyanotosylmethyl)-3-methoxyandrosta-3,5-diene (**14a**, Scheme 5).[4b] Reaction of this compound with formaldehyde and MeOH, in much the same way as compound **4a**, gave 2-methoxy-3-oxazolinylsteroid **15a** in 96% yield (using powdered KOH in THF, *i.e.* method B of Table 1). Methoxyoxazoline **15a** (an analog of **10a** without the double bond at C16,C17) apparently is formed via deprotonation at C20. Acid

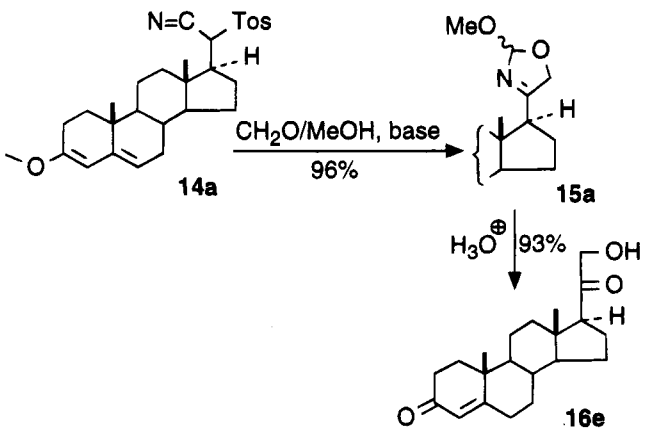
Table 3. Formates 13 Prepared by Partial Hydrolysis of Methoxyoxazolines 12



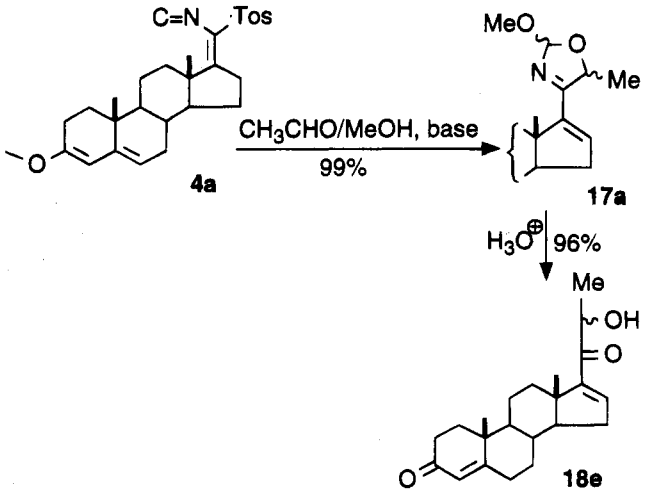
entry	starting compd[a]	product[b]	yield[c] (%)	mp (°C)
1	**12a**	**13e**	69	140–143
2	**12b**	**13g**	75	213–220[d]
3	**12c**	**13h**	31	125–132
4	**12f**	**13f**	79	122–124

[a] Crude materials were used. [b] See ref 7 and Chart 1. [c] Purified materials. [d] Mp with dec.

Scheme 5



Scheme 6



hydrolysis of **15a** (4 N H_2SO_4, THF, rt, 40 h) gave 21-hydroxypregn-4-ene-3,20-dione (desoxycorticosterone, **16e**)[7] in 93% yield.

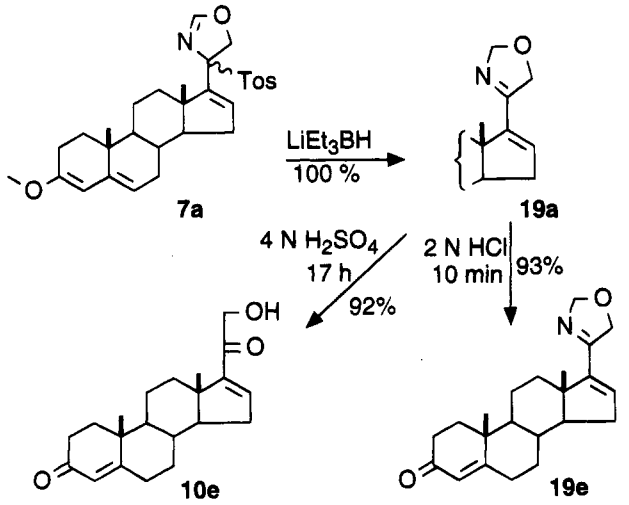
The formation of methoxyoxazolines is not restricted to the use of formaldehyde. Reaction of **4a** with acetaldehyde and MeOH gave 2-methoxy-5-methyloxazoline **17a** as a mixture of two pairs of epimers (Scheme 6). Acid hydrolysis of this mixture (3 N H_2SO_4, THF, rt, 36 h) gave 21-hydroxy-21-methylpregna-4,16-diene-3,20-dione (**18e**) in 96% yield (based on **4a**).

