A NEW SYNTHESIS OF STEROID SIDE CHAIN VIA STEREOCONTROLLED PROTONATION: SYNTHESIS OF NATURALLY OCCURRING METHYL (20S)-3β-HYDROXYCHOLENATES

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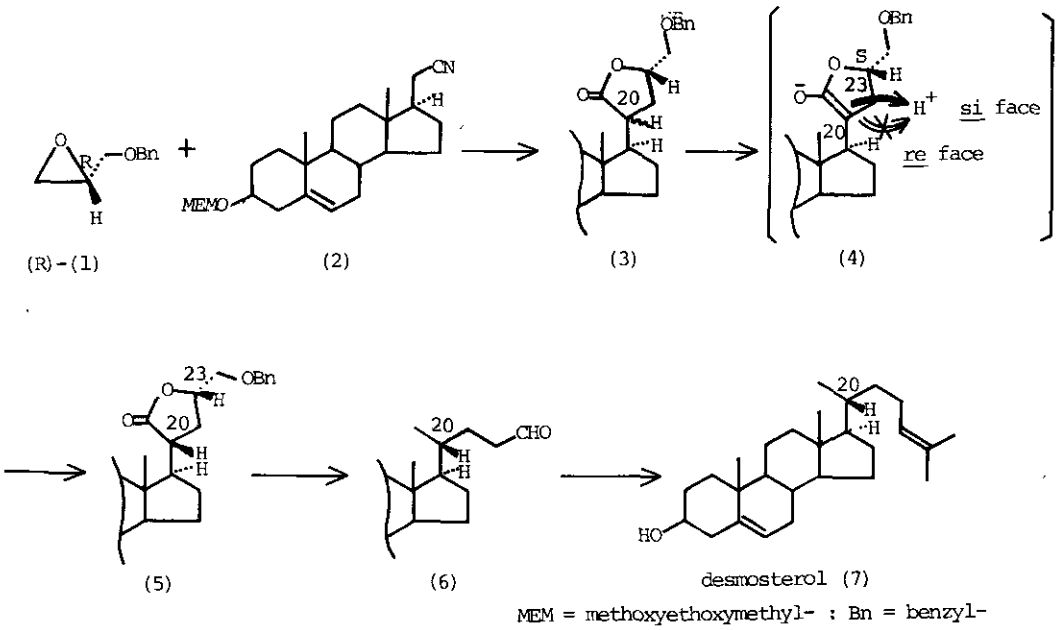
Abstract----Protonation of the steroidal γ-lactone enolate (10), obtained from the 20-cyano steroid (2) and (S)-benzyl 2,3-epoxypropyl ether (S-1), with saturated aqueous sodium sulfate affords the 20(R)-lactone (9a) as a major isomer which is then converted into methyl (20S)-3β-hydroxycholenates (19) and (22) isolated from a sea pen, Ptilosarcus gurneyi.

Recently, we developed a highly stereocontrolled protonation reaction using the γ-lactone substrates with a chirality at the γ-position[1]. Employing the reaction we achieved a highly stereoselective construction of the steroid side chain with "natural" 20β-H configuration from (R)-benzyl 2,3-epoxypropyl ether (R-1) and the 20-cyano steroid (2) in which virtually complete selective protonation occurred from less hindered si face of the (22-S)-enolate (4) (Scheme 1)[2]. Since this seemed to indicate that the observed selectivity was directed merely by the chirality of the γ-position of the lactone moiety regardless of the stereochemistry of the steroid residue, we now attempt to extend the reaction to synthesize the cholenic acid derivatives (20) and (23) possessing the side chain with "unnatural" 20α-H configuration which were recently found in the sterols from a sea pen, Ptilosarcus gurneyi, by Vanderah and Djerassi[3].

(S)-Benzyl 2,3-epoxypropyl ether (S-1)[4] was condensed with the 20-cyano steroid (2)[2] in the presence of lithium hexamethyldisilazide (THF, 0°C) to give a 1 : 1 mixture of the epimeric cyano-alcohol (8). Upon alkaline hydrolysis (KOH, EtOH, reflux, 48 h), followed by acid work-up, 8 gave the (23R)-γ-lactone (9) in 72 % overall yield from 2 as an inseparable 1 : 1 mixture.

