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Synthesis of 20-oxo steroids[1]

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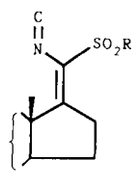
Abstract. The synthesis is described of a series of eighteen 16-dehydro-20-isocyano-20-sulfonylpregnanes (**5** and **8–14**) by C-20 alkylation of 17-[isocyano(sulfonyl)methylene]androstanes **1–3**. The geminal isocyano and sulfonyl groups at C-20 (compounds **5**, **8–14**) are removed by acid hydrolysis to provide a new entry into 20-oxo steroids (**6**, **15–19**). The C-20 alkylation also includes halomethylation and alkoxymethylation to form 21-halo- and 21-alkoxy-16-dehydro-20-oxopregnanes, respectively. As an attractive alternative to acid hydrolysis, the isocyano group is first oxidized with $Pb(OAc)_4$ to an isocyanato group prior to hydrolysis (of the geminal isocyanato and sulfonyl groups) to the same 20-oxo steroids. The latter conversion is carried out under non-acidic conditions at room temperature in a slurry of alumina in dichloromethane.

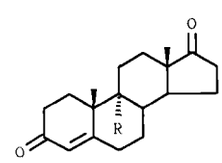
Recently, we have described the conversion of 17-oxo steroids **4** into 17-[isocyano(tosyl)methylene] steroids **1** and related sulfonyl compounds **2** and **3**[2a]. These isocyano steroids **1–3** are useful precursors in the synthesis of 20-oxo pregnane derivatives, as will be shown in this paper. Scheme I (top) provides an example of the high-yield, two-step transformation of **1a** into 16-dehydroprogesterone **6e****. The same scheme (bottom) shows an attractive, four-step alternative via $Pb(OAc)_4$ oxidation of isocyanide **5e** to isocyanate **7e**, followed by hydrolytic conversion on alumina to **6e**. The latter step offers the advantage of mild conditions over strongly acidic hydrolysis of **5a** to **6e**. Comparable yields were obtained in the 9α-hydroxy series, except for reaction **5b** → **6g** (Scheme 1, R = OH); further examples are given in Tables I, II and III.



1 R = 4-MeC_6H_4
2 R = 4-$MeOC_6H_4$
3 R = Me

17-Oxo steroids, in particular androst-4-ene-3,17-dione (**4e**) and its 9α-hydroxy derivative **4g**, are important, industrially available, synthetic intermediates in steroid modification processes[3]. As a first step in C-17-side-chain construction, the C-20 carbon atom is introduced in a formal condensation of, for example, the dienol ether of androstenedione **4a** and tosylmethyl isocyanide (TosMIC) to give **1a**[4]. Such a condensation is widely applicable with a large variety of 17-oxo steroids, as well as several different protective groups for the enone function of the A-ring and different sulfonyl groups RSO_2[2,5]. Isocyano steroids, such as **1–3**, are stable, non-smelling, and readily available starting materials. We are presently engaged in a program demonstrating their versatility as synthetic intermediates[5].

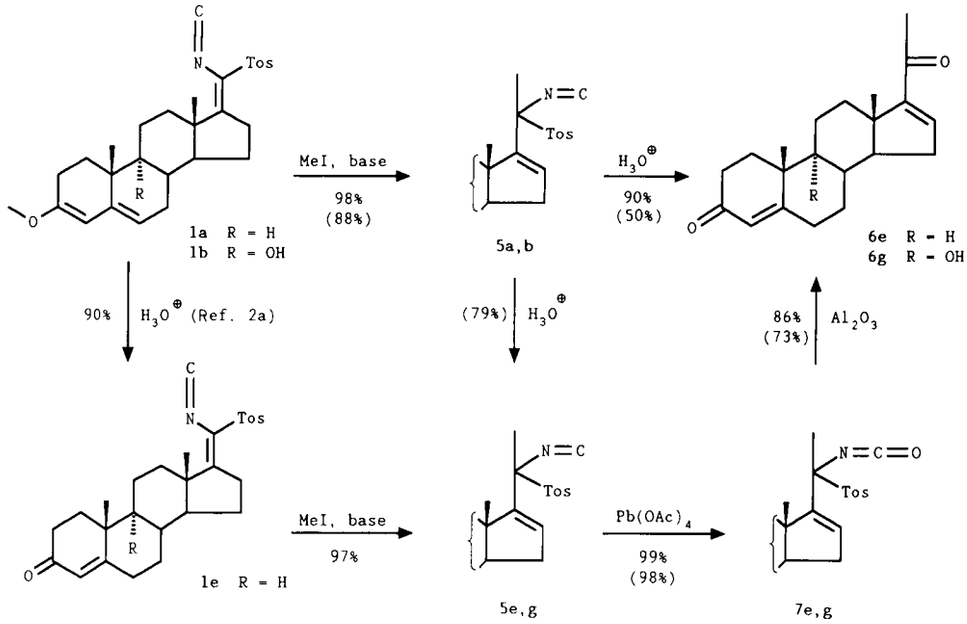
α,β-Unsaturated sulfonylmethyl isocyanides **1–3**, which in effect are masked carbonyl compounds of reversed polarity, bear a nucleophilic C-20 carbon (through allylic deprotonation at C-16). As such, this type of compounds acts as effective enone precursors[6].



4e R = H
4g R = OH

The easy access[3] to the 17-oxo steroids **4e** and **4g** has led to several new approaches to pregnanes and, in particular, to corticoids[7,8]. A variety of carbon nucleophiles has been used for the construction of side chains in reaction with these 17-oxo steroids[8]. Representative examples of the introduction of a two-carbon unit are based on addition of HC≡N or CH≡CH. The cyano group is converted into 17-acetyl with methyllithium or methylmagnesium halide[8a,b]. The latter method requires epimerization at C-17 to obtain the pregnane configuration. An interesting C-17 inversion,

** The letter symbols in the compound numbers refer to the structure of the A, B and C rings, as depicted in the Chart.



Scheme 1. Examples of reactions of Tables I and II[a].

[a] The letter symbols a and b in the compound numbers refer tot the A, B and C ring structures as indicated; for e and g see Chart. Yields without brackets refer to a, e series, yields between brackets refer to b, g series. For yields of further examples, see Tables I–III.

due to *VanRheenen* and *Sheppard*, involves a pericyclic rearrangement of an ethynyl sulfenate[8c]. Furthermore, various condensation reactions to $\Delta^{17(20)}$ steroids have been employed, using *inter alia* ethyl dichloromethoxyacetate[8d], nitromethane[8e], ethyl isocyanoacetate[8f], ethylidenetriphenylphosphorane[8g], diethyl (1-cyanoethyl)phosphonate[8h], diethyl (1-isocyanoethyl)phosphonate[8i] and diethyl (isocyanomethyl)phosphonate[8j]. With these methods, functionalization of the $\Delta^{17(20)}$ or Δ^{16} double bond usually provides the desired configuration at C-17. The 20-oxo group is obtained by acid hydrolysis of functionalities such as enol ethers[8d], α,β-unsaturated formamides or isocyanides[8f] and oximes[8e], which are formed either directly in the condensation step or by subsequent transformations. In some cases, the 21-CH_2OH group has been introduced by the use of formaldehyde[5a,8e].

The synthesis of 16-dehydroprogesterone (**6e**) was taken as a model for the preparation of 20-oxopregnane derivatives and has, therefore, been investigated in much detail (Scheme 1; Table I, entries 1–3; Table II, entries 1–4). Introduction of the C-21 carbon in **1a** with MeI to give **5a** proceeded equally as well with *t*-BuOK in 1,2-dimethoxyethane [(DME), −30 to +20°C, 1 h[6]; Method A] as under phase-transfer conditions [(PTC), 10% $PhCH_2NEt_3Cl$ (BTEAC), benzene/50% aqueous NaOH, 80°C, 1 h, Method B]. Protection of the enone function of the A ring of **4e** (necessary for the synthesis of **1a**)[2a] is no longer needed in C-20 alkylation, as appears from the conversion of **1e** to **5e** (Scheme 1; Table I, entry 7). The C-20 methylated product **5a** was obtained by both methods A and B as a mixture of C-20 epimers, with a melting range of 140–155°C (dec.; Table I, entry 1). The epimer ratio of about 2:1 was determined on the basis of the C-18 methyl signals in ^1H NMR at δ 0.87 and δ 1.00. The major epimer, mp 155–157°C (dec.), was obtained in a pure state, but no configurational assignment was made. Acid hydrolysis of the epimeric mixture **5a** to 16-dehydroprogesterone (**6e**) was best achieved in a mixture of 40% aqueous solution of $HClO_4$, Et_2O and CH_2Cl_2 (90% yield, 20°C, 3 min, Method C, Table II, entry 1). Alternatively, 5N HCl in Et_2O was used at 20°C for 30 min to give **6e** in 75% yield (Method D, Table II, entry 1). Under acid-hydrolysis conditions, the dienol ether protective group of the A ring is removed concomitantly. Separation and purification of the C-20 epimers of **5a** caused considerable loss of material. However, since the configuration of C-20 is lost in the next hydrolysis step, there is no need for such a separation. Thus, the recommended procedure for the synthesis of the 20-oxo compounds **6**, **7**, **15–19**, **21** is to hydrolyze the epimeric mixtures of **5**, **8–14** without purification. This approach has been followed for the further examples of Tables I and II.

