158. Stereoselective Introduction of Steroid Side Chains at C(17) and C(20)

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Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

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Summary

A simple and efficient new method for the highly stereoselective (at C(17) and C(20)) introduction of steroid side chains which are suitably functionalized for further elaboration is presented. The ene reaction of (17*Z*)-ethylidene steroids, which are readily obtained from 17-keto steroids *via* a *Wittig* reaction, with various enophiles such as formaldehyde and acrylate esters leads to useful intermediates which contain the natural steroid configuration at C(20). Catalytic hydrogenation of the Δ^{16}-double bond occurs from the α-face to stereospecifically generate the correct configuration at C(17). An additional chiral center at C(23) is also introduced stereoselectively by the use of methyl 2-chloroacrylate as the enophile.

In recent years, the discovery of biologically important new steroidal natural products containing modified cholesterol side chains [1] has stimulated much synthetic activity. We have been interested in developing practical new routes to the therapeutically valuable vitamin D_3 metabolites [2] (25-hydroxy-, 1,25-dihydroxy-, and 24*R*,25-dihydroxycholecalciferol) and bile acids (chenodeoxycholic acid). For our purpose, 17-ketosteroids seemed especially attractive as starting materials because of their potential large-scale availability from microbial degradation of abundant plant steroids and because of the ease at which they can be further modified chemically or microbially [3] (*e.g.* 1α- [4] and 7α- [5] hydroxylation). The key aspect in utilizing such starting materials is the stereospecific generation of the asymmetric center at C(20).

At the outset of our research, the only known stereospecific steroid side chain synthesis made use of organopalladium intermediates [6]. In the interim, there appeared a synthesis which involved stereoselective alkylation of an initially introduced 17-acetic acid ester side chain followed by conversion of the ester function to the C(21) methyl group [7]. More recently, the elaboration of pregnenolone derivatives (which would require additional steps to prepare from 17-keto steroids) by *Carroll* [8] and oxy-*Cope* [9] rearrangements have been reported.

We describe here a new approach to the introduction of the desired side chain utilizing, as the key step, an ene reaction of an appropriately substituted (17*Z*)-

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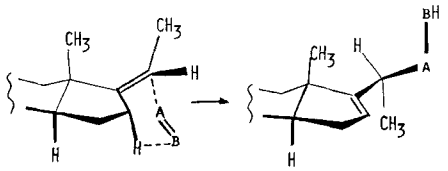
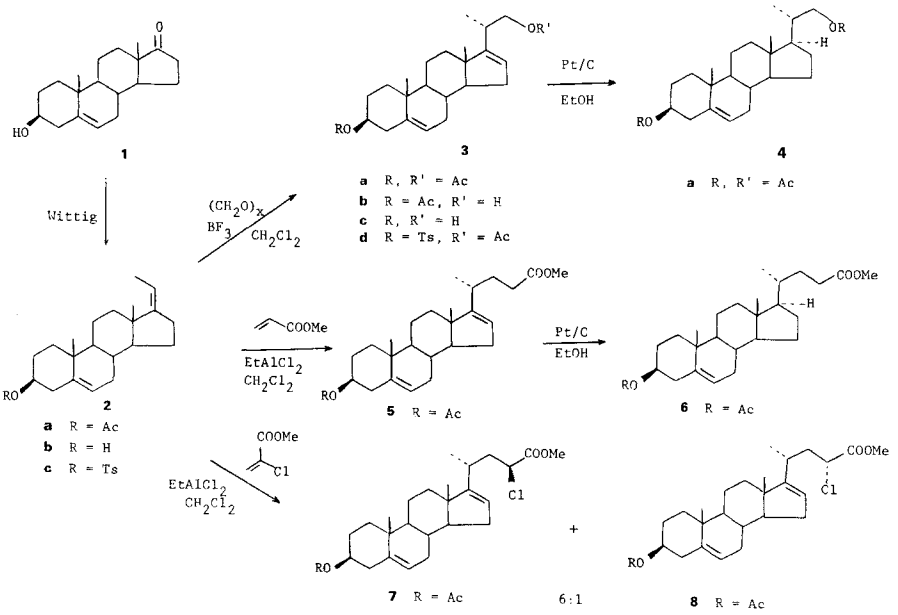
Scheme 1



Scheme 2



ethylidene steroid to stereospecifically generate the natural configuration at C(20). The stereochemical control is attributed to the virtually exclusive attack of the enophile at C(20) from the less hindered α-face of the molecule *(Scheme 1)*.