Treatment of the mixture with lithium hexamethyldisilazide (THF, -78°C) generated the (23-R)-enolate (10) which was then exposed to an excess amount of saturated aqueous sodium sulfate in one portion at the same temperature. In contrast to the (23-S)-counterpart (4)[2], the product isolated in 83 % yield was revealed to be an inseparable 3 : 1 mixture of 20S-(9a) and 20R-(9b) epimers which could be separated after the reduction[5]. This clearly indicated that the stereochemistry of the C-20 center was directed not only by the chirality of the lactone residue, but also by those of steroid residue in this case though an

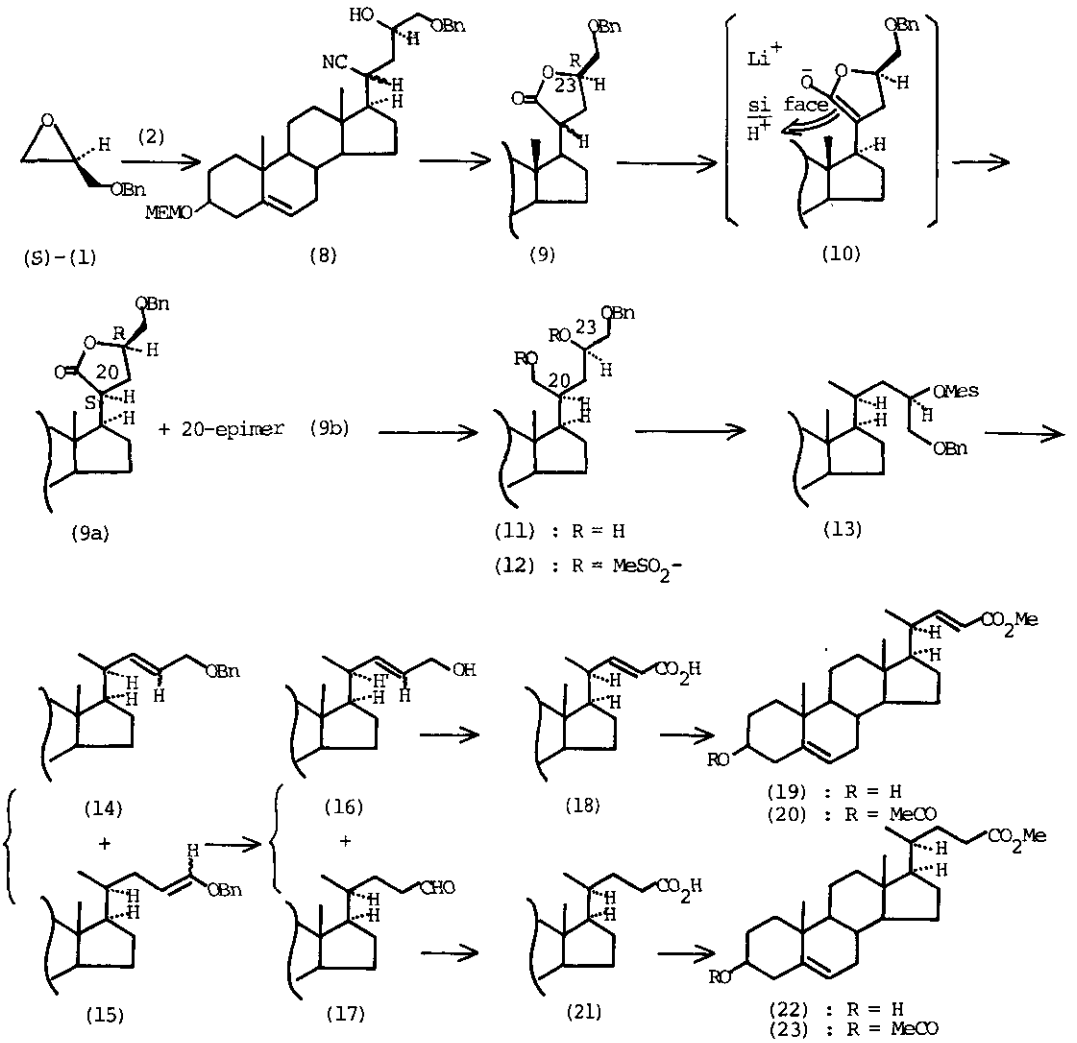


Scheme 1

influence of the former to be overwhelmed. The observed stereochemical outcome may be resulted by the *19-methyl group which shields re face of the enolate (10) significantly.*

The mixture was reduced with lithium aluminum hydride to give a mixture of diols in 90 % yield which was separated into three parts of the (20S)-isomer (11), $[\alpha]_D$ - 34.5° (c 1.102, $CHCl_3$), and one part of the (20R)-isomer by silica gel column chromatography. Methanesulfonation of 11 gave the dimesylate (12) which on reduction with lithium triethylborohydride[6] at room temperature (THF, 5 min) allowed selective demesylation at the primary center to give the 20-methyl mesylate (13), $[\alpha]_D$ - 46.5° (c 1.032, $CHCl_3$), in 81 % overall yield. The observed selective removal of the primary mesylate in the existence of the secondary one in the same molecule was unprecedented and would be noteworthy. Treatment of the monomesylate (13) with diazabicycloundecene in toluene at 200°C using a sealed tube afforded a mixture of the allyl benzyl ether (14)[7] and the benzyl vinyl ether (15)[7] which without separation was reduced with lithium in liquid ammonia in the presence of ethanol at -78°C to give three parts of the allyl alcohol (16)[7], $[\alpha]_D$ - 43.0° (c 1.60, $CHCl_3$), and two parts of the aldehyde (17), $[\alpha]_D$ - 52.9° (c 1.25, $CHCl_3$), in 51 % total yield from 13, after a separation by silica gel column chromatography.