Alternative Approaches to 17-(Hydroxyacetyl)-steroids. Above, we have shown that 2-methoxy-3-oxazolines **12** are much more attractive synthetic inter-

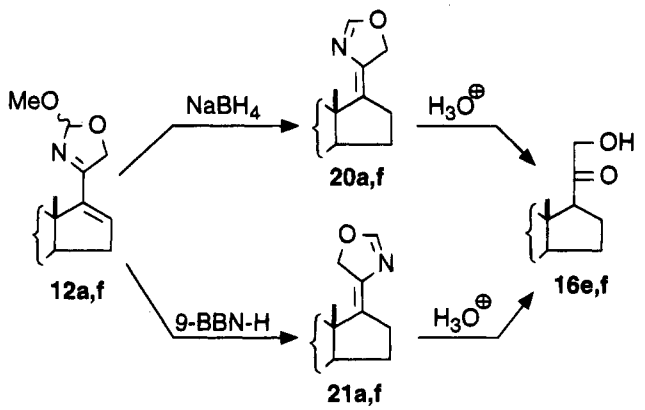
(12) Gardi, R.; Ercoli, A. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Reinhold: New York, 1972; Vol. I, Chapter 7.

(13) The formyl-protected 17-(hydroxyacetyl) group of **13b** has been effectively exploited in a 16,17-bishydroxylation as part of a new synthesis of 11β,21-dihydroxy-9-fluoro-16α,17-(isopropylidenedioxy)-pregna-1,4-diene-3,20-dione (triamcinolone acetonide): van Leusen, D.; van Leusen, A. M., to be published.

Scheme 7



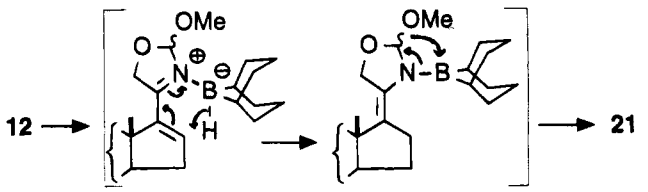
Scheme 8



mediates than the 4-tosyl-2-oxazolines **7** through which they are prepared. Acid hydrolysis of the (cyclic) *N,O,O*-orthoformate type structure of compounds **12** gives a good entry into the 17-(hydroxyacetyl) groups of **10** (and **13**). However, the C2′-methoxy group of **12** is not strictly necessary for this conversion: *N,O*-acetyl type compounds, such as the oxazolines **19**, **20**, and **21** (Schemes 7 and 8), in principle could do the same job.[14a] In fact there could be an advantage in using such *N,O*-acetals because elimination of MeOH (to oxazoles **8**, a potential side reaction in the hydrolysis of **12**, see Table 2) is no longer possible.

According to Scheme 7, freshly prepared tosyloxazoline **7a** was reduced with lithium triethylborohydride to give 3-oxazoline **19a** in nearly quantitative yield. Compound **19a** turned out to be more stable than 2-methoxy-3-oxazoline **12a**. For instance, it is possible to selectively hydrolyze the dienol ether group of **19a** to **19e** (2 N HCl, rt, 10 min) without affecting the oxazoline part of the molecule. A similar selective hydrolysis of 2-methoxy-3-oxazoline **12a** is not possible. Hydrolysis of **19a** under more drastic conditions (4 N H_2SO_4, rt, overnight) gave hydroxy ketone **10e** in 92% yield.

Scheme 9



Reductive removal of the C2′-methoxy group of methoxyoxazolines **12** gave the 2-oxazolines **20** and **21** (different from **19**), which upon acid hydrolysis gave 17-(hydroxyacetyl)steroids **16** (Scheme 8). The reductions were carried out with **12a** as well as **12f**. Reduction with $NaBH_4$ gave oxazolines **20a** and **20f**, respectively, in nearly quantitative yields, and with exclusive formation of the *Z* configuration. The *E* isomers **21a** and **21f** were obtained when the reductions were carried out with 9-BBN-H in 78 and 72% yield, respectively. Both **20a** and **21a** were converted by acid hydrolysis (4 N H_2SO_4, THF, rt, 70 h) to desoxycorticosterone **16e**[7] in 94 and 100% yield, respectively.

The structures of oxazoline **19e**[15] and **21f**[16] were confirmed by X-ray analysis.

The preference for the *E* configuration of **21** in the 9-BBN-H reduction of **12** is explained by assuming internal hydride delivery in the borane complex as in Scheme 9, whereas the *Z* configuration obtained with $NaBH_4$ could result from methoxy elimination in **12a** in the *s-trans* conformation (as found in the solid state, see above) upon hydride attack at C16.

Experimental Section

General Remarks. All reactions were carried out under nitrogen, with the exception of those in which aqueous acid was used. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ at 200 MHz (unless stated otherwise). APT ^{13}C NMR spectra were recorded at 75.43 MHz. Downward CH and CH_3 signals are reported as (−) chemical shifts; assignments are given for the sp^2 carbons only. Centrifugal liquid chromatography (CLC) separations were carried out on a Hitachi CLC-5 centrifugal liquid chromatograph ("Chromatotron"). For letter indicators **a**−**p**, see footnote 7 and Chart 1. THF was distilled from $LiAlH_4$.

(4′*R*)- and (4′*S*)-3-Methoxy-17-(4-tosyl-2-oxazolin-4-yl)-androsta-3,5,16-triene (7a). Method A: Phase Transfer Procedure. To a mixture of isocyanide 4a[5] (0.95 g, 2.0 mmol), 37% aqueous solution of formaldehyde (0.5 mL, 6 mmol), and BTEAC (0.04 g, 0.2 mmol) in benzene (40 mL) was added 50% aqueous NaOH (20 mL). The mixture was stirred vigorously for 2 h at rt. The organic layer was washed with brine (20 mL) and concentrated to give 0.85 g (87%) of crude 7a as a pale yellow solid. Attempts to purify 7a by crystallization or chromatography failed, due to its instability. Therefore 7a should be used immediately after preparation: no elemental analysis made; IR (Nujol) 1655, 1630, 1620, 1313, 1150 cm^{-1}; ^1H NMR (60 MHz) δ 0.6−2.7 (m), 0.63, 0.79 (2 × s), 0.95 (s), 2.42 (s), 3.5 (s), 4.0−5.4 (m), 5.9−6.2 (m), 6.95 (br s), 7.19, 7.32, 7.64 and 7.78 (AB q).