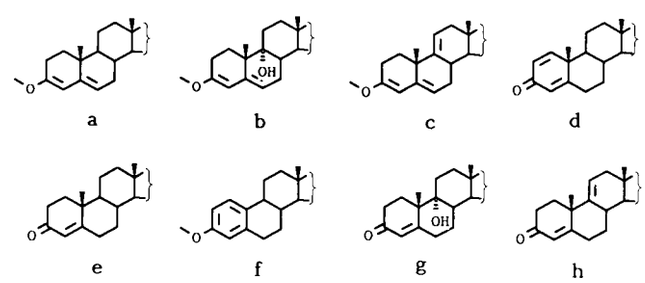
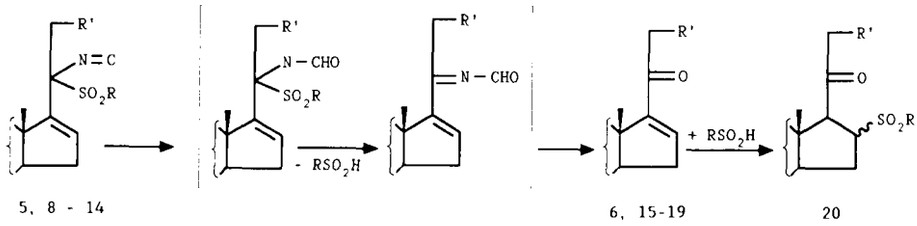
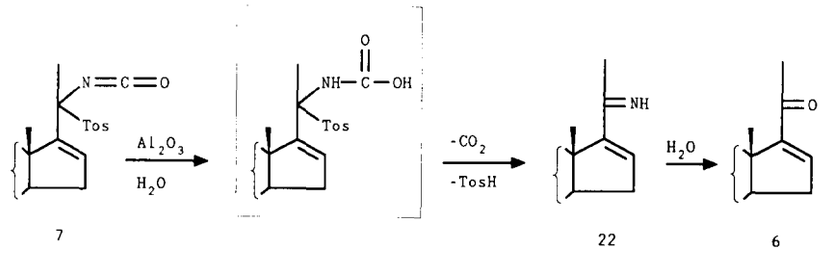


Chart. Structure of the A, B and C moieties of the steroids 1–22.

A problem associated with the hydrolytic removal of the geminal isocyano and sulfonyl groups from compounds **5**, **8–14** is formulated in Scheme 2. Sulfinic acid (RSO_2H), liberated in the course of the reaction, tends to add (in an acid-catalyzed reaction)[9] to the enone function of products **6**, **15–19** to form C-16-sulfonylated side products **20**. This became especially apparent after prolonged reaction times. For example, when the hydrolysis of **5a** was carried out for 4 hours with 5N HCl (instead of 30 min, as above), compound **20e** was formed in 90% yield. Therefore, acid hydrolysis of compounds **5**, **8–14** should be carried out at reaction times as short as possible, with acids (preferably $HClO_4$) at concentrations as high as the system will tolerate.



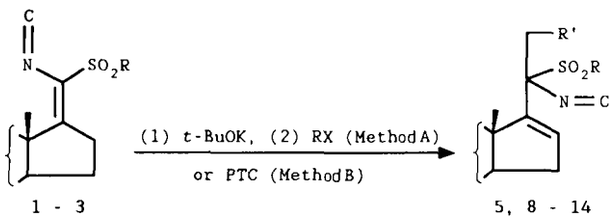
Scheme 2



Scheme 3

The disadvantage of the use of strong acids in the hydrolysis step is circumvented by $Pb(OAc)_4$ oxidation of the isocyanide group of **5e**[10] to isocyanate **7e** (Table III, entry 1). The C-20 geminal isocyanato and tosyl groups of **7e** are converted much more easily to the oxo group than the corresponding isocyano compound **5e**. 16-Dehydroprogesterone (**6e**) was obtained in 86% yield by simply stirring a slurry of **7e** and alumina (activity grade II–III) in CH_2Cl_2 at room temperature for 3 h (Method E, Table II, entry 2). Further examples of the $Pb(OAc)_4$ oxidation are given in Table III, and of the alumina-mediated hydrolysis in Table II (Method E).

Table I



Entry	Starting materials	Product				
		No.	R	R'	Yield[a] (%)	
					Method A	Method B
1	**1a** + MeI	**5a**	4-MeC_6H_4	H	98	93
2	**2a** + MeI	**8a**	4-$MeOC_6H_4$	H		92
3	**3a** + MeI	**9a**	Me	H		100
4	**1b** + MeI	**5b**	4-MeC_6H_4	H	88	
5	**1c** + MeI	**5c**	4-MeC_6H_4	H		94
6	**1d** + MeI	**5d**	4-MeC_6H_4	H		95
7	**1e** + MeI	**5e**	4-MeC_6H_4	H	97	
8	**1f** + MeI	**5f**	4-MeC_6H_4	H	>97[b]	
9	**1a** + EtI	**10a**	4-MeC_6H_4	Me		89
10	**1a** + CH_2Cl_2	**11a**	4-MeC_6H_4	Cl		89
11	**1f** + CH_2Cl_2	**11f**	4-MeC_6H_4	Cl		95
12	**1a** + CH_2Br_2	**12a**	4-MeC_6H_4	Br		76
13	**1a** + $MeOCH_2Cl$	**13a**	4-MeC_6H_4	MeO		74
14	**1a** + $PhCH_2OCH_2Cl$	**14a**	4-MeC_6H_4	$PhCH_2O$		54
15	**1d** + $PhCH_2OCH_2Cl$	**14d**	4-MeC_6H_4	$PhCH_2O$		80
16	**1f** + $PhCH_2OCH_2Cl$	**14f**	4-MeC_6H_4	$PhCH_2O$	36[c]	50
17	**5b**	**5g**	4-MeC_6H_4	H	79	
18	**11a**	**11e**	4-MeC_6H_4	Cl	85	

[a] Unless stated otherwise in the Experimental Section, the yields refer to C-20 epimeric mixtures in isolated but not completely purified state. [b] Compound was not isolated. Hydrolysis of the complete reaction mixture gave 20-oxo steroid **6f** in 97% yield. [c] Yield of one of the epimers.

It seems reasonable to assume that the conversion of **7** to **6** is initiated by hydration of the isocyanato group of **7** by water absorbed on the alumina, followed by elimination of CO_2 and TosH, and then hydrolysis of imine **22**, as depicted in Scheme 3. Evolution of gas (CO_2) was observed when compounds **7** and **21e** were brought in contact with alumina. 20-Imino steroid **22g** was also identified upon incomplete hydrolysis of isocyanato steroid **7g** (see Experimental under compound **6g**, Method E).

Equally high yields of C-20 methylation were achieved with MeI when **1a** (R = 4-tolyl) was replaced by **2a** or **3a** (R = 4-methoxyphenyl or methyl; Table I, entries 2 and 3, respectively). However, for R = *t*-butyl, methylation was no longer successful under the same reaction conditions, presumably for steric reasons. The methylation products **8a** and **9a** were also hydrolyzed to 16-dehydroprogesterone (**6e**); the yields, however, were not optimized (Table II, entries 3 and 4). All further reactions were carried out with TosMIC-based steroid derivatives **1a–1f** (R = 4-tolyl).

Entries 4–8 of Table I provide additional examples of efficient C-20 methylation of other steroid compounds, and entries 5, 7–9 of Table II give the results of some further acid hydrolyses. Reaction of EtI followed the same pattern as with MeI (Table I, entry 9; Table II, entry 10).

Chloromethylation of **1a** and **1f** at C-20 was achieved successfully under PTC conditions at 20°C using CH_2Cl_2 both as organic phase and as reagent (Table I, entries 10 and 11). Acid hydrolysis of the chloromethylation products **11** to 21-chloropregnenes **16** needed more drastic reaction conditions than the 21-unsubstituted steroids **5**, causing lower yields (Method D, 12N HCl, 10 min, 20°C, Table II, entries 11 and 13). An improvement in yield was obtained by using 40% aqueous $HClO_4$ in Et_2O (50% of **16e**, Method C, 10 min, 30°C, entry 11).

Hydrolysis of 21-bromo steroid **12a** with concentrated HCl (Method D) led to a complex mixture, which was not separated. Spectral analysis of the mixture suggested the presence of some **17e** and also some **16e** (by replacement of the C-21 bromine for chlorine). However, the conversion into **17e** was successful when the reaction was carried out with $HClO_4$ (Method C, 10 min, 30°C, Table II, entry 14).

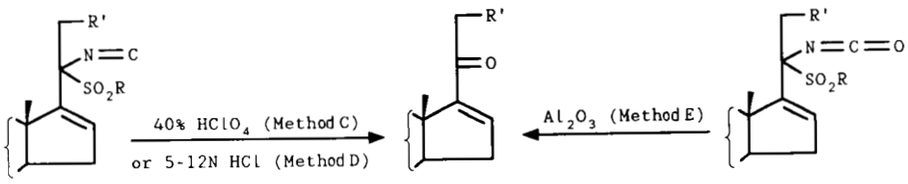
Reaction of isocyano steroid **1a** with chloromethyl methyl ether, using the PTC conditions of previous methylations (Method B), provided the C-21 methoxy compound **13a** (Table I, entry 13). Compound **13a** was obtained in an impure state; all attempts to purify this material were unsuccessful. Hydrolysis of freshly prepared crude **13a** (using Method D) gave 21-methoxy 20-oxo steroid **18e** in 38% yield, based on **1a** (Table II, entry 15).

