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Stereocontrolled Synthesis of (22*R*)-22-Hydroxycholesterol Guided by α-Silyl Radical Stabilization

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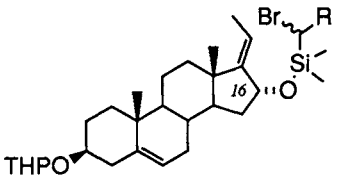
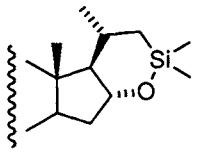
The synthesis of (22*R*)-22-hydroxycholesterol, featuring formation of three contiguous chiral centers (C-17, 20, and 22) in a single step by the use of a 6-endo α-silyl radical-mediated cyclization is presented. Additionally, an interesting protiodesilylation used to activate a cyclic siloxane towards C-Si bond oxidation, and a modified, bulky aryl thionocaronate reagent for regioselective diol-monodeoxygenation are described.

We have recently reported[1] that the radical generated from the allylic α-bromosilyl ether **1** undergoes smooth cyclization to give **2** with complete stereocontrol; the process occurs exclusively through the 6-endo mode, a minor pathway in the cyclization of all carbon 5-hexen-1-yl systems.[2] We now wish to detail an application of this radical-mediated chirality transmission approach to the synthesis of (22*R*)-22-hydroxycholesterol (**3**)[3,4] which establishes three contiguous chiral centers, C-17, 20, and 22, in a single cyclization step. Furthermore, a unique protiodesilylation reaction and a modified thionocarbonate reagent for regioselective deoxygenation are described. The synthetic route to **3** outlined in Scheme 1 appeared quite feasible based on our model studies.[1] Complete stereoselectivity was expected at both C-17 and 20 in this radical cyclization; however, the stereochemical outcome at C-22 was less predictable. The progenitor of this stereocenter is a secondary, non-annular radical carbon atom. While the 5-exo cyclization of secondary radicals result in predominant formation of the cis-product, insufficient evidence exists to determine whether the stereo-chemical preference of 1-substituted alkenyl



1: R = H; **4**: R = isoamyl



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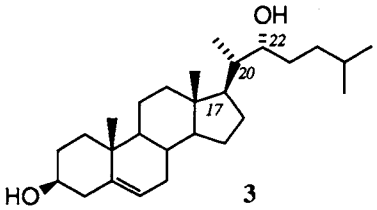

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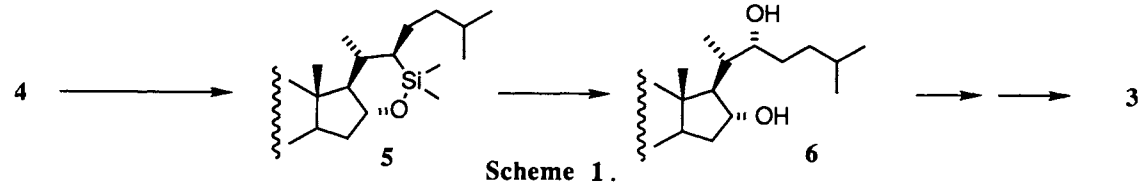

Scheme 1.

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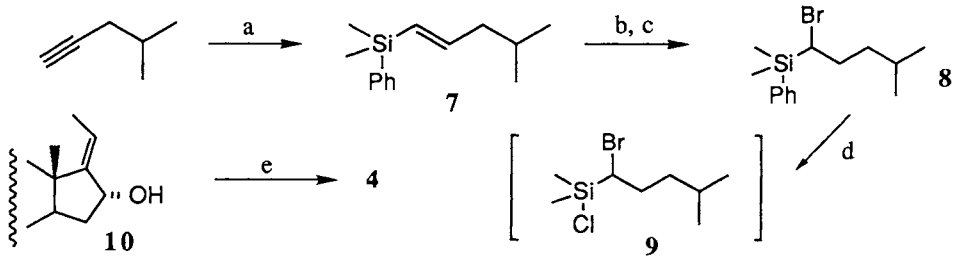