Method B: Homogeneous Procedure. To a mixture of isocyanide **4a**[5] (2.39 g, 5.0 mmol) and 37% aqueous formaldehyde (1 mL, 13 mmol) in THF (45 mL) was added powdered KOH (5 g). The mixture was stirred for 3 min at rt and then filtered through a layer of Na_2SO_4 (*ca.* 25 g) and concentrated

(14) (a) It should be pointed out that even oxazoles **8** formally belong to this category of *N,O*-acetals, but acid hydrolysis to **10** does not seem a realistic proposition due to aromatic stabilization.[14b] However, we have been able to show that oxazoles **8a** (in 96% yield from **4a**, see Experimental Section) and **8f** (as well as their C16,C17 saturated counterparts) can be converted to 17-(hydroxyacetyl)steroids via activation of the oxazole ring by N-methylation (using TosOMe),[14c] followed by reductive ring opening ($LiAlH_4$), and O-acetylation (Ac_2O) to 17-[2-acetoxy-1-(dimethylamino)ethenyl]steroids. Upon acid hydrolysis, these compounds gave the C21 *O*-acetyl derivatives of **10a**, **10f**, **16a**, and **16f** in overall yields of 34, 30, 33, and 78%, respectively.[14d] (b) Turchi, I. J. *J. Heterocycl. Comp.* **1986**, *45*, 1. (c) Ott, D. G.; Hayes, F. N.; Herr, V. N. *J. Am. Chem. Soc.* **1956**, *78*, 1941. (d) Reference 11, p 93 ff.

(15) Reference 11, p 122 ff.

(16) Meetsma, A.; van Leusen, D.; van Leusen, A. M. *Acta Cryst.* **1993**, *C49*, 351.

to give a slightly yellow solid. The solid was dried in vacuum (0.01 Torr) for 15 min to give 2.5 g (100%) of **7a**. According to ^{1}H NMR, **7a** was more than 95% pure.

3-Methoxy-17-(oxazol-4-yl)androsta-3,5,16-triene (8a). A mixture of isocyanide **4a**[5] (5.95 g, 12.5 mmol), Na_2CO_3 (4.0 g, 37 mmol), paraformaldehyde (2.0 g, 66 mmol), and MeOH (100 mL) was refluxed for 5 h. The mixture was concentrated and water (100 mL) was added. This mixture was extracted with CH_2Cl_2 (50, 25, and 25 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. By column chromatography (alumina, CH_2Cl_2) 4.22 g (96%) of 8a was obtained, mp 115–135 °C. Analytically pure 8a: mp 135–136 °C (from Et_2O); IR (KBr) 3130, 3050 (oxazole), 1650, 1625 cm^{-1}; ^{1}H NMR δ 1.0–2.5 (m), 1.00 (s), 1.03 (s), 3.58 (s), 5.15 (s), 5.26 (m) 6.30 (m), 7.60 and 7.84 (2 × s); ^{13}C NMR δ 155.2, 150.6 (d), 144.5, 141.0, 136.0, (−)132.5, (−)128.2, (−)118.0, (−)98.5, (−)57.2, (−)-54.2, (−)48.6, 46.3, 35.3, 33.7, 31.4, (−)30.2, 25.2, 21.0, (−)-18.9, (−)16.1. Anal. Calcd for $C_{23}H_{29}NO_2$ (351.493): C, 78.60; H, 8.32; N, 3.98. Found: C, 78.6; H, 8.4; N, 4.0.

17-(Oxazol-4-yl)androsta-4,16-dien-3-one (8e). By Hydrolysis of 8a. A mixture of oxazole **8a** (7.10 g, 20.2 mmol), CH_2Cl_2 (50 mL), and 2 N HCl (25 mL) was stirred vigorously for 30 min at rt. The organic layer was separated, dried (Na_2SO_4), and concentrated to give 6.35 g (93%) of **8e**, mp 190–194 °C. Analytically pure **8e** was obtained by crystallization from MeOH, mp 200–201 °C: $[\alpha]^{20}_{578}$ +161° (*c* 1.0, $CHCl_3$); IR (KBr) 3120, 3035, 1660, 1610 cm^{-1}; ^{1}H NMR δ 0.7–2.7 (m), 0.98 (s), 1.20 (s), 5.60 (s), 6.0–6.2 (m), 7.40 and 7.64 (2 × s); ^{13}C NMR δ 199.4, 171.0, 150.7 (d), 144.3, 135.9, (−)132.5, (−)-128.0, (−)124.0, (−)56.3, (−)54.0, 46.2, 38.7, 35.5, 35.1, (−)-33.9, 32.7, 31.7, 31.4, 20.9, (−)17.2, (−)16.1. Anal. Calcd for $C_{22}H_{27}NO_2$ (337.466): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.2; H, 8.0; N, 4.1.