Chloromethyl benzyl ether reacts with compounds **1** in a similar way to give 2:1 mixtures of C-20 epimers of 21-benzyloxy 20-isocyano steroids **14** (Table I, entries 14–16). The major epimer of **14f** was obtained in pure state by crystallization. Compounds **14a** and **14d** were hydrolyzed to the 21-benzyloxy 20-oxo steroids **19e** and **19d** in 50 and 47% yield, respectively, based on **1d** (Table II, entries 16 and 17).

Selective hydrolytic removal of the dienol ether protection of the enone function of the A ring in the 20-isocyano 20-tosyl steroids **5b** and **11a** was achieved with 2N HCl in CH_2Cl_2 for 30 min at 20°C (Table I, entries 17 and 18).

We have shown that the 17-[isocyano(sulfonyl)methylene]-androstanes (**1–3**) are useful intermediates in the synthesis

Table II

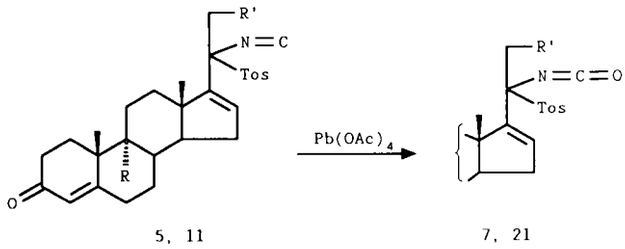


5, 8 - 14 [a] 6, 15 - 19 7, 21

Entry	Starting material	Product					
		No.	R' =	M.p. (°C)	Yield (%)		
					Method A	Method D	Method E
1	**5a**	**6e**	H	182–185[b]	90	75	
2	**7e**	**6e**	H	"			86
3	**8a**	**6e**	H	"		57	
4	**9a**	**6e**	H	"		35	
5	**5b**	**6g**	H	153–180		50	
6	**7g**	**6g**	H	"			73
7	**5c**	**6h**	H	190–195[c]		60	
8	**5d**	**6d**	H	200–204[d]		68[e]	
9	**5f**	**6f**	H	187[f]		97	
10	**10a**	**15e**	Me	141–142		60	
11	**11a**	**16e**	Cl	161–164[g]	50	15	
12	**21e**	**16e**	Cl	"			95
13	**11f**	**16f**	Cl	134–141		29	
14	**12a**	**17e**	Br	141–143	80	–	
15	**13a**	**18e**	MeO	105–110		38[h]	
16	**14a**	**19e**	$PhCH_2O$	129–130		50	
17	**14d**	**19d**	$PhCH_2O$	193–198[i]		47[j]	

[a] For R see Table I. [b] Lit.[11] 186–188°C. [c] Lit.[12] 199–201°C. [d] Lit.[13] 210–213°C. [e] Based on **1d**. [f] Lit.[14] 193–194°C. [g] Lit.[15] 164–166°C. [h] Based on **1a**. [i] With decomposition. [j] Based on **1d**.

Table III



5, 11 7, 21

Entry	Starting material	Product					
		No.	R	R'	Yield[a] (%)	M.p. (°C)[b]	Ratio C-20 Epimers
1	**5e**	**7e**	H	H	99	148–150	2:1
2	**5g**	**7g**	OH	H	98	180	4:1
3	**11e**	**21e**	H	Cl	80	130–150	7:3

[a] Unless states otherwise in the Experimental Section, the yields refer to C-20 epimeric mixtures in isolated but not completely purified state. [b] With decomposition.

of 20-oxo steroids. In fact, compounds **1–3** are to be considered as ketene *N,S*-acetals. Deprotonation at C-16 and alkylation of the resulting allylic anion at C-20 provides *N,S*-acetals of 16-dehydro-20-oxopregnanes (**5, 8–14**). Acid hydrolysis of these acetals gives 16-dehydro-20-oxopregnanes in good overall yields. The alternative mild hydrolysis on alumina after oxidation of the isocyano group to isocyanate (compounds **7** and **21**, *N,S*-acetals in their own right) shows promise when acid-labile functions elsewhere in the steroid are to be maintained). Finally, the C-16–C-17 double bond offers the possibility of further functionalization towards corticoids, as will be shown in a future publication.

Experimental

For *General remarks* and *Starting materials*, see also Ref. 2a. Centrifugal liquid chromatography (CLC) separations were carried out on a Hitachi CLC-5 centrifugal liquid chromatograph (Chromatotron). Benzene, when necessary dried by azeotropic distillation before use, was purchased from Janssen; benzyltriethylammonium chloride (BTEAC), dibromomethane and methyl iodide from Janssen; chloromethyl methyl ether from Aldrich; dimethoxyethane (DME), $HClO_4$ and $Pb(OAc)_4$ from Merck; Celite 535 from Fluka.

The letter suffixes **a–h** in compound numbers refer to the structure of the A, B and C ring moiety, as given in the Chart.

*(20R)- and (20S)-20-Isocyano-3-methoxy-20-tosyl*pregna-3,5,16--triene* (**5a**)

Method A: homogeneous procedure. *t*-BuOK (0.12 g, 1.0 mmol) was added to a suspension of (*E*)-17-(isocyanotosylmethylene)--3-methoxyandrosta-3,5-diene[2a] (**1a**, 0.24 g, 0.50 mmol) in dimethoxyethane (DME, 5 ml) at −40 °C. After stirring for 3 min, MeI (0.065 ml, 1.0 mmol) was added. Stirring was continued and the temperature was raised from −40 to +20 °C over a period of $1\frac{1}{2}$ h. The reaction mixture was poured into 20 ml of water. The mixture was extracted with three portions (25, 15 and 10 ml) of CH_2Cl_2. The combined extracts were washed with brine (25 ml), dried over Na_2SO_4 and concentrated to give 0.24 g (98%) of **5a** as an epimeric mixture (20*R* and 20*S*), m.p. 140–155 °C (dec.). This material was identical by ^1H NMR and IR with the product obtained below.

* Tosyl = *p*-tolylsulfonyl = 4-$CH_3C_6H_4SO_2$

Method B: phase-transfer procedure. Aqueous NaOH (50%, 20 ml) was added to a mixture of isocyanide **1a**[2a] (0.95 g, 2.0 mmol), MeI (0.30 ml, 4.8 mmol), benzyltriethylammonium chloride (BTEAC, 0.040 g, 0.17 mmol) and benzene (40 ml). The mixture was stirred vigorously for 1 h at 80 °C. The upper layer was separated, washed with brine (10 ml), dried over Na_2SO_4 and concentrated to give 0.91 g (93%) of **5a** as an epimeric mixture, m.p. 140–155 °C (dec.). This material, over 95% pure according to ^1H NMR, was used for the synthesis of **6e**. Analytically pure **5a** (0.2 g, one of the epimers, stereochemistry not assigned) was obtained by crystallization from CH_2Cl_2/MeOH, m.p. 155-157 °C (dec.); $[\alpha]_D^{20}$ −174° (*c* 1.0, $CHCl_3$). IR (Nujol): 2160 (N=C), 1670, 1620, 1600 (C=C), 1330, 1155 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H, H-18), 1.00 (s, 3H, H-19), 1.1–2.8 (m), 1.93 (s, H-21), 2.49 (s, 3H, 4-CH_3), 3.60 (s, 3H, CH_3O), 5.0–5.4 (m, 2H, H-4 and H-6), 6.1–6.3 (m, 1H, H-16), 7.32, 7.49, 7.82 and 7.98 (AB q, 4H, arom). Anal. calcd. for $C_{30}H_{37}NO_3S$ (491.695): C 73.28, H 7.58, N 2.85, S 6.52; found: C 73.2, H 7.7, N 2.8, S 6.4%. The ^1H NMR spectrum of the epimeric mixture, before crystallization, was nearly identical with that of the analytically pure sample; the NMR of the epimeric mixture gave an additional signal at δ 1.00 (H-18).

Pregna-4,16-diene-3,20-dione (**6e**)

Method C. A crude mixture of 20*R* and 20*S* isocyanide **5a** (0.125 g, 0.25 mmol, see above), CH_2Cl_2 (5 ml), Et_2O (15 ml) and 40% $HClO_4$ (10 ml) was stirred vigorously for 3 min at 20 °C. The mixture was poured into saturated aqueous $NaHCO_3$ (150 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 0.085 g (90% based on NMR) of **6e** as a white solid.

Method D. A crude epimeric mixture of **5a** (0.246 g, 0.50 mmol), Et_2O (50 ml) and 5N HCl (20 ml) was stirred for 30 min at room temperature. The ether layer was washed with saturated aqueous $NaHCO_3$ solution (20 ml), with brine (20 ml), dried over Na_2SO_4 and concentrated to give **6e** as an oil (0.13 g). The yield was about 75% (based on ^1H NMR). Pure **6e** was obtained by column chromatography (alumina, CH_2Cl_2) followed by one crystallization from Et_2O, m.p. 182–185 °C; $[\alpha]_D^{20}$ +168° (*c* 1.0, $CHCl_3$) [lit.[11] m.p. 186–188 °C, $[\alpha]_D^{20}$ +154° (EtOH)]. IR (Nujol): 1685, 1670 (C=O), 1625, 1595 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–2.9 (m), 0.92 (s, H-18), 1.20 (s, H-19), 2.22 (s, H-21), 5.69 (s, 1H, H-4), 6.5–6.7 (m, 1H, H-16).