Our initial choice of carrying out an ene reaction with formaldehyde [10] as the enophile led to the stereoselective introduction of an acetyloxymethyl group with the natural (*S*)-configuration at C(20). Thus (*Z*)-3-acetyloxy-pregna-5,17(20)-diene (**2a**)[1]) [11] and paraformaldehyde in the presence of 10 mol% of boron trifluoride etherate in acetic anhydride/methylene chloride at room temperature for 5 h afforded the $\Delta^{5,16}$-diacetate **3a**[2]) (59%), m.p. 117–118° (CH_3CN), $[\alpha]_D - 44{,}4°$ [^{1}H-NMR.: 5.39 (br. *m*, 2 H, H–C(6) and H–C(16)), 4.11 ($d \times d$, $J = 12$ and 6, 1 H,

[1]) In our hands, the *Wittig* reaction generally produced mixtures of (*Z*)- and (*E*)-elofins. The (*Z*)-olefins could be obtained pure by crystallization. Due to limitations of GC. and ^{1}H-NMR. analyses, the presence of 1–2% of the (*E*)-isomer could not be excluded.

[2]) All substances were completely characterized spectrally and gave satisfactory combustion analyses. All rotations were carried out at 25° on 1% solutions in chloroform. ^{1}H-NMR. spectra were obtained in $CDCl_3$ on a *Varian* XL-100 NMR. spectrometer in the *Fourier*-transform mode.

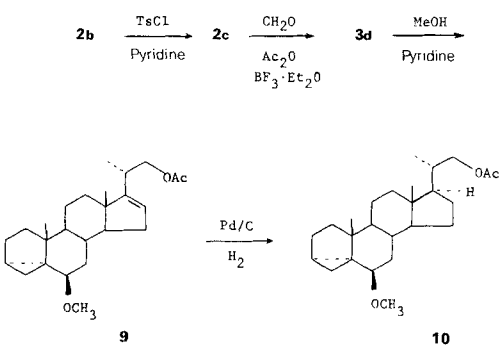
H–C(22)); 3.93 ($d \times d$, $J = 12$ and 8, 1 H, H–C(22)); 2.01 (*s*, 6 H, 2 CO-Me); 1.04 (*s*, 3 H, H_3C–C(19)); 1.04 (*d*, $J = 6.5$, 3 H, H_3C–C(21)); 0.78 (*s*, 3 H, H_3–C(18))].

The inertness of the Δ^5-double bond to both the ene reaction and to the subsequent catalytic reduction [12] was most advantageous. The catalyst delivers hydrogen exclusively to the less hindered α-face of the Δ^{16}-double bond to produce the desired natural configuration at C(17) [13]. Thus, hydrogenation at atmospheric pressure in ethanol using 5% Pt/C ceased cleanly with the absorption of one mol to give the Δ^5-diacetate **4a** (71%, m.p. 125–127° ([14]: m.p. 127–129°)).

With this method we had in hand a novel and practical new route to steroidal C(22) alcohols. However, since further elaboration of the side chain required differentiation of the C(22) and C(3) acetates, we realized that the task of performing selective reactions could be circumvented if a free C(22) alcohol function could be introduced directly. This was achieved by carrying out the ene reaction with formaldehyde under non-acetylating conditions [10]. Consequently, by omitting the acetic anhydride and shortening the reaction time to 15 min, a high yield of the respective free C(22) alcohol **3b** (84%) [m.p. 168–170° (EtOAc); $[\alpha]_D = -75.1$; ^{1}H-NMR.: 5.41 (br. *m*, 2 H, H–C(6) and H–C(16)); 3.62 (*s*, 1 H, H–C(22)); 3.45 (*s*, 1 H, H–C(22)); 1.04 (*s*, 3 H, H_3C–C(19)); 1.02 (*d*, $J = 6.5$, 3 H, H_3C–C(21)); 0.81 (*s*, 3 H, H_3C–C(18))] was obtained. The main side reaction to be avoided was formation of formaldehyde acetals of the resulting alcohol product. A variety of acids (both *Lewis* and protic) were found to be more or less effective as catalysts in hydrocarbon or chlorocarbon solvents as well as in aqueous media.

