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METHYLATION AND HYDROXYMETHYLATION INVOLVING FREE RADICALS. AN APPLICATION TO STEREOSELECTIVE CONSTRUCTION OF 20(S) STEROL SIDE-CHAIN

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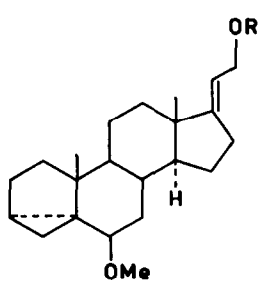
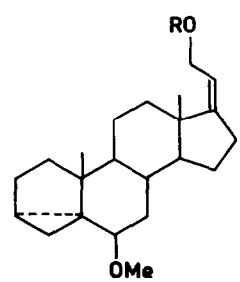
Summary: Reductive radical cyclization of bromomethyl-silyl-ethers 1b and 2b was found to proceed in 5-exo-mode. Epimeric cyclic siloxanes 3 were transformed stereoselectively into 20(S) 25-hydroxycholesterol. Unsaturated (E) ester 4 was converted to its (Z) isomer 7 via saturation and selective dehydrogenation.

Cyclization of hex-5-en-1-yl and related alkenyl and oxaalkenyl radicals has been studied in detail.[1] The analogous silicon-containing radical species have received less attention. In view of the synthetic potential of methylation and hydroxymethylation, as developed by Nishiyama et al.[2] and independently by Stork et al.[3] it is now important to recognize the stereoelectronic and steric factors governing the reactions of radicals in α-position to the silicon atom. Unsaturated silyl ethers 1b and 2b (Chart 1) display the same pattern of double bond substitution but differ in the unbonding interactions between the bromomethyl group and the remote parts of the molecule. It was thought that scrutiny of cyclization of the respe-

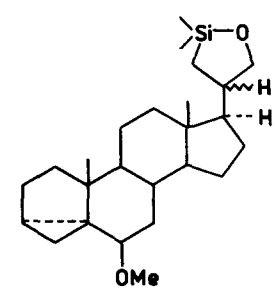
Chart 1



1a, R=H
b, R=SiMe$_2$CH$_2$Br



2a, R=H
b, R=SiMe$_2$CH$_2$Br



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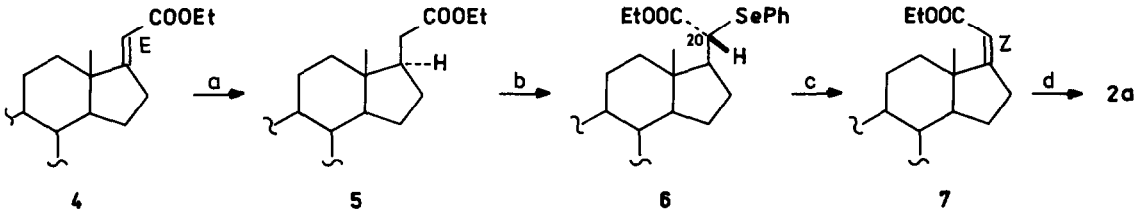
ctive radicals generated by cleavage of the C-Br bond may provide some information on the steric requirements of such reactions. It was also envisioned that the products of 5-exo cyclization could be used for stereoselective construction of the sterol side-chain.

The key intermediates for preparation of bromo silyl ethers 1b and 2b consist of the corresponding allylic alcohols 1a and 2a. The E alcohol 1a was obtained by reduction of the

easily available[4] unsaturated ester 4 ($LiAlH_4$, Et_2O, 95% yield). The isomeric Z alcohol 2a was synthesized also from E ester 4 by the route presented in Scheme 1. The selectivity of formation of 20(R) phenylselenide 6 was predicted by analogy to the previously described alkenylation of pregnan-21-oic esters.[5] The preponderance of syn-elimination of benzeneselenenic acid

Scheme 1



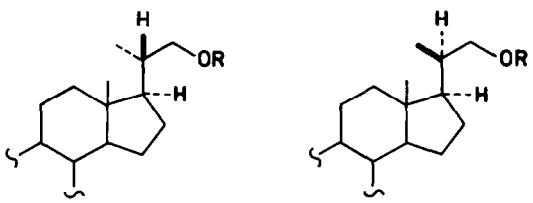
4 5 6 7

a. H_2/Pt/EtOH,100%; b. lithium diisopropylamide, PhSeCl, THF, HMPA, -78°C, 60%; c.AcOOH, THF, -5°C then reflux, 70%; d. $LiAlH_4$, Et_2O, 95%
All partial structures refer to 6β-methoxy-i-androstane skeleton as in 1 - 3.

in the course of fragmentation of phenylselenyl oxide derivatives is well documented.[6]

Alcohols 1a and 2a were converted to the respective (bromomethyl)dimethylsilyl ethers, 1b and 2b, which were purified by chromatography and treated with tri-n-butyltin hydride and azobisisobutylnitrile, according to the described procedure.[2,3b] The intermediate unstable siloxanes 3 (Chart 1) were without isolation subjected to protodesilylation.[3b,7] The products were separated by chromatography on silica gel and identified as free alcohols (8a, 9a) and corresponding acetates (8b, 9b, Chart 2). The results are compiled in Table 1.