Method E. A slurry of crude epimeric mixture of isocyanate **7e** (0.49 g, 1.0 mmol, see below), CH_2Cl_2 (10 ml) and alumina (10 g, activity grade II–III) was stirred for 3 h at 20 °C. The mixture was filtered and the alumina was extracted with CH_2Cl_2 (3 × 25 ml). The filtrate and extracts were combined and concentrated to give

0.27 g (86%) of **6e**, m.p. 178–183°C, identical with **6e** obtained from **5a** (see above) by mixture m.p., IR and ^{1}H NMR.

(20R)- and (20S)-20-Isocyano-3-methoxy-20-tosylpregna-3,5,16-trien-9-ol (**5b**)

The title compound was prepared analogously to **5a** (method A) from (*E*)-17-(isocyanotosylmethylene)-3-methoxyandrosta-3,5-dien-9-ol[2a] (**1b**, 2.47 g, 5.0 mmol), *t*-BuOK (1.12 g, 10 mmol) and MeI (0.6 ml, 10 mmol) in DME (50 ml). After work-up, the concentrate was crystallized from MeOH (20 ml) to give 2.23 g (88%) of **5b**, m.p. 190–200°C (dec.). IR (KBr): 3540 (OH), 2135 (N=C), 1650, 1620 (C=C), 1325, 1152 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–3.0 (m), 0.81 (s, H-18), 1.09 (s, H-19), 1.98 (s, H-21), 2.45 (s, 4-CH_3), 3.58 (s, 3H, CH_3O), 5.1–5.4 (m, 2H, H-4 and H-6), 6.1–6.4 (m, 1H, H-16), 7.31, 7.46, 7.80, 7.95 (AB q, 4H, arom). Exact mass: *m/z* 507.242, calcd. for $C_{30}H_{37}NO_4S$: 507.244.

(20R)- and (20S)-9-Hydroxy-20-isocyano-20-tosylpregna-4,16-dien-3-one (**5g**, entry 17, Table I)

The 3-methoxy group of **5b** was removed by selective hydrolysis. A mixture of **5b** (1.01 g, 2.0 mmol), CH_2Cl_2 (10 ml), and 2N HCl (0.4 ml) was stirred vigorously for ½ h at room temperature. The organic layer was washed with aqueous $NaHCO_3$ (10 ml), and once with water, dried over Na_2SO_4 and concentrated to give 1.0 g of solid. This crude material was washed with MeOH (20 ml) and dried to give 0.77 g (79%) of **5g**, m.p. 185–190°C (dec.). IR (KBr): 3480 (OH), 2122 (N=C), 1650 (C=O), 1610 (C=C), 1340, 1150 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–2.9 (m), 0.89 (s, H-18), 1.35 (s, H-19), 1.95 (s, H-21), 2.47 (s, 4-CH_3), 5.87 (s, 1H, H-4), 6.1–6.3 (m, 1H, H-16), 7.32, 7.48, 7.80, 7.94 (AB q, 4H, arom). Exact mass: *m/z* 493.288, calcd. for $C_{29}H_{35}NO_4S$: 493.229.

9-Hydroxypregna-4,16-diene-3,20-dione (**6g**)

Method D. HCl (8N, 10 ml) was added to a stirred epimeric mixture of **5b** (0.253 g, 0.50 mmol), Et_2O (30 ml) and CH_2Cl_2 (5 ml) at 20°C. After 10 min, the organic layer was washed once with water and once with aqueous $NaHCO_3$, then dried over Na_2SO_4 and concentrated. By CLC (silica, CH_2Cl_2/MeOH 98.5/1.5), 0.8 g (50%) of **6g** was obtained, m.p. 153–180°C (dec.). Crystallization of **6g** from MeOH did not change the melting point; $[\alpha]_{578}^{20}$ + 149° (*c* 1.0, CH_2Cl_2). IR (KBr): 3460 (OH), 1652 (C=O), 1610 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H, H-18), 1.1–3.0 (m), 1.34 (s, H-19), 2.26 (s, H-21), 5.89 (s, 1H, H-4), 6.6–6.9 (m, 1H, H-16). Anal. calcd. for $C_{21}H_{28}O_3$ (468.657): C 76.79, H 8.59; found: C 76.9, H 8.6%.

Method E. A slurry of the crude epimeric mixture of isocyanate **7g** (0.71 g, 1.4 mmol, see below), CH_2Cl_2 (15 ml) and alumina (15 g, activity grade II–III) was stirred for 1½ h at 20°C. The mixture was filtered and the alumina was extracted with CH_2Cl_2 containing 2% of MeOH (3 × 25 ml). The filtrate and extracts were combined and concentrated to give a mixture of two compounds. Separation by CLC (alumina, CH_2Cl_2/MeOH 98/2) yielded 0.31 g (60%; first fraction) of **6g**, m.p. 153–180°C (dec.), identical with **6g** obtained from **5b** (see above) by mixture m.p., IR and ^{1}H NMR and 0.060 g (13%, second fraction) consisting of a 1:9 mixture of **6g** and 9-hydroxy-20-iminopregna-4,16-dien-3-one (**22g**). IR (KBr): 3450 (OH and NH), 1650 (C=O), 1610 (strong C=NH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 3H, H-18), 1.1–3.0 (m), 1.33 (s, H-19), 2.21 (s, H-21), 5.87 (s, 1H, H-4), 6.4–6.6 (m, 1H, H-16). MS: the parent peak was found at *m/z* 327 (calcd. for $C_{21}H_{29}NO_2$: 327). Addition of one drop of 2N HCl to a solution of **22g** in $CDCl_3$ (0.4 ml) gave ketone **6g** within 5 min, according to ^{1}H NMR.

(20R)- and (20S)-20-Isocyano-3-methoxy-20-tosylpregna-3,5,9(11),16-tetraene (**5c**) and *pregna-4,9(11),16-triene-3,20 dione* (**6h**)

Compound **5c** was prepared analogously to **5a** (Method B) from isocyanide **1c**[2a] (0.48 g, 1.0 mmol), MeI (0.15 ml, 2.4 mmol), BTEAC (0.02 g, 0.1 mmol), benzene (20 ml) and 10 ml of 50% aqueous NaOH. The crude product was dissolved in CH_2Cl_2 and filtered through a layer (3 × 3 cm i.d.) of alumina. The alumina was eluted with CH_2Cl_2 (200 ml) and the combined filtrates were concentrated to give 0.46 g (94%) of **5c** as a white solid, which was used as such for the synthesis of **6h**. IR (Nujol): 2140 (N=C), 1655, 1630 (C=C), 1320, 1150 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.6–2.9 (m), 0.73 and 0.96 (2s, H-18), 1.17 (s, H-19), 1.98 (s, H-21), 2.48 (s, 4-CH_3), 3.58 (s, 3H, CH_3O), 5.1–5.6 (m, 3H, H-4, H-6 and H-11), 6.1–6.4 (m, 1H, H-16), 7.27, 7.41, 7.76 and 7.90 (AB q, 4H, arom). HCl (6N, 20 ml) was added to a solution of **5c** (0.25 g, 0.50 mmol) in CH_2Cl_2 (10 ml) and Et_2O (40 ml) at 0°C. The mixture was stirred vigorously for 1½ h at 0°C. The organic layer was washed with water (10 ml), with saturated aqueous $NaHCO_3$ (20 ml) and with brine (20 ml), dried over Na_2SO_4 and concentrated to give 0.13 g of a solid residue, which consisted of a 3:1 mixture of **6h** and **5h** (*i.e.*, starting material **5c** of which the dienol ether protection was hydrolytically removed). The total yield of **6h** based on ^{1}H NMR was 60%. After two crystallizations from MeOH, **6h** was obtained with m.p. 190–195°C (lit.[12a] m.p. 199–201°C); $[\alpha]_D^{20}$ + 225°C (*c* 1.0, $CHCl_3$) (lit.[12b] $[\alpha]_D^{25}$ + 237° (*c* 1.0, $CHCl_3$). IR (Nujol): 1665 (C=O), 1620, 1600 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.8–3.0 (m), 0.89 (s, H-18), 1.38 (s, H-19), 2.29 (s, H-21), 5.4–5.7 (m, 1H, H-11), 5.77 (s, 1H, H-4), 6.6–6.9 (m, 1H, H-16).