The ene reaction has also been carried out with the unprotected alcohol **2a** [11] to give **3c** (61%) [m.p. 183–184° (EtOAc); $[\alpha]_D = -75.8°$. – ^{1}H-NMR.: 5.44 (br. *m*, 1 H, H–C(6)); 5.38 (br. *s*, 1 H, H–C(16)); 1.04 (*d*, $J = 6.5$, 3 H, H_3C–C(21)); 1.05 (*s*, 3 H, H_3C–C(19)); 0.83 (*s*, 3 H, H_3C–C(18))], but the corresponding THP and cyclosteroid (i-steroid) ethers were labile under the reaction conditions. However, the cyclosteroid **10** [m.p. 116–123° ([17]: m.p. 124–125°) identical to an authentic sample by ^{1}H-NMR. and TLC.] was prepared indirectly (*Scheme 3*) from the 3-tosylate **2c** [m.p. 119–119.5° (hexane); $[\alpha]_D = -50.8°$. – ^{1}H-NMR.: 7.78 (*d*, 2 H, H–C(2′,6′)); 7.33 (*d*, 2 H, H–C(3′,4′)); 5.32 (br. *d*, 1 H, H–C(6)); 5.13 (br. *m*, 1 H, H–C(20)); 2.42 (*s*, 3 H, H_3C–Ar); 1.64 (*d*, $J = 6.5$, 3 H, H_3C–C(21)); 0.98 (*s*, 3 H, H_3C–C(19));

Scheme 3



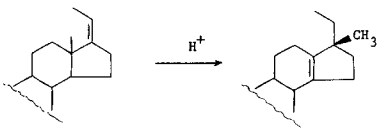
9 **10**

0.88 (*s*, 3 H, $H_3C-C(18)$)] *via* an ene reaction to **3d** [m.p. 109–110° (hexane); $[\alpha]_D = -36.9°$. – ^{1}H-NMR.: 5.40 (br. *m*, 1 H, H–C(16)); 5.32 (br. *m*, 1 H, H–C(6)); 4.08 (*d*×*d*, 1 H, H–C(22); 3.90 (*d*×*d*, 1 H, H–C(22)); 2.42 (*s*, 3 H, H_3C–Ar); 2.01 (*s*, 3 H, CH_3CO); 1.03 (*d*, *J* = 6.5, 3 H, $H_3C-C(21)$); 0.99 (*s*, 3 H, $H_3C-C(19)$); 0.76 (*s*, 3 H, $H_3C-C(18)$)], cyclization (pyridine in MeOH) to **9** [amorphous; $[\alpha]_D = +57.8°$. – ^{1}H-NMR.: 5.41 (br. *m*, 1 H, H–C(16)); 4.12 (*d*×*d*, *J* = 12 and 6, 1 H, H–C(22)); 3.91 (*d*×*d*, *J* = 12 and 8, 1 H, H–C(22)); 3.86 (*s*, 3 H, CH_3O); 1.06 (*s*, 3 H, $H_3C-C(19)$); 1.05 (*d*, *J* = 6.5, $H_3C-C(21)$); 0.83 (*s*, 3 H, $H_3C-C(18)$)], and subsequent hydrogenation.

Further elaboration of **3b** and the C(22) alcohol derived from **10** to the vitamin D metabolites, 25-hydroxy- [15–17] and 24*R*, 25-dihydroxycholecalciferol [18] has already been described. Application of our methodology to the synthesis of 1,25-dihydroxycholecalciferol will be described in a forthcoming paper.

Efforts to utilize other enophiles, either thermally [19] or with the usual *Lewis* acid catalysts [20] [21] were unsuccessful, except for diethyl methylidenemalonate, until ethyl aluminum dichloride was tried. Generally, failure was attributed to a rapid *Wagner-Meerwein* rearrangement [22] [23] of the 17-ethylidene steroids due to the presence of protic acid impurities.

Scheme 4



Preliminary reports [24] of the effectiveness of ethylaluminum dichloride, which serves as a proton scavenger as well as a *Lewis* acid [25], in ene reactions of propiolate esters [26] stimulated us to investigate this system. Our initial success [27] with ethylaluminum dichloride in the stereospecific high yield reactions of (*Z*)-ethylidene steroids with methyl propiolate prompted us to investigate the use of the more economical acrylate esters. In contrast to the discouraging results in the literature [28], we found methyl acrylate also gave high yields of ene products with the steroid substrates, although the reactions proceeded more slowly (24–48 h *vs.* 2 h) than with methyl propiolate.

An important aspect of using ethylaluminum dichloride is that stoichiometric amounts are necessary to overcome the basicity of certain functional groups, one equivalent is required for each ester function present in the ene component as well as in the enophile [25]. The (17*Z*)-ethylidene acetate **2a**, with 2 mol-equiv. of methyl acrylate and 2.9 mol-equiv. of $EtAlCl_2$ in CH_2Cl_2 at room temperature for 24 h with an additional 1 mol-equiv. of methyl acrylate added after 8 h, was converted *via* the $\Delta^{5,16}$-cholic ester **5**[3]) (85%) [m.p. 121–123° (MeOH); $[\alpha]_D = -62.4°$;

[3]) In addition to unreacted starting material **2a** (10%), 2% of the unnatural isomer, (20*S*)-3β-acetyloxychola-5,16-dienoic acid methyl ester, was produced (separated by LC.); m.p. 112.5–113.5° (MeOH); $[\alpha]_D = -55.9°$. – ^{1}H-NMR.: 5.35 (br. *m*, 1H, H–C(6)); 5.34 (br. *m*, 1H, H–C(16)); 3.65 (*s*, 3 H, CH_3O); 2.02 (*s*, 3 H, CH_3CO); 1.07 (*d*, *J* = 6.5, 3 H, $H_3C-C(21)$); 1.05 (*s*, 3 H, $H_3C-C(19)$); 0.80 (*s*, 3 H, $H_3C-C(18)$).