From Methoxyoxazoline 12a. Gaseous HCl was injected from a syringe into a solution of oxazoline **12a** (see below, 0.19 g, 0.5 mmol) in 10 mL of THF. After 15 min, the solution was concentrated to give 0.17 g (100%) of **8e**, mp 188–192 °C, identical with **8e** obtained from **8a** by ^{1}H NMR and IR.

21-Hydroxypregna-4,16-diene-3,20-dione (10e). From 12a. To a solution of crude methoxyoxazoline **12a** (0.17 g, prepared from 0.5 mmol of isocyanide **4a**,[5] using method A, see below) in THF (10 mL) was added 4 N H_2SO_4 (2.5 mL). After standing for 18 h at rt, 10 mL of water was added, and the mixture was concentrated to *ca.* 12 mL. The solid was collected, washed with water, and dried in vacuum (over KOH) to give 0.15 g (90%, based on **4a**) of **10e**, mp 190–210 °C. **10e** was obtained by crystallization from acetone/petroleum ether (bp 40–60 °C): mp 215–220 °C; $[\alpha]^{20}_D$ +142° (*c* 1.0, $CHCl_3$) {lit.[17] mp 227–232 °C; $[\alpha]^{20}_D$ +148° (*c* 0.9, $CHCl_3$)}; IR (Nujol) 3450, 1665, 1620 cm^{-1}; ^{1}H NMR δ 0.8–2.6 (m), 0.96 (s), 1.21 (s), 3.58 (br s), 4.33, 4.42, 4.48, 4.57 (AB q), 5.72 (s), 6.74 (m); ^{13}C NMR δ 199.4, 196.4, 170.6, 151.2, (−)144.4, (−)124.0, 65.0, (−)55.3, (−)54.0, 46.5, 38.7, 35.5, 34.3, 33.9, (−)33.7, 32.6, 32.5, 31.7, 20.7, (−)17.2, (−)16.0.

From 12i. Hydrolysis of **12i** (0.222 g, 0.54 mmol) in THF (15 mL) and 2 N H_2SO_4 (4.5 mL) for 16 h at rt gave 0.178 g of a mixture which was incompletely hydrolyzed. Therefore, hydrolysis was prolonged with 4 N H_2SO_4 (5 mL) in THF (15 mL) for another 16 h to give eventually 0.162 g (92%) of 21-hydroxypregna-4,16-diene-3,20-dione (**10e**). IR and ^{1}H NMR were identical with the spectra of **10e** obtained from **12a**, which is described above.

From 12j: see supplementary material.

9,21-Dihydroxypregna-4,16-diene-3,20-dione (10g). To a solution of crude oxazoline **12b** (0.40 g, 1.0 mmol, see below) in THF (15 mL) was added 2 N H_2SO_4 (2.5 mL). After standing for 22 h at rt, the mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (50, 25 and 15 mL). The combined extracts were washed with aqueous $NaHCO_3$ (25 mL) and with brine, dried (Na_2SO_4), and concentrated. By CLC (silica, CH_2Cl_2/MeOH 98:2) 0.15 g (43%) of **10g** was obtained, mp 215–220 °C dec. Analytically pure **10g** was obtained after one crystallization from CH_2Cl_2/Et_2O, mp 220–222 °C dec; $[\alpha]^{20}_{578}$ +128° (*c* 0.6, $CHCl_3$); IR (KBr) 3400, 1664, 1612, 1579 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.99 (s), 1.37 (s), 2.95 (br s), 3.58 (br s), 4.40–4.54 (AB q), 5.81 (s), 6.81 (t). Anal. Calcd for $C_{21}H_{28}NO_4$ (344.455): C, 73.23; H, 8.19. Found: C, 72.9; H, 8.2.

21-Hydroxypregna-4,9(11),16-triene-3,20-dione (10h) from 4c via 12c Using Method A. To a mixture of isocyanide **4c**[5] (0.48 g, 1.0 mmol), paraformaldehyde (0.3 g, 28 mmol), MeOH (0.4 mL, 10 mmol), and BTEAC (0.02 g, 0.1 mmol) in benzene (20 mL) was added NaOH (8 mL, 50% aqueous solution). The mixture was stirred vigorously for 2 h at rt. The aqueous layer was extracted with benzene (5 mL). The extract was combined with the organic layer and filtered through a layer of alumina (neutral, act. II/III; CH_2Cl_2; 2 × 3 cm i.d.) to give crude **12c** which was dissolved in a mixture of THF (15 mL) and 3 N H_2SO_4 (5 mL). After standing for 18 h at rt, 10 mL of water was added and the mixture was concentrated to a volume of ca. 15 mL. The solid was collected, washed with water, and dried in vacuum (over KOH) to give 0.30 g (93%) of **10h**, mp 180–193 °C. Pure **10h** was obtained by two crystallizations from CH_2Cl_2/Et_2O (2:7): mp 200–205 °C; $[\alpha]^{20}_D$ +204° (*c* 1.0, $CHCl_3$) {lit.[15] mp 204–209 °C; $[\alpha]^{24}_D$ +194° (*c* 1.0, $CHCl_3$)}; IR (Nujol) 3500, 1665, 1610, 1590 cm^{-1}; ^{1}H NMR δ 0.90 (s), 1.0–2.7 (m), 1.36 (s), 3.30 (t, J = 5 Hz), 4.40, 4.47, 4.51, 4.59 (d-AB q, J = 5 Hz), 5.7 (m), 5.75 (s), 6.77 (m); ^{13}C NMR δ 199.2, 196.3, 169.3, 149.7, 145.3, (−)144.2, (−)-124.1, (−)119.1, 65.1, (−)52.1, 44.7, 37.4, (−)35.0, 34.2, 33.7, 33.3, 32.6, 31.7, (−)26.2, (−)15.6.