(20R)- and (20S)-20-Isocyano-20-tosylpregna-1,4,16-trien-3-one (**5d**) and *pregna-1,4,16-triene-3,20-dione* (**6d**)

Compound **5d** was prepared analogously to **5a** (Method B) from isocyanide **1d**[2a] (0.46 g, 1.0 mmol), MeI (0.15 ml, 2.4 mmol), BTEAC (0.02 g, 0.1 mmol), benzene (20 ml) and 10 ml of 50% aqueous NaOH to give 0.45 g (95%) of crude 20-isocyanopregnatrienone **5d**, m.p. 160–175°C (dec.), which was used without purification for the synthesis of **6d**. IR (Nujol): 2140 (N=C), 1660 (C=O), 1620 (C=C), 1330, 1160 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–3.3 (m), 0.92 and 1.01 (2s, H-18), 1.23 (s, H-19), 1.91 (s, H-21), 2.47 (s, 4-CH_3), 5.9–6.4 (m, 3H, H-4, H-2 and H-16), 6.92, 7.09 (d, 1H, H-1), 7.28, 7.40, 7.73 and 7.86 (AB q, 4H, arom).
A solution of crude **5d** (0.45 g, from 1.0 mmol **1d**) in CH_2Cl_2 (15 ml) and Et_2O (30 ml) was violently shaken with concentrated HCl (2 ml) for 2 min. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (20 ml) and once with brine (20 ml), dried over Na_2SO_4 and concentrated. The residue was filtered through a layer of alumina (4 × 5 cm i.d.). The alumina was eluted with CH_2Cl_2 (250 ml) and the combined solutions were concentrated to give 0.235 g (68%) of crude **6d** (90% pure by ^{1}H NMR). After one crystallization from MeOH, m.p. 200–204°C (lit.[13] m.p. 210–213°C); $[\alpha]_D^{20}$ + 134° (*c* 1.0, $CHCl_3$) (lit.[13] $[\alpha]_D$ + 140° (*c* 1.0, $CHCl_3$). IR (Nujol): 1670 (C=O), 1640, 1615, 1600 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–2.7 (m), 0.97 (s, H-18), 1.25 (s, H-19), 2.23 (s, H-21), 5.9–6.4 (m, 2H, H-2 and H-4), 6.5–6.8 (m, 1H, H-16), 6.96, 7.12 (d, 1H, H-1).

(20R)- and (20S)-20-Isocyano-20-tosylpregna-4,16-dien-3-one (**5e**)

Compound **5e** was prepared analogously to **5a** (Method A) from isocyanide **1e**[2a] (2.00 g, 4.3 mmol), *t*-BuOK (0.96 g, 8.5 mmol) and MeI (0.5 ml, 8 mmol). After work-up, 2.0 g (97%) of **5e** was obtained as a mixture of C-20 epimers (by ^{1}H NMR), which was used as such for the synthesis of **7e**. Crystallization from CH_2Cl_2 (4 ml) and MeOH (40 ml) yielded 1.6 g (67%) of **5e**, m.p. 155–158°C (dec.) as a 2:1 mixture of epimers. IR (KBr): 2122 (N=C), 1660 (C=O), 1610 (C=C), 1325, 1152 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–2.7 (m), 0.89 and 1.00 (2s, H-18), 1.19 (s, H-19), 1.96 (s, H-21), 2.48 (s, 4-CH_3), 5.72 (s, 1H, H-4), 6.0–6.3 (m, 1H, H-16), 7.30, 7.45, 7.79 and 7.93 (AB q, 4H, arom). Exact mass: *m/z* 477.233, calcd. for $C_{29}H_{35}NO_3S$: 477.234.

(20R)- and (20S)-20-Isocyano-3-methoxy-20-tosyl-19-norpregna-1,3,5(10),16-tetraene (**5f**) and *3-methoxy-19-norpregna-1,3,5(10),16-tetraen-20-one* (**6f**)

t-BuOK (0.10 g, 0.8 mmol) was added to a solution of isocyanide **1f**[2a] (0.23 g, 0.5 mmol) in DME (3 ml) at −40°C. After stirring for 10 min, MeI (0.038 ml, 0.60 mmol) was added and the temperature was raised over 2 h + 10°C. Without isolation of **5f**, the contents of the flask were added to a mixture of Et_2O (30 ml) and concentrated HCl (2 ml). This mixture was shaken vigorously for 2 min in a separation funnel, after which the organic layer was immediately separated and filtered through a layer of alumina (3 × 3 cm i.d.) to give upon concentration 0.15 g (97%) of **6f**, m.p. 175–180°C. Crystallization from EtOAc raised the melting point to 187°C; $[\alpha]_D^{20}$ + 112° (*c* 1.0, $CHCl_3$) (lit.[14] m.p. 193–194°C, $[\alpha]_D^{25}$ + 115° (*c* 1, $CHCl_3$). IR (Nujol): 1665 (C=O), 1620, 1595

(C=C + Ar), 1245 (C–O–C) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 0.91 (s, 3H, H-18), 1.0–3.1 (m), 2.23 (s, H-21), 3.69 (s, 3H, CH_3O), 6.4–6.8 (m, 3H, H-16, H-2 and H-4), 6.9-7.4 (m, 1H, H-1).

(20R)- and (20S)-20-Isocyanato-20-tosylpregna-4,16-dien-3-one (**7e**)

$Pb(OAc)_4$ (1.2 g, 2.5 mmol) was added to a solution of isocyanide **5e** (0.98 g, 2.0 mmol) in dry benzene (20 ml). After stirring for 1½ h at 20°C, water (10 ml) was added and the mixture was filtered through Celite. The filter cake was extracted with EtOAc (2 × 25 ml). The organic layer, of the combined filtrate and extracts, was washed with water, dried over Na_2SO_4 and concentrated to give 1.0 g (99%) of **7e**, m.p. 147–150°C (dec.). Analytically pure **7e** (0.67 g) was obtained after one crystallization from CH_2Cl_2/Et_2O, m.p. 148–150°C. IR (KBr): 2240 (N=C=O), 1663 (C=O), 1608 (C=C), 1320, 1145 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.55 and 0.89 (2s, ratio 2:1, H-18), 1.0–3.0 (m), 1.16 (s, H-19), 2.45 (s, 4-CH_3), 5.72 (s, 1H, H-4), 5.9–6.1 (m, *ca.* 0.3H, H-16), 6.1–6.3 (m, *ca.* 0.6H, H-16), 7.28, 7.41, 7.68 and 7.81 (AB q, 4H, arom). Anal. calcd. for $C_{29}H_{35}NO_4S$ (493.667): C 70.56, H 7.15, N 2.84, S 6.49; found: C 70.2, H 7.2; N 2.8, S 6.4%.

(20R)- and (20S)-9-Hydroxy-20-isocyanato-20-tosylpregna-4,16-dien-3-one (**7g**)

The title compound was prepared analogous to **7e** from isocyanide **5g** (0.70 g, 1.4 mmol) and $Pb(OAc)_4$ (0.90 g, 1.9 mmol) in 0.72 g (98%) yield, m.p. 180°C (dec.). This material was used as such for the synthesis of **6g**. IR (KBr): 3450 (OH), 2240 (N=C=O), 1660 (C=O), 1615 (C=C), 1315, 1145 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.54 (s, *ca.* 2.3H, H-18), 0.87 (s, *ca.* 0.7H, H-18), 1.0–3.0 (m), 1.29 (s, H-19), 1.93 (s, H-21), 2.45 (s, 4-CH_3), 5.87 (s, 1H, H-4), 6.0–6.3 (m, 1H, H-16), 7.30, 7.44, 7.72 and 7.86 (AB q, 4H, arom).

(20R)- and (20S)-20-Isocyano-3-methoxy-20-(4-methoxyphenylsulfonyl)-pregna-3,5,16-triene (**8a**) and *pregna-4,16-diene-3,20-dione* (**6e**, see also above)

Isocyanide **8a** was prepared analogously to **5a** (Method B) from (*E*)-17-[isocyano[(4-methoxyphenyl)sulfonyl]methylene]-3-methoxyandrosta-3,5-diene[2a] (**2a**, 0.48 g, 1.0 mmol), MeI (0.15 ml, 2.4 mmol), BTEAC (0.02 g, 0.1 mmol), benzene (20 ml) and 10 ml of 50% aqueous NaOH to give 0.47 g (92%) of crude **8a**, m.p. 160–180°C (dec.). IR (Nujol): 2160 (N=C), 1660, 1635, 1600, 1585 (C=C + Ar), 1335, 1150 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.6–2.7 (m), 0.89 (s, H-18), 0.98 (s, H-18 and H-19), 1.98 (s, H-21), 3.55 (s, 3H, CH_3O), 3.88 (s, 3H, 4-CH_3O), 5.0–5.4 (m, 2H, H-4 and H-6), 6.0–6.3 (m, 1H, H-16), 6.93, 7.08, 7.78 and 7.93 (AB q, 4H, arom). Hydrolysis of **8a** (0.100 g, 0.20 mmol) in CH_2Cl_2 (3 ml) and Et_2O (10 ml) with concentrated HCl (5 ml) for 1½ min and work-up as described for **6e** (Method D, see above) gave 0.036 g of **6e** (57%). The product was identical (by ^{1}H NMR) with material obtained by hydrolysis of **5a** (see above).

(20R)- and (20S)-20-Isocyano-3-methoxy-20-(methylsulfonyl)pregna-3,5,16-triene (**9a**) and *pregna-4,16-diene-3,20-dione* (**6e**, see also above)

Isocyanide **9a** was prepared analogously to **5a** (Method B) from isocyanide **3a**[2a] (0.20 g, 0.50 mmol), MeI (0.075 ml, 1.2 mmol), BTEAC (0.01 g, 0.05 mmol), benzene (10 ml) and 50% aqueous NaOH (5 ml) to give 0.21 g (100%) of crude **9a**. IR (Nujol): 2160 (N=C), 1660, 1640 (C=C), 1330, 1160 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (0.7–2.7 (m), 1.00 (s, H-18), 1.10 (s, H-19), 1.97 and 2.00 (2s, H-21), 3.02 (s, 3H, CH_3), 3.55 (s, 3H, CH_3O), 5.0–5.4 (m, 2H, H-4 and H-6), 6.1–6.3 (m, 0.35H, H-16), 6.4–6.6 (m, 0.65H, H-16).
Hydrolysis of **9a** (0.20 g, 0.50 mmol) in CH_2Cl_2 (3 ml) and Et_2O (10 ml) with concentrated HCl (5 ml) for 2 min and work-up as described for **6e** (Method D, see above) gave 0.04 g (35%) of **6e**. The product was identical (by ^{1}H NMR) with material obtained by hydrolysis of **5a** (see above).