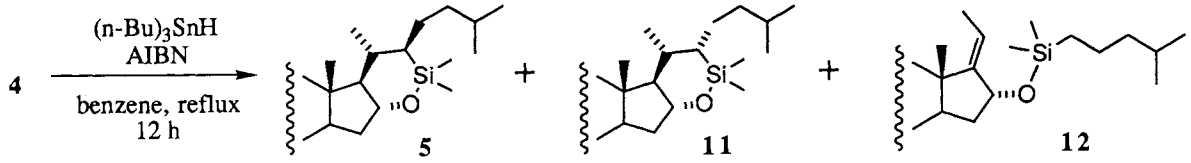
Conditions: a. $(PhMe_2Si)_2CuLi \cdot LiCN$ (1.05 equiv.)/THF, 0 °C, 0.5 h[6] (96%); b. $BH_3 \cdot THF$ (1.8 equiv.)/THF, 0 °C - room temperature, 5 h; 30% H_2O_2 (excess), 3 M NaOH (excess), 60 °C, 5 h (82%);[7] c. $Ph_3P \cdot Br_2$ (2.0 equiv.), CH_3CN, 0 °C - room temperature, 1.5 h (81%);[8] d. ICl (2.0 equiv.)/CH_2Cl_2, reflux, 2 h;[9] e. **9** (generated from 1.8 equiv. of **8**), Et_3N (1.8 equiv.)/$CHCl_3$, 0 °C - room temperature, 3 h (98%).

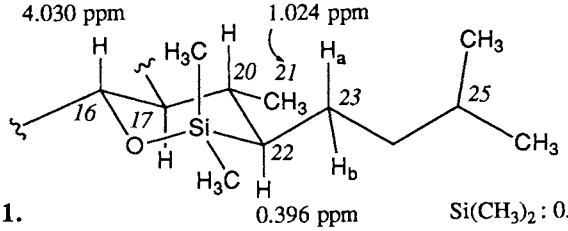
Scheme 2.

radical is of steric or electronic origin.[5] Even less is known for corresponding 6-endo cyclizations; thus, the extent of stereochemical control at C-22 upon cyclization was not assessable and was of great interest to us.

The requisite α-bromosilyl ether **4** was obtained by coupling allylic alcohol **10**[1] with the previously unknown silyl chloride **9**. The synthesis of **9** was designed based on the versatility of arylsilanes (Scheme 2). These compounds are inert to a wide variety of reagents but are susceptible to halodesilylation making them excellent surrogates for the highly electrophilic halosilanes. Thus, the silyl chloride **9** was generated *in situ* from **8** through iododesilylation with ICl,[9] and was efficiently appended to the steroid nucleus **10**, providing **4** in 98% yield.

The crucial radical cyclization was carried out by slowly adding a solution of $(n\text{-}Bu)_3SnH$ and AIBN in benzene to a dilute (0.04 M), refluxing solution of **4** in the same solvent. The cyclization products were obtained in 65% yield as a 4:1 mixture of desired **5** and its C-22 epimer **11** together with the reduction product **12** (15-20%). A single recrystallization of the mixture of **5** and **11** from CH_3CN conveniently provided **5** as a pure, white, crystalline solid leaving **11** and a small amount of **5** behind as an oil. The structure of **5** was deduced based on its 360 MHz ^1H NMR data (Fig. 1) and was subsequently verified by its transformation to **3**. As evidenced by the values of the coupling constants, the siloxane ring of **5** adopts a chair conformation with the isoamyl chain in the less sterically constrained equatorial orientation. Cyclization reactions of non-stabilized carbon radicals are known to be under kinetic rather than thermodynamic control, generally producing product mixtures which do not reflect product stability.[10] Therefore, the degree of





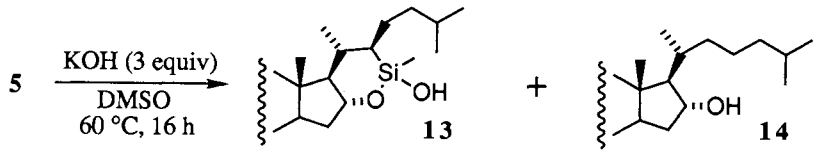
$J_{16,17}$	9.6 Hz
$J_{20,21}$	6.3 Hz
$J_{20,22}$	10.3 Hz
$J_{22,23a \text{ or } b}$	10.3 Hz
$J_{22,23b \text{ or } a}$	3.5 Hz

$Si(CH_3)_2$: 0.148 and 0.188 ppm

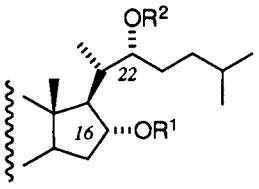
Fig. 1.