21-Hydroxy-16ξ-tosylpregn-4-ene-3,20-dione (11e). To a solution of freshly prepared tosyloxazoline **7a** (0.51 g, *ca.* 1 mmol) in THF (25 mL) was added 4 N H_2SO_4 (2.5 mL). After standing for 17 h at rt, the mixture was poured into water (150 mL) and extracted with EtOAc (25, 10, and 10 mL). The combined extracts were washed with aqueous $NaHCO_3$ and once with water, dried (Na_2SO_4), and concentrated to give 0.44 g of a solid. According to ^{1}H NMR the product was a 3:1:6 mixture of 21-hydroxypregna-4,16-diene-3,20-dione (**10e**), 17-(oxazol-4-yl)androsta-4,16-dien-3-one (**8e**), and 21-hydroxy-16ξ-tosylpregn-4-ene-3,20-dione (**11e**), respectively. The less polar oxazole **8e** was separated by CLC (silica, CH_2Cl_2/MeOH, 99:1). The second fraction, a mixture of **10e** and **11e**, was dissolved in THF (20 mL). To this solution were added 2 N HCl (5 mL) and sodium *p*-toluenesulfinate (0.50 g, 2.8 mmol), and the mixture was stirred for 70 h at rt. The THF was removed and the remainder was extracted with CH_2Cl_2 (25, 10, and 10 mL). The combined extracts were washed with aqueous $NaHCO_3$ (25 mL) and with brine (25 mL), dried (Na_2SO_4), and concentrated to give 0.39 g (80% based on **4a**) of **11e**, which was crystallized from CH_2Cl_2/Et_2O, mp 148–155 °C; IR (KBr) 3400, 1725, 1665, 1640, 1600, 1340, 1310, 1150 cm^{-1}; ^{1}H NMR δ 0.56 (s), 0.7–2.5 (m), 1.07 (s), 2.35 (s), 2.9 (br), 2.95, 2.98 (d), 3.5–4.3 (m), 5.64 (s), 7.24, 7.26, 7.61 and 7.64 (AB q); ^{13}C NMR δ 206.5, 198.8, 169.5, 144.9, 134.9, (−)-129.8, (−)128.3, (−)123.8, 69.1, (−)64.3, (−)62.7, (−)59.1, (−)-53.9, 45.6, 38.2, 37.8, 35.3, (−)35.0, 34.1, 33.7, 32.2, 31.6, 27.0, (−)21.4, 20.5, (−)17.0, (−)15.8; exact mass calcd for $C_{28}H_{36}O_5S$ *m/e* 484.228, found 484.227.

(2′*R*)- and (2′*S*)-3-Methoxy-17-(2-methoxy-3-oxazolin-4-yl)androsta-3,5,16-triene (12a). Method A: Phase Transfer Procedure. To a mixture of isocyanide **4a**[5] (0.24 g, 0.5 mmol), 37% aqueous formaldehyde (0.2 mL, 2.5 mmol), MeOH (0.2 mL, 5 mmol), and BTEAC (0.015 g, 0.05 mmol) in benzene (10 mL) was added 50% aqueous NaOH (4 mL). The mixture was stirred vigorously for 5 h at rt. The aqueous layer was extracted with benzene (5 mL). The extract was combined with the organic layer and filtered through a layer of alumina (neutral, act. II/III; CH_2Cl_2; 2 × 3 cm i.d.) to give 0.17 g (90%) of crude **12a**, mp 110–120 °C. Analytically pure **12a** was obtained by crystallization from CH_2Cl_2/Et_2O: mp 123–128 °C; IR (KBr) 1655, 1630 cm^{-1}; ^{1}H NMR δ 0.8–2.6 (m), 1.04 (s), 1.02 (s), 3.35 and 3.36 (2 × s, ratio 2:1, C2′C*H*$_3$O), 3.57 (s), 4.6–4.8 (m), 5.14 (s), 5.24 (m), 6.28 (m), 6.55 (m); ^{13}C NMR δ 168.9, 168.7, 155.4, 147.2, (−)141.4, (−)141.2, (−)122.4, (−)-122.2, (−)117.6, (−)98.5, 73.4, (−)56.9, (−)54.3, (−)51.9, (−)-48.7, 46.9, 35.4, 34.8, 33.6, 32.5, 31.5, (−)30.2, 25.2, 20.8, (−)18.8, (−)15.9. Anal. Calcd for $C_{24}H_{33}NO_3$ (383.536): C, 75.16; H, 8.67; N, 3.65. Found: C, 75.1; H, 8.7.; N, 3.9.

(17) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1955**, *77*, 1028.

Method B: Homogeneous Procedure. To a stirred mixture of isocyanide **4a**[5] (2.38 g, 5.0 mmol), 37% aqueous formaldehyde (0.7 mL, 9 mmol), and MeOH (1 mL, 25 mmol) in THF (35 mL) cooled in an ice bath was added powdered KOH (1.3 g, 22 mmol). The ice bath was removed and stirring was continued for 1 h at rt. To the reaction mixture was added Na_2SO_4 (5 g), and after 5 min the mixture was filtered through a layer of alumina (neutral, act. II/III; CH_2Cl_2; 2 × 8 cm i.d.) to give 1.80 g (94%) of crude oxazoline **12a**, mp 118–122 °C.

