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A NEW CLAISEN APPROACH TO THE STEREOSPECIFIC INTRODUCTION OF A STEROID SIDE CHAIN AT C-20. A SIMPLE SYNTHESIS OF 20-EPICHOLESTEROL VIA THE β-FACE REARRANGEMENT

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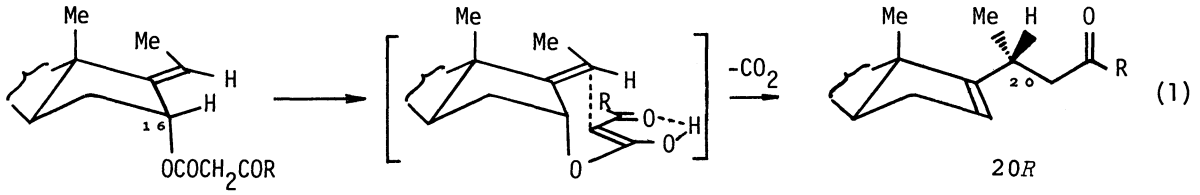
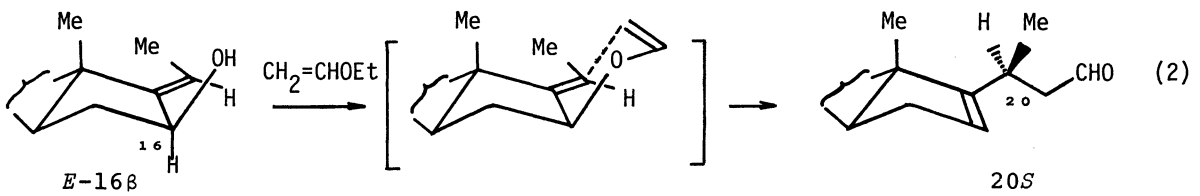
A simple synthesis of 20-epicholesterol is described which relies on the unprecedented β-face Claisen rearrangement of an *E*-$\Delta^{17(20)}$-16β-vinyloxy steroid leading exclusively to the "unnatural" 20*S* chirality.

The stereospecific introduction of steroid side chains onto the basic steroid nucleus has attracted a good deal of current interest, and hence a number of methodologies have been developed.[1,2] Recently Tanabe and Hayashi have reported a highly stereocontrolled approach to either cholesterol (1) or 20-epicholesterol (2) that relies on the α-face Claisen rearrangement (the Carroll variant) as illustrated by Eq. 1.[3] We now report, for the first time, that the Claisen rearrangement is also feasible even on the sterically congested β-face (Eq. 2)[4] by employing the enol ether variant (the Saucy-Marbet variant)[5] within the context of the synthesis of 20-epicholesterol (2) from the readily available 16α,17α-epoxypregnenolone (3).



E-16α (R=$CH_2CH(CH_3)_2$)

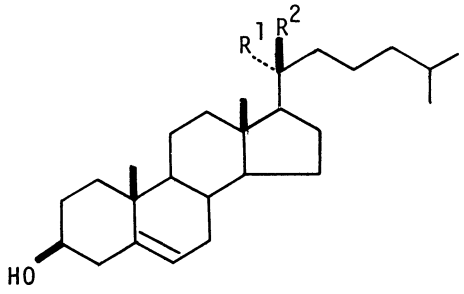


E-16β

Protection of 3[6] as the 3α,5α cyclo ether derivative (4) followed by the Wharton reaction according to the reported procedure[3] provided the *E* allylic alcohol 5 (*ca.* 60%), along with the *Z* isomer 6 (*ca.* 15%). Oxidation of the major *E* isomer 5 was best carried out with manganese dioxide[7] to give quantitatively the *E* enone 7 which was then reduced with lithium aluminum hydride to afford 97% of the 16β alcohol 8 as a single stereoisomer at C-16.[2] The crucial step for the introduction of the *S* configuration at C-20 was first attempted by the ester enolate Claisen rearrangement (the Ireland variant)[8] using the 16β acetoxy derivative 9 as a substrate. Not surprisingly, the ester 9 failed to undergo the β-face rearrangement apparently due to the steric crowding in the transition state(s). In contrast, the less sterically demanding enol ether Claisen variant was found to proceed cleanly. Thus, the alcohol 8 was heated in ethyl vinyl ether in the presence of mercury(II) acetate at 85 °C for 22 h, and then at 125 °C for 4.5 h to give the rearranged 20*S* aldehyde 10 in 84% isolated yield as a single stereoisomer at C-20. The stereospecific generation of the 20*S* configuration is ascribable to the chairlike transition state involved in the β-face process (see Eq. 2). The 20*S* configuration of 10 was confirmed through its NMR comparison with the 20*R* isomer (13) prepared from the 16α alcohol (5) *via* a similar but α-face Claisen process(*vide infra*).[9] The most definitive distinguishing feature of the two isomers is the NMR chemical shift for the C-21 signals (δ 1.16 for 10 and δ 1.07 for 13).

