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APPLICATION OF SELENOSULFONATION TO MARINE STEROL SYNTHESIS. PREPARATION OF 24,28-DEHYDROAPLYSTEROL, XESTOSTEROL AND OSTREASTEROL FROM A COMMON ACETYLENIC INTERMEDIATE

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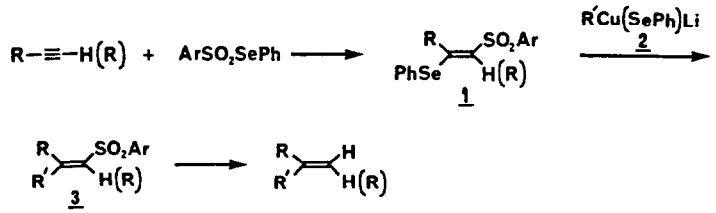
Abstract: The title compounds were synthesized from a readily available steroidal acetylene by a protocol employing selenosulfonation, introduction of the appropriate side chain at C-24 via an alkyl selenocuprate, and reductive desulfonylation.

The free-radical additions of selenosulfonates ($ArSO_2SePh$) to olefins[1-3], allenes[4] and acetylenes[5,6] have recently been described, along with further synthetically valuable transformations of the resulting products. The selenosulfonation of acetylenes thus affords 1,2-adducts 1 in a highly regio- and stereoselective manner (Scheme 1). Their subsequent reactions with alkyl selenocuprates 2 permit the stereoselective substitution of the phenylseleno group of 1 with the cuprate alkyl moiety to produce vinyl sulfones 3.[7] Reductive desulfonylation by standard methods then provides 1,1-disubstituted or trisubstituted olefins. This protocol thus permits the convenient 2-alkylation of a terminal acetylene.

Scheme 1



We now report that selenosulfonation methodology provides a novel approach to the synthesis of several marine sterols.

Marine sterols have attracted considerable attention in recent years.[8] Many display unusual, highly branched side chains which render them of both synthetic and biosynthetic interest. It occurred to us that certain marine sterols containing the 24-methylene moiety would be accessible from a common acetylenic precursor by the application of the sequence in Scheme 1. We now describe the syntheses of 24,28-dehydroaplysterol (4),[9] xestosterol (5)[10] and the more ubiquitous ostreasterol[11] (24-methylenecholesterol, 6) in this manner, as indicated in Scheme 2.

The required acetylene 8 was obtained in 73% yield from the reaction of the readily available iodide 7[12] with $LiCH_2C{\equiv}CSiMe_3$, followed by desilylation with $nBu_4N^+F^-$. Selenosulfonation[5] of 8 in the presence of a catalytic amount of AIBN afforded the 1,2-adduct 9 (80%). Compound 9 was then treated with the appropriate cuprate reagent 2, prepared in situ from the corresponding alkyllithium[13] and CuSePh as described previously,[7] to provide the substitution products 10 in 39-56% yield. The accompanying formation of 7-29% of the acetylene 8 was noted in these reactions, indicating that reductive elimination[14] competes with the desired substitution process. Desulfonylation of 10 with sodium amalgam[15] followed by acid-catalyzed hydrolysis of the 6-methoxy cyclosterol moiety of the resulting crude olefins 11 afforded the desired products 4, 5 and 6 in 67-97% yield. All reactions were performed on a relatively small scale using ca. 50 mg of 9, and no attempt was made to optimize them. Consequently improvements in the yields may be possible. The structures of all products were consistent with their IR, NMR and mass spectra and the identities of compounds 4, 5 and 6 were confirmed by comparison with authentic samples. Product 4, in which a new chiral center at C-25 has been created, was almost certainly a mixture of two isomers which are inseparable by HPLC and possess virtually identical NMR spectra.

In conclusion, the selenosulfonation adduct 9 provides the means for a novel, short and facile entry to marine sterols 4, 5 and 6, in overall yields of 38%, 38% and 35%, respectively.

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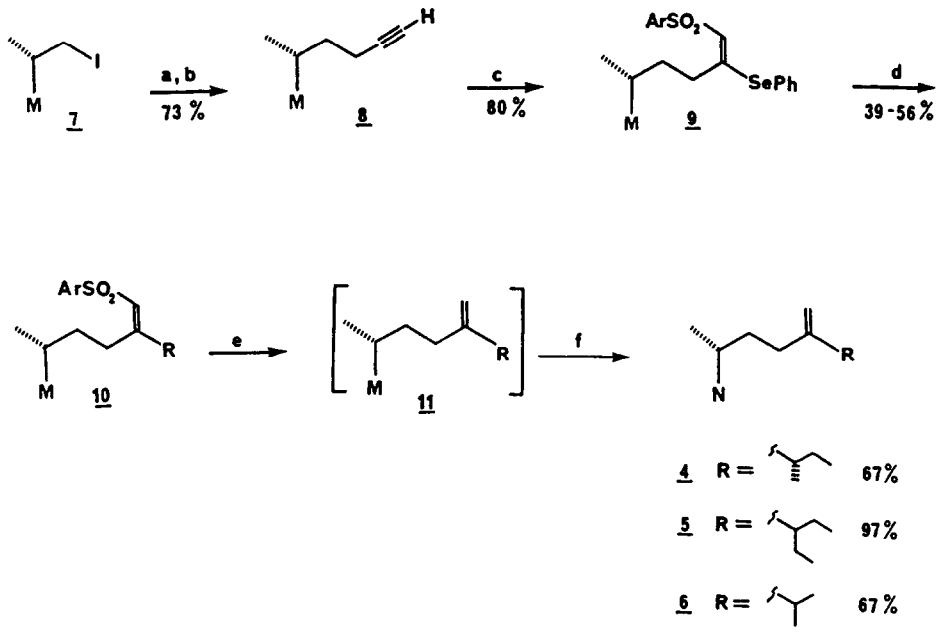
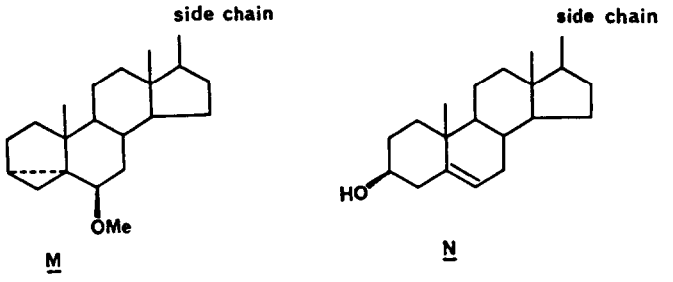
Scheme 2





M N

(a) excess $LiCH_2C{\equiv}CSiMe_3$, THF-HMPA, 18 h, R.T. (b) n-$Bu_4N^+F^-$, THF, 30 min, R.T. (c) $ArSO_2SePh$ (Ar = p-tolyl), AIBN (5 mol %), C_6H_6, reflux, 18 h. (d) RCu(SePh)Li,[7] THF, 1-2 h at 0°C., then 1-2 h at R.T. (e) 2% Na/Hg, Na_2HPO_4, THF-MeOH, 20 h, R.T. (f) TsOH (catalyst), dioxane-H_2O, 80°C., 1 h.

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