(20R)- and (20S)-20-Isocyano-3-methoxy-21-methyl-20-tosylpregna-3,5,16-triene (**10a**)

The title compound was obtained from **1a**[2a] (0.95 g, 2.0 mmol) and EtI (0.40 ml, 5.0 mmol) using the procedure of **5a** (Method B). Crude **10a** was passed through a short column of alumina (3 × 3 cm i.d.) with CH_2Cl_2 to give 0.90 g (89%) of pregnatriene **10a**, m.p. 115–135°C (dec.), which was used for the synthesis of **15e**. Analytically pure **10a** was obtained after one crystallization from MeOH, m.p. 121–135°C (dec.). IR (Nujol): 2170 (N=C), 1660, 1635 (C=C), 1340, 1160 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.5–2.7 (m), 0.60 (s, H-18), 0.94 (s, H-19), 1.03 (t, *J* 7 Hz, H-22), 2.40 (s, 4-CH_3), 3.47 (s, 3H, CH_3O), 4.9–5.3 (m, 2H, H-4 and H-6), 5.8–6.0 (m, 0.3H, H-16), 6.2–6.4 (m, 0.7H, H-17), 7.08, 7.24, 7.58 and 7.74 (AB q, 4H, arom). Anal. calcd. for $C_{30}H_{39}NO_3S$ (493.711): C 72.99, H 7.96, N 2.84, S 6.49; found: C 73.3, H 7.9, N 2.7, S 6.2%.

21-Methylpregna-4,16-diene-3,20-dione (**15e**)

The title compound was prepared analogously to **6h** from the epimeric mixture **10a** (0.25 g, 0.50 mmol) to give 0.14 g (72%) of crude **15e**, purity 85% by ^{1}H NMR. CLC (silica, CH_2Cl_2/MeOH 99/1) followed by one crystallization from Et_2O gave analytically pure **15e**, m.p. 159–160°C; $[\alpha]_D^{20}$ + 168° (*c* 1.0, CH_2Cl_2). IR (Nujol): 1670 (C=O), 1620 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.5–3.0 (m), 0.94 (s, H-18), 1.05 (t, *J* 7 Hz), 1.20 (s, H-19), 5.62 (s, 1H, H-4), 6.4–6.7 (m, 1H, H-16). Anal. calcd. for $C_{22}H_{30}O_2$ (326.483): C 80.94, H 9.26; found: C 81.0, H 9.3%.

(20R)- and (20S)-21-Chloro-20-isocyano-3-methoxy-20-tosylpregna-3,5,16-triene (**11a**)

Aqueous NaOH (50%, 5 ml) was added to a solution of **1a**[2a] (0.48 g, 1.0 mmol) and BTEAC (0.02 g, 0.1 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred vigorously for 2 h at 20°C. The organic layer was separated, dried over Na_2SO_4 and filtered through a layer of alumina (3 × 3 cm i.d.). The alumina was eluted with CH_2Cl_2 (100 ml) and the combined filtrates were concentrated to give 0.47 g (89%) of crude **11a**, m.p. 145–150°C (dec.), which was used for the synthesis of **16e** and **11e**. IR (Nujol): 2160 (N=C), 1655, 1630 (C=C), 1340 and 1155 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.5–2.7 (m), 0.65 and 1.02 (2s, H-18), 0.97 (s, H-19), 2.45 (s, 4-CH_3), 3.52 (s, 3H, CH_3O), 3.8–4.4 (m, 2H, H-21), 5.0–5.4 (m, 2H, H-4 and H-6), 6.0–6.3 (m, 0.4H, H-16), 6.3–6.6 (m, 0.6H, H-16), 7.29, 7.42, 7.74 and 7.88 (AB q, 4H, arom). Exact mass: *m/z* 525.210, calcd. for $C_{30}H_{36}ClNO_3S$: 525.210.

(20R)- and (20S)-21-Chloro-20-isocyano-20-tosylpregna-4,16-dien-3-one (**11e**)

The title compound was prepared by selective hydrolysis of dienol ether **11a** (0.74 g, 1.4 mmol) analogous to the procedure described for **5g** to give 0.60 g (85%) of **11e**, m.p. 140–148°C (dec.), which was used as such for the synthesis of isocyanate **21e**. IR (KBr): 2120 (N=C), 1660 (C=O), 1620 (C=C), 1330, 1150 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.5–3.0 (m), 0.69 and 1.02 (2s, ratio *ca.* 2:1, H-18), 1.19 (s, H-19), 2.48 (s, 4-CH_3), 4.0 (br. s, 2H, H-21), 5.73 (s, 1H, H-4), 6.0–6.2 (m, 0.3H, H-16), 6.4–6.6 (m, 0.7H, H-16), 7.35, 7.50, 7.81 and 7.96 (AB q, 4H, arom).

21-Chloropregna-4,16-diene-3,20-dione (**16e**)

Method D. Concentrated HCl (2 ml) was added to a solution of crude **11a** (0.47 g, 0.90 mmol) in CH_2Cl_2 (5 ml) and Et_2O (25 ml). The mixture was vigorously shaken for 5 min. The organic layer was washed with water (10 ml), with saturated aqueous $NaHCO_3$ solution (10 ml) and with brine (10 ml), dried over Na_2SO_4 and concentrated. The residue was passed through a column of alumina (10 × 1 cm i.d., eluent CH_2Cl_2). The eluent was concentrated to give 0.055 g (15%) of **16e**, m.p. 161–164°C from Et_2O (lit.[15] m.p. 164–166°C). IR (Nujol): 1675 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.7–2.7 (m), 0.98 (s, H-18), 1.21 (s, H-19), 4.34 (s, 2H, H-21), 5.73 (s, 1H, H-4), 6.6–6.9 (m, 1H, H-16). Exact mass: *m/z* 346.169, calcd. for $C_{21}H_{27}ClO_2$: 346.170.
The same compound **16e** was obtained by Method A in 50% yield from **11a** and $HClO_4$, using the procedure described below for **17e**.
Method E. A crude mixture of epimeric isocyanates **21e** (0.37 g, 0.70 mmol, see below), CH_2Cl_2 (7 ml) and alumina (7 g, activity grade II–III) was stirred for 2 h at 20°C. The mixture was filtered and the alumina was extracted with CH_2Cl_2 containing 2% of MeOH (3 × 25 ml). The filtrate and extracts were combined, washed with 2N HCl (10 ml), with aqueous $NaHCO_3$ and once with brine to give 0.23 g (95%) of **16e**, m.p. 148–160°C. One crys-

tallization from CH_2Cl_2/Et_2O raised the melting point to 161–164°C. This compound was identical by IR and ^1H NMR with material obtained from **11a**.

(20R)- and (20S)-21-Chloro-20-isocyano-3-methoxy-20-tosyl-19-norpregna-1,3,5(10),16-tetraene (**11f**) and *21-chloro-3-methoxy-19-norpregna-1,3,5(10),16-tetraen-20-one* (**16f**)

Compound **11f** was prepared analogously to **11a** from isocyanide **1f**[2a] (0.46 g, 1.0 mmol) to give 0.51 g (95%) of a solid which was a mixture of C-20 epimers. IR (Nujol): 2160 (N=C), 1345, 1155 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–3.2 (m), 0.65 and 1.01 (2s, H-18), 2.48 (s), 3.77 (s, 3H, CH_3O), 3.9–4.2 (m, 2H, H-21), 6.1–6.3 (m, *ca.* 0.5H, H-16), 6.4–6.8 (m, *ca.* 2.5H), 7.0–7.6 (m, *ca.* 3H), 7.81 and 7.94 (0.5 AB q, 2H).

The mixture of epimeric isocyanides **11f** (0.51 g, 0.90 mmol), CH_2Cl_2 (7.5 ml), Et_2O (20 ml), and concentrated HCl (10 ml) was stirred vigorously for 10 min at 20°C. The organic layer was washed with water (10 ml), saturated aqueous $NaHCO_3$ solution (10 ml) and with brine (10 ml), dried over Na_2SO_4 and concentrated to give 0.13 g of an oil. By column chromatography (alumina, 10 × 1 cm i.d., Et_2O) 0.10 g (29%) of **16f** was obtained, m.p. 134–141°C. IR (Nujol): 1680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.5–3.3 (m), 0.92 (s, H-18), 3.72 (s, 3H, CH_3O), 4.33 (s, 2H, H-21), 6.5–6.9 (m, 3H), 7.0–7.3 (m, 1H). Exact mass: *m/z* 344.153, calcd. for $C_{21}H_{25}ClO_2$: 344.154.