Chart 2



8a, R=H
b, R=Ac

9a, R=H
b, R=Ac

Table 1

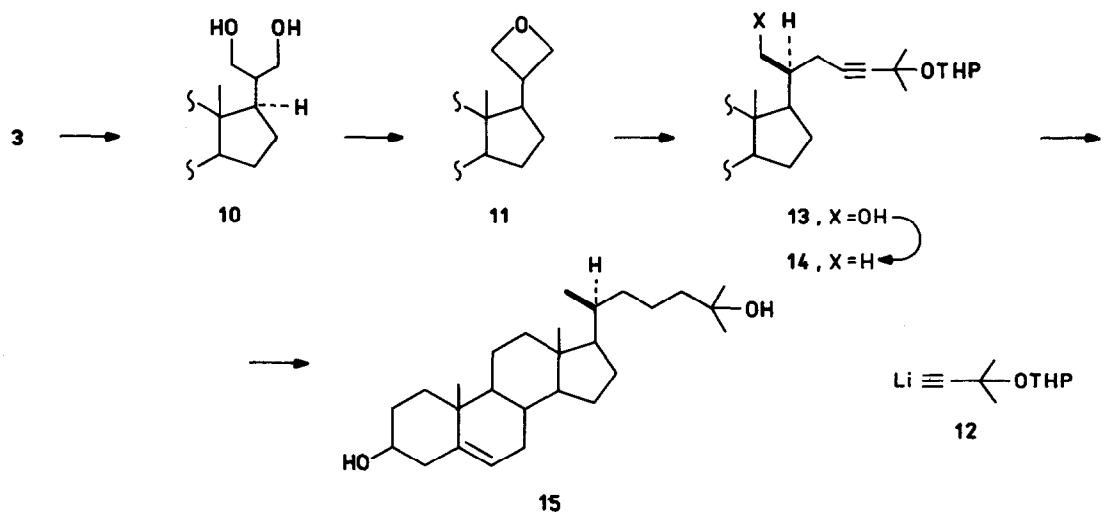
Bromide	Cyclization product	
	Yield,%	8a : 9a ratio
1b (E)	54	43 : 57
2b (Z)	56	50 : 50

As it may be deduced from Table 1, cyclization of both silylethers proceeds exclusively in the 5-exo-mode. Interestingly, in the literature predominant[2] or exclusive[3] 5-exo- and predominant[8] or exclusive[9] 6-endo-cyclizations have been reported. As concerns the stereochemistry of the newly formed chiral centers, in both cases the addition of hydrogen atom to C_{17} occurred from α-side and the addition of the radical moiety to C_{20} took place in almost equal proportions from α- and β- sides. It is noteworthy that the apparent hinderance of the approach to the β-side of the double bond in isomer Z (2b) failed to be reflected in the product composition.

In the sterol synthesis, isolation of epimeric alcohols, 8a and 9a, can be circumvent in the following way (Scheme 2). Siloxanes 3 (the crude product from cyclization of 1b) were oxidized[2,10] (H_2O_2, KF, DMF) to give diol 10 (77% yield) and the starting alcohol 1a (18%).[11]

Diol 10 was transformed into oxetane 11 using a two step - one pot procedure[12] (82%).Treatment of oxetane 11 with lithium acetylenide 12 and $BF_3 \cdot Et_2O$[13] (10 equivalents of each) gave adduct 13 (58%) and unchanged oxetane 11 (30%). Alcohol 13 was reduced to the methyl derivative 14 in the conventional way (TsCl/Py then $LiAlH_4$/THF, 83%). In the ^1H NMR spectrum of compound 14 a broadened doublet at δ 0.94 ppm appeared. This signal was assigned to protons of the C_{21} methyl group, the broadening being attributed to isomers related to the chiral center in the tetrahydropyranyl moiety. The signal of protons of the C_{21} methyl group in the NMR spectrum of the 20(R) epimer of compound 14 has been reported[14] to appear at δ1.03 ppm, J= 7 Hz. The difference between these values (0.09 ppm) is consistent with the 20(S) configuration of our product.

Scheme 2



Finally, compound 14 was hydrogenated (H_2/Pd-$CaCO_3$/EtOH), and the saturated derivative was treated with p-toluene sulphonic acid in aqueous dioxane.[14] 20(S) 25-Hydroxycholesterol 15 was obtained (62% yield from 14); its physical and spectroscopic properties were in good agreement with the reported ones.[14]

The above presented selective synthesis of a sterol with 20(S) configuration extends the methodology for the side-chain construction[15] and can be useful as an approach to some marine products.[16] The stereochemical aspects of the BF_3-mediated reaction of oxetane 11 and lithium acetylenide 12 will be discussed in a full paper. It should be mentioned, however, that the configuration of the product (13) proved to be different than that expected on the assumption of the reagent's approach from the less hindered side to oxetane ring in conformation having the proton on C_{20} oriented toward the angular methyl group (cf. formation of phenylselenide 6).

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