(2′*R*)- and (2′*S*)-9-hydroxy-3-methoxy-17-(2-methoxy-3-oxazolin-4-yl)androsta-3,5,16-triene (12b) were prepared analogously to **12a** (method B) from isocyanide **4b**[5] (2.47 g, 5.0 mmol) in a crude yield of 1.69 g (84%). This material was crystallized twice from Et_2O/petroleum ether (bp 40–60 °C) to give analytically pure **12b**: mp 80–120 °C; IR (KBr) 3540, 1652, 1627 cm^{-1}; ^1H NMR (60 MHz) δ 0.9–2.7 (m), 1.01 (s), 1.12 (s), 3.24, 3.30 (2 × s, C2′CH_3O), 3.50 (s), 4.5–4.8 (m), 5.0–5.4 (m), 6.1–6.4 (m), 6.4–6.7 (m). Anal. Calcd for $C_{24}H_{33}NO_4$ (399.536): C, 72.15; H, 8.33; N, 3.51. Found: C, 71.8; H, 8.5; N, 3.4.

(2′*R*)- and (2′*S*)-3-methoxy-17-(2-methoxy-3-oxazolin-4-yl)androsta-3,5,9(11),16-tetraene (12c) were prepared analogously to **12a** (method B) from isocyanide **4c**[5] (2.38 g, 5.0 mmol) in a yield of 1.74 g (91%), mp 93–125 °C. Analytically pure **12c** was obtained after two crystallizations from MeOH: mp 146–148 °C; IR (KBr) 1648, 1620 cm^{-1}; ^1H NMR (60 MHz) δ 0.7–3.0 (m), 0.97 (s), 1.15 (s), 3.30 (s), 3.51 (s), 4.6–4.8 (m), 5.0–5.6 (m), 6.2–6.4 (m), 6.4–6.6 (m). Anal. Calcd for $C_{24}H_{31}NO_3$ (381.520): C, 75.56; H, 8.19; N, 3.67. Found: C, 75.5; H, 8.3; N, 3.6.

3,20-Dioxopregna-4,16-dien-21-yl Formate (13e). Oxazoline **12a** (0.58 g, 1.5 mmol) was dissolved in aqueous 60% formic acid (10 mL) at rt. After 45 min the solution was poured into brine (50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The extracts were combined, washed once with aqueous $NaHCO_3$ and with water, dried (Na_2SO_4), and concentrated to give, after one crystallization from Et_2O (10 mL), 0.37 g (69%) of **13e**, mp 140–143 °C. Analytically pure **13e** was obtained after one crystallization from CH_2Cl_2/Et_2O: mp 141–143 °C; $[\alpha]^{20}_D$ +146° (*c* 1.0, $CHCl_3$); IR (KBr) 1730, 1680, 1665, 1620 cm^{-1} (C=C); ^1H NMR δ 0.8–2.6 (m), 0.99 (s), 1.20 (s), 4.92, 5.00, 5.08, 5.16 (AB q), 5.72 (s), 6.77 (m), 8.17 (s); ^{13}C NMR δ 199.7, 189.3, 171.0, 160.1 (d), 151.8, (−)144.5, (−)124.0, 64.9, (−)55.2, (−)53.9, 46.8, 38.7, 35.4, 35.3, 34.3, 34.1, (−)33.7, 31.7, 31.4, 20.6, (−)17.1, (−)15.9. Anal. Calcd for $C_{22}H_{28}O_4$ (356.466): C, 74.13; H, 7.92. Found: C, 73.8; H, 8.0.

9-Hydroxy-3,20-dioxopregna-4,16-dien-21-yl formate (13g) was prepared analogously to **13e** from oxazoline **12b** (0.60 g, 1.5 mmol) in a yield of 0.42 g (75%), mp 213–220 °C dec, after one crystallization from CH_2Cl_2 (5 mL): $[\alpha]^{20}_D$ +130° (*c* 1.0, $CHCl_3$); IR (KBr) 3520, 1728, 1682, 1650 cm^{-1}; ^1H NMR δ 0.95 (s), 1.32 (s), 1.4–2.6 (m), 4.90, 4.98, 5.07, 5.15 (AB q), 5.84 (s), 6.77 (m), 8.15 (s); ^{13}C NMR δ 199.0, 189.3, 168.7, 160.0 (d), 151.4, (−)144.5, (−)126.8, 76.5, 64.9, (−)48.5, 46.6, 44.5, (−)35.7, 33.9, 32.3, 31.5, 30.1, 28.4, 26.9, 24.9, (−)19.7, (−)14.9. Anal. Calcd for $C_{22}H_{28}O_5$ (372.465): C, 70.94; H, 7.58. Found: C, 70.7; H, 7.5.

3,20-Dioxopregna-4,9(11),16-trien-21-yl formate (13h) was prepared analogously to **13e** from oxazoline **12c** (0.34 g, 0.9 mmol) in a yield of 0.18 g (57%), mp 141–143 °C. One crystallization from CH_2Cl_2/Et_2O raised the mp to 143–144 °C: $[\alpha]^{20}_D$ +196° (*c* 1.0, $CHCl_3$); IR (KBr) 1720, 1672, 1660, 1610, 1590 cm^{-1}; ^1H NMR (60 MHz) δ 0.7–3.3 (m), 0.89 (s), 1.33 (s), 4.98 (s), 5.3–5.6 (m), 5.65 (s), 6.6–6.9 (m) 8.07 (s). Anal. Calcd for $C_{22}H_{26}O_4$ (354.450): C, 74.55; H, 7.39. Found: C, 74.4; H, 7.4.