(20R)- and (20S)-21-Bromo-20-isocyano-3-methoxy-20-tosylpregna-3,5,16-triene (**12a**) and *21-bromopregna-4,16-diene-3,20-dione* (**17e**)

A 50% aqueous NaOH solution (5 ml) was added to a solution of **1a**[2a] (0.48 g, 1.0 mmol), BTEAC (0.034 g, 0.15 mmol) and CH_2Br_2 (5 ml). The mixture was stirred vigorously for 2 h at 20°C. The aqueous layer was extracted once with CH_2Cl_2 (20 ml). The extract and the organic layer were combined, washed with water, dried over Na_2SO_4 and concentrated to give 0.44 g (76%) of crude **12a**. This solid was used as such for the synthesis of **17e**. IR (Nujol): 2150 (N=C), 1655, 1630 (C=C), 1335, 1150 (SO_2) cm^{-1}. After one crystallization from MeOH (20 ml) 0.25 g (43%) of one of the epimers (stereochemistry not assigned) was obtained. ^1H NMR ($CDCl_3$): δ 0.5–2.7 (m), 0.65 (s, H-18), 0.97 (s, H-19), 2.44 (s, 4-CH_3), 3.51 (s, 3H, CH_3O), 3.86 (s, 2H, H-21), 5.0–5.3 (m, 2H, H-4 and H-6), 6.3–6.6 (m, 1H, H-16), 7.27, 7.41, 7.73 and 7.88 (AB q, 4H, arom).

Concentration of the mother liquor gave a 1:1 mixture of both C-20 epimers. ^1H NMR of the minor isomer ($CDCl_3$): δ 0.5–2.7 (m), 0.97 (s, H-19), 1.04 (s, H-18), 2.43 (s, 4-CH_3), 3.5–4.5 (m, *ca.* 5H, H-21 and CH_3O), 5.0–5.4 (m, 2H, H-4 and H-6); 5.9–6.2 (m, 1H, H-16), 7.29, 7.43, 7.73 and 7.88 (AB q, 4H, arom).

Aqueous $HClO_4$ (40%, 30 ml) was added to a suspension of the crude epimers **12a** (0.14 g, 0.25 mmol) in Et_2O (60 ml). After stirring for 10 min at 30°C, the mixture was poured into a saturated aqueous $NaHCO_3$ solution (200 ml). The ether layer was washed with brine, dried over Na_2SO_4 and concentrated to give 0.09 g (80%, by ^1H NMR) of crude **17e**. After crystallization from Et_2O, m.p. 141–143°C (dec.). IR (Nujol): 1670 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–2.7 (m), 0.98 (s, H-18), 1.21 (s, H-19), 4.10 (s, 2H, H-21), 5.70 (s, 1H, H-4), 6.7–7.0 (m, 1H, H-16), Exact mass: *m/z* 390.118, calcd. for $C_{21}H_{27}BrO_2$: 390.119.

(20R)- and (20S)-3,21-Dimethoxy-20-isocyano-20-tosylpregna-3,5,16-triene (**13a**) and *21-methoxypregna-4,16-diene-3,20-dione* (**18e**)

Compound **13a** was prepared analogously to **5a** (Method B) from isocyanide **1a**[2a] (0.48 g, 1.0 mmol) and chloromethyl methyl ether (0.20 ml, 2.7 mmol) in benzene (15 ml) to give 0.39 (74%) of crude **13a** as a mixture of C-20 epimers (ratio *ca.* 2:1). IR (Nujol): 2160 (N=C), 1340, 1150 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.5–3.0 (m), 0.79 (s, *ca.* 2H, H-18), 1.00 (s, H-19), 1.04 (s, H-18), 2.45 (s, 4-CH_3), 3.39 (s, 3H, CH_3O), 3.56 (s, 3H, CH_3O), 3.95 (br. s, 2H, H-21), 5.0–5.4 (m, 2H, H-4 and H-6), 6.0–6.3 (m, 0.3H, H-16), 6.3–6.6 (m, 0.7H, H-16), 7.30, 7.45, 7.80 and 7.95 (AB q, 4H, arom).

Aqueous NaOH (50%, 5 ml) was added to a solution of isocyanide **1a**[2a] (0.48 g, 1.0 mmol), chloromethyl methyl ether (0.3 ml, 4 mmol) and BTEAC (0.030 g, 0.13 mmol) in benzene (15 ml). The mixture was stirred vigorously for 1 h at 80°C. The benzene layer was separated and stirred with 8N HCl (7.5 ml) for 3 h, then washed with a $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated to give 0.38 g of a solid. Ketone **18e** (0.13 g, 38%) was obtained after chromatography (alumina, 17 × 2 cm i.d., CH_2Cl_2), m.p. 105–110°C. IR (Nujol): 1685, 1665 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–2.8 (m), 0.97 (s, H-18), 1.21 (s, H-19); 3.40 (s, 3H, CH_3O), 4.28 (s, 2H, H-21); 5.72 (s, 1H, H-4), 6.7–6.9 (m, 1H, H-16). Exact mass: *m/z* 342.218, calcd. for $C_{22}H_{30}O_3$: 342.219.

(20R)- and (20S)-21-Benzyloxy-20-isocyano-3-methoxy-20-tosylpregna-3,5,16-triene (**14a**) and *21-(benzyloxy)pregna-4,16-diene-3,20-dione* (**19e**)

Aqueous NaOH (50%, 20 ml) was added to a solution of isocyanide **1a**[2a] (0.95 g, 2.0 mmol), chloromethyl benzyl ether[16] (0.47 g, 3.0 mmol), and BTEAC (0.05 g, 0.2 mmol) in benzene (40 ml). This mixture was stirred vigorously for 1 h at 80°C. The upper layer was separated washed with brine (10 ml), dried over Na_2SO_4 and filtered through a layer of alumina (3 × 4 cm i.d.). The alumina was eluted with CH_2Cl_2 (75 ml) and the combined filtrates were concentrated to give a yellow oil. By addition of MeOH (10 ml) and cooling to −20°C, 0.65 g (54%) of **14a** was obtained, m.p. 90–115°C (dec.), which was used as such for the hydrolysis to **19e**. IR (Nujol): 2160 (N=C), 1650, 1630 (C=C), 1325, 1145 (SO_2), 1090 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–2.8 (m), 0.76 (s, H-18), 0.98 (s, H-19), 2.40 (s, 4-CH_3), 3.53 (s, 3H, CH_3O), 3.77, 3.94, 4.02, 4.19 (q, 2H, H-21), 4.54 (s, 2H, CH_2), 5.0–5.3 (m, 2H, H-4 and H-6), 6.3–6.5 (m, 1H, H-16), 6.9–7.5 (m, 7H, arom), 7.70, 7.83 (0.5 AB q, 2H, arom).

A solution of isocyanide **14a** (0.45 g, 0.75 mmol) in CH_2Cl_2 (15 ml) and Et_2O (45 ml) was stirred vigorously for $\frac{1}{2}$ h with 8N HCl (20 ml) at 0°C. The organic layer was washed with water (10 ml), saturated aqueous $NaHCO_3$ solution (25 ml) and once with brine (25 ml), dried over Na_2SO_4 and concentrated to give 0.21 g of a solid, as a 3:1 mixture of **19e** (50%) and **14e** (*i.e.*, starting material **14a** of which the A-ring protection is hydrolytically removed). Analytically pure **19e** was obtained by CLC (alumina, CH_2Cl_2/MeOH 99/1), followed by one crystallization from MeOH, m.p. 129–130°C. IR (Nujol): 1670 (C=O), 1620, 1590 (C=C and Ar) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.7–3.0 (m), 0.97 (s, H-18), 1.19 (s, H-19), 4.33 (s, 2H, CH_2), 4.57 (br. s, 2H, H-21), 5.70 (s, 1H, H-4), 6.6–6.8 (m, 1H, H-16), 7.29 (s, 5H, arom). Anal. calcd. for $C_{28}H_{34}O_3$ (418.581): C 80.35, H 8.19; found: C 80.0, H 8.2%.

(20R)- and (20S)-21-Benzyloxy-20-isocyano-20-tosylpregna-1,4,16-trien-3-one (**14d**) and *21-(benzyloxy)pregna-1,4,16-diene-3,20-dione* (**19d**)

Aqueous NaOH (50%, 10 ml) was added to a solution of isocyanide **1d**[2a] (0.46 g, 1.0 mmol), chloromethyl benzyl ether[16] (0.21 g, 1.5 mmol), and BTEAC (0.02 g, 0.1 mmol) in benzene (20 ml). This mixture was stirred vigorously for 1 h at 80°C. The upper layer was separated washed with brine (10 ml), dried over Na_2SO_4 and filtered through a layer of alumina (3 × 3 cm i.d.). The alumina was eluted with CH_2Cl_2 (75 ml) and the combined filtrates were concentrated to give 0.625 g of an oil, as a mixture of **14d** (80%) and chloromethyl benzyl ether, which was used as such for the preparation of **19d**. ^1H NMR[17] ($CDCl_3$): δ 0.5–3.0 (m), 0.81 and 1.02 (2s, H-18), 1.19 (s, H-19), 2.38 (s, 4-CH_3), 3.7–4.3 (m, 2H, H-21), 4.53 (s, 2H, CH_2), 5.9–6.5 (m, 3H, 6.8–7.5 (m, 8H), 7.70, 7.84 (0.5 AB q, 2H, arom).