The allyl alcohol (16) was oxidized successively with Jones reagent and alkaline silver oxide to give the α,β-unsaturated carboxylic acid (18) which upon reflux with methanol containing a catalytic amount of sulfuric acid furnished methyl (20S,22E)-3β-hydroxychola-5,22-dienate (19)[3], $[\alpha]_D$ - 85.7° (c 0.54, $CHCl_3$), in 65 % overall yield via concomitant esterification and demethoxyethoxymethylation. For comparison, 19 was treated with acetic anhydride in the presence of a catalytic amount of



Scheme 2

4-dimethylaminopyridine (pyridine, 0°C) to give the acetate (20), mp 149-150°C, $[\alpha]_D$ - 83.2° (c 0.19, $CHCl_3$) (lit.[3] mp 151-151.5°C, $[\alpha]_D$ - 85° (c 0.14, $CHCl_3$)), in 95 % yield, of which spectral data (^{1}H-nmr and MS) were identical with those reported[3].

On the other hand, the aldehyde (17) was oxidized with alkaline silver oxide to give the carboxylic acid (21) which was refluxed with methanol containing a catalytic amount of sulfuric acid to give methyl (20S)-3β-hydroxychol-5-enate (22), $[\alpha]_D$ - 64.1° (c 0.90, $CHCl_3$), in 80 % overall yield via concomitant esterification and demethoxyethoxymethylation. For comparison, 22 was acetylated as for 19 to give the acetate (23), mp 118.5-120°C, $[\alpha]_D$ - 53.7° (c 0.57, $CHCl_3$) (lit.[3] mp 119-120°C, $[\alpha]_D$ - 54.3° (c 0.9, $CHCl_3$), in 91 % yield, of which spectral data (^{1}H-nmr and MS) were identical with those reported[3].

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7. Only a single isomer was generated. However, actual configuration of the side chain double bond could not be determined because of ambiguous coupling constant (ca. 7Hz).

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