(2′*R*)- and (2′*S*)-3-methoxy-17β-(2-methoxy-3-oxazolin-4-yl)androsta-3,5-diene (15a) were prepared analogously to **12a** (method B) from 17β-(isocyanotosylmethyl)-3-methoxyandrosta-3,5-diene[4b] (**14a**, 2.40 g, 5.0 mmol) in a yield of 1.86 g (96%): mp 110–120 °C; IR (Nujol) 1655, 1635 cm^{-1}; ^1H NMR (60 MHz) δ 0.6–2.8 (m), 0.74 (s), 0.99 (s), 3.37 (s), 3.56 (s), 4.4–4.7 (m), 5.1–5.4 (m), 6.3–6.6 (m); exact mass calcd for $C_{24}H_{35}NO_3$ *m/e* 385.262, found 385.264.

21-Hydroxypregn-4-ene-3,20-dione (16e). To a solution of **15a** (1.86 g, 4.8 mmol) in THF (100 mL) was added 4 N H_2SO_4 (5 mL). After standing for 40 h at rt, water (50 mL) was added. The mixture was concentrated to a volume of ca. 50 mL, and this was extracted with CH_2Cl_2 (40, 25 and 10 mL). The combined extracts were washed with aqueous $NaHCO_3$ and with brine, dried (Na_2SO_4), and concentrated to give 1.48 g (93%) of **16e**, mp 128–135 °C. This material was crystallized from Et_2O, mp 134–138 °C: $[\alpha]^{20}_D$ +171° (*c* 1.5, acetone) {lit.[18] mp 141–142 °C; $[\alpha]^{22}_D$ +178° (*c* 1.5, acetone)}; IR (KBr) 3490, 1695, 1670, 1615 cm^{-1}; ^1H NMR δ 0.5–3.4 (m), 0.69 (s), 1.19 (s), 4.15 (s), 5.70 (s).

(2′*R*,5′*R*)-, (2′*R*,5′*S*)-, (2′*S*,5′*R*)-, and (2′*S*,5′*S*)-3-Methoxy-17-(2-methoxy-5-methyl-3-oxazolin-4-yl)androsta-3,5,16-triene (17a): (21*R*)- and (21*S*)-21-Hydroxy-21-methylpregna-4,16-diene-3,20-dione (18e). Oxazoline **17a** was prepared analogously to **12a** (method B) from isocyanide **4a**[5] (0.48 g, 1.0 mmol) and acetaldehyde (0.2 mL, 4 mmol) in a crude yield of 0.40 g (100%): IR (KBr) 1650, 1620, 1580 cm^{-1}; ^1H NMR δ 0.6–2.7 (m), 1.01 (s), 1.07 (s), 1.26 and 1.37 (d), 3.31 (s), 3.58 (s), 4.7–5.4 (m), 6.0–6.4 (m), 6.4 and 6.6 (m). To a solution of crude **17a** (0.40 g) in THF was added 3 N H_2SO_4 (1 mL). Water (10 mL) was added, after standing for 36 h at rt. The mixture was extracted with CH_2Cl_2 (25, 10 and 10 mL). The combined extracts were washed with dilute aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 0.33 g (96%, based on **4a**) of **18e** which was a mixture of C-21 epimers: IR (KBr) 3450, 1670, 1615, 1590 cm^{-1}; ^1H NMR δ 0.7–2.8 (m), 0.92 (s), 0.99 (s), 1.22 (s), 3.3–4.0 (m), 4.4–5.0 (m), 5.71 (s), 6.5–7.0 (m). Crystallization from Et_2O yielded 0.04 g (12%) of one of the epimers: mp 187–189 °C; ^1H NMR (300 MHz) δ 0.9–2.5 (m), 0.92 (s), 1.21 (s), 1.36 (d, *J* = 7 Hz), 3.47 (br), 4.67 (q, *J* = 7 Hz), 5.73 (s), 6.75 (t, *J* = 2 Hz); ^{13}C NMR δ 200.0, 199.2, 170.4, 150.6, (−)145.1, 123.9, (−)69.1, (−)55.4, (−)53.9, 46.6, 38.6, 35.4, 34.7, 33.8, (−)33.8, 32.4, 31.6, (−)22.9, 20.7, (−)17.1, (−)15.8. Anal. Calcd for $C_{22}H_{30}O_3$ (342.482): C, 77.16; H, 8.83. Found: C, 76.7; H, 8.7.