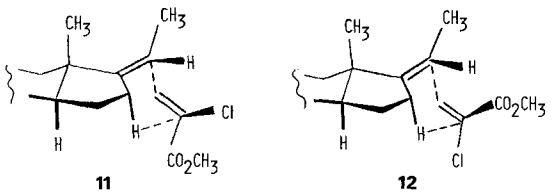
^{1}H-NMR.: 5.36 (br. *m*, 1 H, H–C(6)); 5.32 (br. *m*, 1 H, H–C(16)); 3.66 (*s*, 3 H, CH_3O); 2.03 (*s*, 3 H, CH_3CO); 1.05 (*s*, 3 H, H_3C–C(19)); 1.01 (*d*, $J=6.5$, 3 H, H_3C–C(21)); 0.78 (*s*, 3 H, H_3C–C(18))] to the Δ^5-cholic ester **6** (93%) [m.p. 158–159°; $[\alpha]_D=-44.4°$ ([29]: m.p. 159–161°; $[\alpha]_D=-45.2°$. – ^{1}H-NMR. spectrum is in agreement with published data). It was subsequently discovered that aluminum chloride (or aluminum bromide) can be an effective catalyst when used in conjunction with a proton scavenger such as pyridine (or substituted pyridines). The aluminum halide also must be used in stoichiometric amounts to neutralize each basic functional group and, of course, the pyridine. This system (in toluene) leads to shorter reaction times (1.5–2 h), but to avoid product decomposition, the reaction time must be as short as possible and the work-up must be carried out very carefully (neutralization with excess pyridine before pouring onto ice-cold *Rochelle* salt solution). Without optimization a 70% yield of **5** was realized using aluminum chloride/pyridine (2 h at room temperature) as the catalyst.

A synthesis of 1α,25-dihydroxycholesterol which utilizes the acrylate methodology will be described in a forthcoming publication.

The use of α-substituted acrylic esters in the ene reaction simultaneously introduces two chiral centers. Methyl 2-chloroacrylate [28] and (*Z*)-3-acetyloxypregna-5,17(20)-diene (**2a**) with $EtAlCl_2$ in CH_2Cl_2 produced, after 2.5 h at room temperature, a mixture of diastereomers **7**[4]) [m.p. 180–181° (CH_3CN); $[\alpha]_D=-74.4°$. – ^{1}H-NMR.: 5.36 (br. *m*, 1 H, H–C(6)); 5.39 (br. *m*, 1 H, H–C(16)); 4.27 (*d*×*d*, $J=4$ and 10, 1 H, H–C(23)); 3.78 (*s*, 3 H, CH_3O); 2.02 (*s*, 3 H, CH_3CO); 1.08 (*d*, $J=7$, 3 H, H_3C–C(21)); 1.06 (*s*, 3 H, H_3C–C(19)); 0.82 (*s*, 3 H, H_3C–C(18))] and **8**[5]) [m.p. 129–130° (MeOH/CH_3CN); $[\alpha]_D=-38.4°$. – ^{1}H-NMR.: 5.37 (br. *m*, 2 H, H–C(6,16)); 4.28 (*t*, $J=7$, 1 H, H–C(23)); 3.77 (*s*, 3 H, CH_3O); 2.01 (*s*, 3 H, CH_3CO); 1.04 (*s*, 3 H, H_3C–C(19)); 1.03 (*d*, $J=7$, 3 H, H_3C–C(21)); 0.77 (*s*, 3 H, H_3C–C(18))] in a 6:1 (23*S*)/(23*R*) ratio. The center at C(20) is formed stereospecifically in the natural steroid (*R*)-configuration. The center at C(23) is generated from attack by the enophile leading to transition states **11** (carbomethoxy *endo*) and **12** (chlorine *endo*) of which the former is preferred [28].

The potential of using chirality at C(23) for stereo control of more remote sites in the further elaboration of steroid side chains is being explored.

Scheme 5



[4]) The structure has been fully secured by single crystal X-ray analysis, for which we are grateful to Dr. *J. F. Blount*.

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