stereoselectivity observed here might suggest the transition state of the present radical cyclization is relatively advanced along the reaction coordinate. This may be ascribable to the increased stability of a secondary α-silyl radical center.[11)]

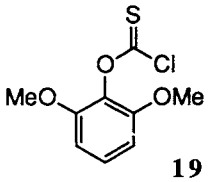
Somewhat unexpectedly, the C_{22}-Si bond in **5** was found to be totally resistant to a variety of conditions known to effect oxidative cleavage of such a bond.[12)] Even under harsh conditions such as 90% H_2O_2/KF/DMF, 60 °C and HF/CH_3CN, reflux, either the starting siloxane **5** was recovered unchanged or deprotection of the THP group was observed. Clearly, the iso-amyl group at C-22 impedes oxidation either by increasing steric congestion at Si or by decreasing electrophilicity at the site through an inductive electron releasing effect. Thus, enhancement of the electrophilicity of the siloxane by introduction of an electronegative atom onto Si was attempted as a means of promoting C-Si bond oxidation. Treatment of siloxane **5** with KOH/DMSO resulted in the formation of a 1:1 stereoisomeric mixture of silanols **13** in 65% yield together with 16α-hydroxycholesterol (**14**) (10-20%). The production of silanols **13** from **5** seemingly involves displacement of a methyl group from Si by hydroxide. While the mechanism of this intriguing reaction remains ambiguous, precedence exists in the literature. Price and Sowa[13)] reported that Me_4Si undergoes protiodesilylation upon treatment with $KOBu^t$ in DMSO at 25 °C to furnish $Me_3(OBu^t)Si$ with the liberation of methane. Furthermore, the presence of **14** as a minor product in the reaction may link these unusual findings to protiodesilylation reactions reported by Hudrlik[14)] and Stork.[15)] The now "activated" silanols **13** smoothly underwent oxidative C_{22}-Si bond cleavage when treated with a stoichiometric amount of $KHCO_3$ and excess 70% H_2O_2 in refluxing MeOH/THF affording diol **6** in 75% yield.



Selective deoxygenation of diol **6** to **3** proved to be somewhat problematic. It was noted that the 16α-OH of **6** is more reactive towards acylating agents than the 22-OH since reaction of **6** with 1.1 equiv. of pivaloyl chloride, pyridine at 0 °C resulted in the isolation of its 16-pivaloate in 64% yield with a 24% recovery of the diol **6**. However, similar treatment of **6** with 1.1 equiv. of ClC(=S)OPh, pyridine/CH_2Cl_2, at room temperature produced both 16-mono- **15** and 16,22-dithionocarbonates **16**, each in 48% yield. We, therefore, undertook development of a new, bulkier aryl chlorothionocarbonate reagent. Optimal results were obtained with 2,6-dimethoxyphenyl chlorothionocarbonate (**19**).[16)] Stirring a 0.02 M CH_2Cl_2 solution of **6** with **19** (1.2 equiv.), pyridine, and DMAP (catalytic) at 0 °C for 3 days provided cleanly 16-monothionocarbonate **17** in 88% yield. While treatment of **17** with



15 R^1 = C(=S)OPh; R^2 = H
16 $R^1 = R^2$ = C(=S)OPh
17 R^1 = C(=S)O-2,6-dimethoxyphenyl
R^2 = H
18 R^1 = C(=S)O-2,6-dimethoxyphenyl
R^2 = TMS



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$(n\text{-Bu})_3SnH$, AIBN in toluene, reflux, 8 h afforded a complex mixture of products, the identical treatment of its TMS derivative **18** (TMS-Cl, pyridine; 90% yield) effected deoxygenation at C-16 (91% yield). The subsequent deprotection of the resulting deoxygenation product with PPTS (catalytic) in EtOH/THF, 60 °C furnished (22*R*)-22-hydroxycholesterol (**3**) in 90% yield.

The results described above indicate that this 6-endo radical-mediated cyclization is a viable, powerful method for the construction of the three contiguous chiral centers not only in the side chain of 22-hydroxylated steroids but also in many similar natural products. The degree of stereoselectivity observed at C-22 is of particular interest since there is little data in the literature pertaining to the stereoslectivity of secondary radicals undergoing 6-endo cyclization. Furthermore, studies to the effect of increasing radical stability on the stereochemical outcome at this site are in progress.

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