Crude **14d** (from 1.0 mmol of **1d**) in CH_2Cl_2 (10 ml) and Et_2O (40 ml) was vigorously shaken with concentrated HCl (2 ml) for $1\frac{1}{2}$ min at 20°C. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (20 ml) and once with brine (20 ml), dried over Na_2SO_4 and concentrated. Crystallization of the residue from MeOH (5 ml) gave 0.20 g (47%) of **19d**, m.p. 193–198°C (dec.). IR (Nujol): 1660 (C=O), 1625, 1605, 1585 (C=C and Ar) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6–2.9 (m), 0.99 (s, H-18), 1.25 (s, H-19), 4.32 (s, 2H, H-21), 4.57 (s, 2H, CH_2), 5.9–6.3 (m, 2H, H-2 and H-4), 6.6–6.8 (m, 1H, H-16), 6.95, 7.12 (d, 1H, H-1), 7.30 (s, 5H, arom). Exact mass: *m/z* 416.234, calcd. for $C_{28}H_{32}O_3$: 416.235.

(20R)- and (20S)-21-Benzyloxy-20-isocyano-3-methoxy-20-tosyl-19-norpregna-1,3,5(10),16-tetraene (**14f**)

t-BuOK (0.10 g, 0.8 mmol) was added to a stirred solution of **1f**[2a] (0.230 g, 0.50 mmol) in DME (3 ml) at −40°C. After 10 min,

chloromethyl benzyl ether[16] (0.10 g, 0.70 mmol) was added. The temperature was raised from −40 to +10°C in $2\frac{1}{2}$ h. Then the mixture was poured into water (50 ml) and extracted with three 20-ml portions of CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, concentrated to a volume of 10 ml and filtered through a layer of alumina (3 × 3 cm i.d.). The alumina was eluted with CH_2Cl_2 (100 ml) and the combined filtrates were concentrated. After one crystallization from MeOH, 0.105 g (36%) of **14f** was obtained, m.p. 153°C (dec.). IR (Nujol): 2190 (N=C), 1620, 1605, 1585 (C=C and Ar), 1330, 1155 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.75 (s, 3H, H-18), 1.0–3.1 (m), 2.38 (s, 4-CH_3), 3.70 (s, 3H, CH_3O), 3.81, 3.99, 4.02, 4.19 (q, 2H, H-21), 4.53 (s, 2H, CH_2), 6.0–6.8 (m, 3H), 6.9–7.4 (m, 8H), 7.64, 7.79 (0.5 AB q, 2H). Anal. calcd. for $C_{36}H_{39}NO_4S$ (581.777): C 74.32, H 6.76, N 2.41, S 5.51; found: C 73.8, H 6.8, N 2.3, S 5.4%.

The same reaction was also performed under phase-transfer conditions, analogous to **14a** (Method B), to give **14f** as a mixture of epimers in 50% yield.

16ξ-Tosylpregn-4-ene-3,20-dione (**20e**)

A solution of isocyanide **5a** (0.495 g, 1.00 mmol) in CH_2Cl_2 (5 ml) and Et_2O (25 ml) was stirred with 5N HCl for 4 h at 20°C. The organic layer was washed with saturated aqueous $NaHCO_3$ (25 ml), with brine (25 ml), dried over Na_2SO_4 and concentrated to give 0.45 g (90%) of crude **20e**. Analytically pure **20e** (from MeOH) melted at 203–205°C (dec.). IR (Nujol): 1715, 1670 (C=O), 1625 (C=C), 1370, 1150 (SO_2) cm $^{-1}$. ^1H NMR ($CDCl_3$): δ 0.5–2.7 (m), 0.63 (s, H-18), 1.15 (s, H-19), 1.97 (s, H-21), 2.41 (s, 4-CH_3), 3.12 (d, *J* 8 Hz, 1H, H-17), 4.0–4.5 (m, 1H, H-16), 5.73 (s, 1H, H-4), 7.24, 7.38, 7.66 and 7.79 (AB q, 4H, arom). Anal. calcd. for $C_{28}H_{36}O_4S$ (468.657): C 71.76, H 7.74, S 6.84; found: C 71.4, H 7.9, S 6.6%.

(20R)- and (20S)-21-Chloro-20-isocyanato-20-tosylpregna-4,16-dien-3-one (**21e**)

The title compound was prepared analogous to **7e** from isocyanide **11e** (0.51 g, 1.0 mmol) to give, after one crystallization from Et_2O, 0.42 g (80%) of **21e**, m.p. 130–150°C (dec.), which was used as such for the synthesis of **16e**. IR (KBr): 2250 (N=C=O), 1670 (C=O), 1610 (C=C), 1320, 1140 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.32 (s, *ca.* 2H, H-18), 0.92 (s, *ca.* 1H, H-18), 0.7–2.8 (m), 1.18 (s, H-19), 2.47 (s, 4-CH_3), 4.18 (br s, 2H, H-21), 5.78 (s, 1H, H-4), 6.0–6.2 (m, 0.3H, H-16), 6.4–6.6 (m, 0.7H, H-16), 7.38, 7.52, 7.78 and 7.92 (AB q, 4H, arom).

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References

[1] Chemistry of Sulfonylmethyl Isocyanides Part 38. For Part 37 see: *D. van Leusen, E. van Echten* and *A. M. van Leusen*, J. Org. Chem. **57**, 2245 (1992).

[2a] *D. van Leusen* and *A. M. van Leusen*, Recl. Trav. Chim. Pays-Bas **110**, 393 (1991);
[b] *D. van Leusen* and *A. M. van Leusen*, Recl. Trav. Chim. Pays-Bas **110**, 402 (1991).

[3] *G. R. Lenz*, Kirk-Othmer Encyclopedia of chemical Technology, 3rd edition, Wiley Interscience, London, **21**, 645 (1983); *W. J. Marsheck, S. Krachy* and *R. D. Muir*, Appl. Microbiol. **23**, 72 (1972); *M. G. Wovcha, F. J. Antosz, J. C. Knight, L.A. Komineck* and *T. R. Pyke*, Biochim. Biophys. Acta. **539**, 308 (1978).

[4] The conversion of **4a** to **1a** has been achieved in a three-step, two-pot procedure in 85% overall yield[2a].

[5a] *D. van Leusen* and *A. M. van Leusen*, Tetrahedron Lett. **25**, 2581 (1984);
[b] *A. M. van Leusen* and *D. van Leusen*, United States patent, US 4,584,278 (1985) to Gist-brocades N.V.;
[c] *A. M. van Leusen* and *D. van Leusen*, United States patent, US 4,551,278 (1985) to Gist-brocades N.V.;
[d] *D. van Leusen* and *A. M. van Leusen*, Synthesis 531 (1991);

[6] *J. Moskal* and *A. M. van Leusen*, Tetrahedron Lett. **25**, 2585 (1984).

[7] *J. Redpath* and *F. J. Zeelen*, Chem. Soc. Rev. **12**, 75 (1983).

[8a] *J. C. Gasc* and *L. Nédélec*, Tetrahedron Lett. 2005 (1971);
[b] *J. R. Bull* and *A. Tuinman*, Tetrahedron **31**, 2150 (1975);
[c] *V. VanRheenen* and *K. P. Shephard*, J. Org. Chem. **44**, 1582 (1979);
[d] *A. R. Daniewski* and *W. Wojciechowska*, Synthesis 132 (1984);
[e] *D. H. R. Barton, W. B. Motherwell* and *S. Z. Zard*, Bull. Soc. Chim. Fr. II, 61 (1987);
[f] *L. Nédélec, V. Torelli* and *M. Hardy*, J. Chem. Soc. Chem. Commun. 775 (1981);
[g] *A. M. Kubriner* and *E. P. Oliveto*, J. Org. Chem. **31**, 24 (1966);
[h] *R. R. Wroble* and *D. S. Watt*, J. Org. Chem. **41**, 2939 (1976);
[i] *D. H. R. Barton, W. B. Motherwell* and *S. Z. Zard*, Nouv. J. Chim. **6**, 295 (1982);
[j] *J. Stoelwinder* and *A. M. van Leusen*, J. Org. Chem. **57**, 2249 (1992).

[9] *M. Kobayashi* and *A. Miura*, Phosphorus and Sulfur **32**, 169 (1987).

[10] The dienol-ether protection of the enone function of **5a** has to be removed prior to oxidation to prevent oxidation of the dienol ether group.

[11] *A. Wettstein*, Helv. Chim. Acta **27**, 1803 (1944).

[12a] *S. A. Szpilfogel* and *V. Gerris*, Recl. Trav. Chim. Pays-Bas **74**, 1462 (1955);
[b] *S. Bernstein, J. J. Brown, L. I. Feldman* and *N. E. Niger*, J. Am. Chem. Soc. **81**, 4956 (1959).

[13] *M. Rubin, H. Wishinsky* and *F. Bompart*, J. Am. Chem. Soc. **73**, 2338 (1951).

[14] *F. Sondheimer, F. Neumann, H. J. Ringold* and *G. Rozenkranz*, J. Am. Chem. Soc. **76**, 2230 (1954).

[15] *M. Georgiadis*, Chim. Chronika **5**, 129 (1976).

[16] *A. Rieche* and *H. Gross*, Chem. Ber. **93**, 259 (1960).

[17] The signals of the chloromethyl benzyl ether in the product are not given.