3-Methoxy-17-(3-oxazolin-4-yl)androsta-3,5,16-triene (19a). Freshly prepared tosyloxazoline **7a** (0.41 g, 0.80 mmol) was added to a stirred solution of $LiEt_3BH$ (2 mL, 1 M solution) in THF (10 mL) at 0 °C. The mixture was stirred for 3.5 h at rt and then poured into 100 mL of brine. The solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 0.30 g (100%) of **19a**, mp 169–172 °C. Analytically pure **19a** was obtained after one crystallization from CH_2Cl_2/MeOH: mp 173–174 °C; $[\alpha]^{20}_{578}$ −101° (*c* 0.5, $CHCl_3$); IR (KBr) 1650, 1625 cm^{-1}; ^1H NMR δ 0.8–2.6 (m), 1.02 (s), 3.58 (s), 4.64 (m), 5.15 (s), 5.26 (m), 5.63 (m), 6.13 (m); ^{13}C NMR δ 164.1, 155.4, 147.3, 141.3, (−)139.0, (−)117.6, (−)98.4, 96.9, 73.4, (−)56.9, (−)54.2, (−)48.7, 46.8, 35.4, 35.0, 33.7, 32.2, 31.5, (−)30.2, 25.3, 20.9, (−)18.9. (−)15.9. Anal. Calcd for $C_{23}H_{31}NO_2$ (353.485): C, 78.15; H, 8.84; N, 3.96. Found: C, 77.6; H, 8.9; N, 3.9.

17-(3-Oxazolin-4-yl)androsta-4,16-dien-3-one (19e). To a solution of **19a** (0.71 g, 2.0 mmol) in CH_2Cl_2 (50 mL) was added 2 N HCl (1 mL), and the mixture was stirred vigorously for 10 min at rt. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated. After one crystallization from MeOH/water, 0.63 g (93%) of **19e** was obtained, mp 187–191 °C. Analytically pure **19e** was obtained after one crystallization from Et_2O: mp 193–194 °C; $[\alpha]^{20}_{578}$ −167° (*c* 0.6, $CHCl_3$); IR (KBr) 1670, 1630, 1620 cm^{-1}; ^1H NMR δ 0.7–2.8 (m), 1.00 (s), 1.21 (s), 4.4–4.8 (m), 5.4–5.9 (m), 5.9–6.3 (s). Anal. Calcd for $C_{22}H_{29}NO_2$ (339.482): C, 77.83; H, 8.61; N, 4.13. Found: C, 77.8; H, 8.7; N, 4.0.

(*Z*)-3-Methoxy-17-(2-oxazolin-4-ylidene)androsta-3,5-diene (20a). $NaBH_4$ (0.19 g, 50 mmol) was added to a stirred suspension of oxazoline **12a** (1.92 g, 5.0 mmol) in THF (50 mL), EtOH (25 mL), and 0.2 N NaOH (10 mL). After stirring for 65 h at rt, the mixture was concentrated. After the addition of water (300 mL), the mixture was extracted with CH_2Cl_2 (50, 25 and 25 mL). The combined extracts were washed with

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brine (25 mL), dried (Na_2SO_4), and concentrated to give 1.78 g (100%) of **20a**, which was pure according to ^1H NMR. Analytically pure **20a** was obtained after crystallization from MeOH, mp 186 °C dec with preceding softening at 160 °C: $[\alpha]^{20}_{578}$ −170° (*c* 1.0, $CHCl_3$); IR (Nujol) 1655, 1630, 1590 cm^{-1}; ^1H NMR δ 0.9−2.8 (m), 0.95 (s), 0.99 (s), 3.57 (s), 4.61 (m), 5.14 (s), 5.25 (m), 7.07 (s); ^{13}C NMR δ 155.4, 141.0, 134.3, (−)-118.0, (−)98.4, 68.6, (−)56.5, (−)54.2, (−)48.4, 44.9, 36.7, 35.3, 33.7, 31.8, (−)31.3, 29.0, 25.3, 24.9, 21.1, (−)18.9, (−)17.4. Anal. Calcd for $C_{23}H_{31}NO_2$ (353.510): C, 78.15; H, 8.84; N, 3.96. Found: C, 77.8; H, 8.9; N, 3.9.

***(E)*-3-Methoxy-17-(2-oxazolin-4-ylidene)androsta-3,5-diene (21a).** To a solution of oxazoline **12a** (0.38 g, 1.0 mmol) in THF (25 mL) was added within 10 min at 0 °C a solution of 9-BBN-H (3 mL, 0.5 M solution in THF). After stirring for 3.5 h, the mixture was poured into an ice-cold solution of NaOH (2 g) in water (70 mL). By extraction (CH_2Cl_2) and one crystallization from Et_2O, 0.28 g (78%) of **21a** was obtained, mp 185−190 °C dec. Analytically pure **21a** was obtained after one crystallization from CH_2Cl_2/Et_2O: mp 188−190 °C dec; $[\alpha]^{20}_{578}$ −193° (*c* 1.0, $CHCl_3$); IR (Nujol) 1645, 1625, 1585 cm^{-1}; ^1H NMR δ 0.8−2.6 (m), 0.88 (s), 0.97 (s), 3.56 (s), 4.7−4.9 (m), 5.12 (s), 5.23 (m), 7.04 (s); ^{13}C NMR δ 157.1 (d, J = 219 Hz), 155.2, 140.7, 135.7, 135.6, (−)118.1, (−)98.5, 67.1, (−)56.1, (−)-54.2, (−)48.1, 43.5, 35.5, 35.2, 33.7, 31.5, (−)31.3, 28.1, 25.2, 24.4, 21.0, (−)18.9, (−)15.5. Anal. Calcd for $C_{23}H_{31}NO_2$ (353.510): C, 78.15; H, 8.84; N, 3.96. Found: C, 78.0; H, 8.8; N, 3.9.

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Supplementary Material Available: Experimental procedures and spectral data of compounds **10d**,**e**,**f**,**h**,**l**,**n**,**p**, **12d**,**f**,**i**,**j**, **13f**, **20f**, and **21f**, as well as spectral peak assignments of compounds described above (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.