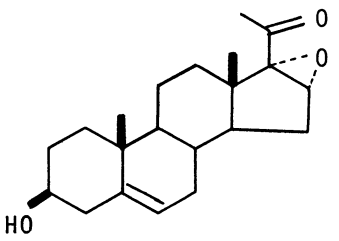
Construction of the epicholesterol side chain was completed as follows. The Wittig reaction of the aldehyde 10 with triphenylphosphonium isobutylide[10] gave the diene 11. Catalytic hydrogenation of the diene 11 with platinum oxide in ethyl acetate from the α-side[11] fixed the 17*R* configuration and afforded the known 3α,5α cyclo ether derivative (12) of the epicholesterol in 90% yield, whose NMR data were in agreement with the reported values[2] (δ 0.81 for the Me-21). Treatment of 12 with aqueous acid in dioxane gave 20-epicholesterol (2)[12] as previously reported.[2]

The cyclo ether derivative (14) of cholesterol (1) was synthesized in a similar way from the 16α alcohol (5). The enol ether Claisen rearrangement under the same conditions as described above afforded 68% yield of the 20*R* aldehyde 13,[9] which was then converted to 14 in 81% overall yield. The NMR data of 14 were in agreement with the reported data[2] (δ 0.91 for the Me-21). Interestingly, control



1, $R^1=CH_3$, $R^2=H$

2, $R^1=H$, $R^2=CH_3$



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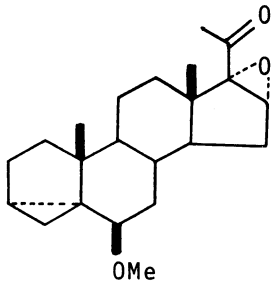

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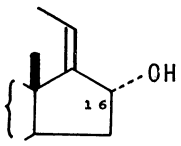
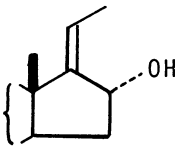


5



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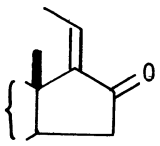

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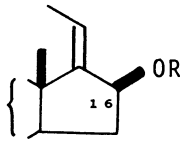
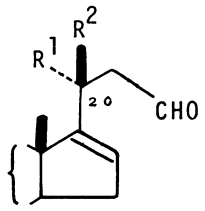


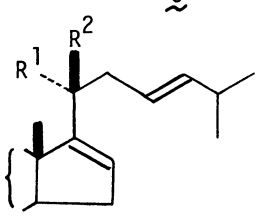
8, R=H

9, R=Ac

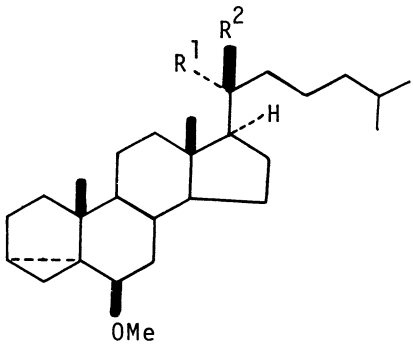


10, $R^1=H$, $R^2=CH_3$

13, $R^1=CH_3$, $R^2=H$



11, $R^1=H$, $R^2=CH_3$



12, $R^1=H$, $R^2=CH_3$

14, $R^1=CH_3$, $R^2=H$

experiments showed that the α-face rearrangement of 5 was significantly faster than the β-face rearrangement of 8 as expected. Thus, these results of this work demonstrate that the enol ether Claisen variant proceeds on either the α- or β-face to create either desired chirality at C-20, thus serving as a key stereo-directing process in steroid side chain synthesis in general.

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4) To our best knowledge, only two reports dealing with β-face reactions for stereocontrol at C-20 have appeared so far: B. M. Trost and T. R. Verhoeven, J. Am. Chem. Soc., 100, 3435 (1978), and their earlier papers [Pd-mediated method]; Ref. 2 [organocuprate-mediated method].

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8) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976).

9) 10 (oil): NMR (300 MHz, $CDCl_3$, TMS), δ 0.87 (s, 3H, Me-18), 1.05 (s, 3H, Me-19), 1.16 (d, J=7.0 Hz, 3H, Me-21), 2.79 (br. t, 1H, 6α-H), 3.34 (s, 3H, OMe) 5.39 (br. m, 1H, 16-H), 9.68 (t, J=3.0 Hz, 1H, CHO); TLC (silica gel, hexane/EtOAc = 20 : 1), R_f= 0.32
13 (oil): NMR (300 MHz, $CDCl_3$, TMS), δ 0.82 (s, 3H, Me-18), 1.03 (s, 3H, Me-19), 1.07 (d, J=7.0 Hz, 3H, Me-21), 2.77 (br. t, 1H, 6α-H), 3.32 (s, 3H, OMe), 5.31 (br. m, 1H, 16-H), 9.63 (t, J=3.0 Hz, 1H, CHO); TLC (silica gel, hexane/EtOAc = 20 : 1), R_f= 0.26.

10) S. G. Wyllil and C. Djerassi, J. Org. Chem., 33, 305 (1968).

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