A New Stereoselective Synthesis of (20*R*)- and (20*S*)-Steroidal Side Chains

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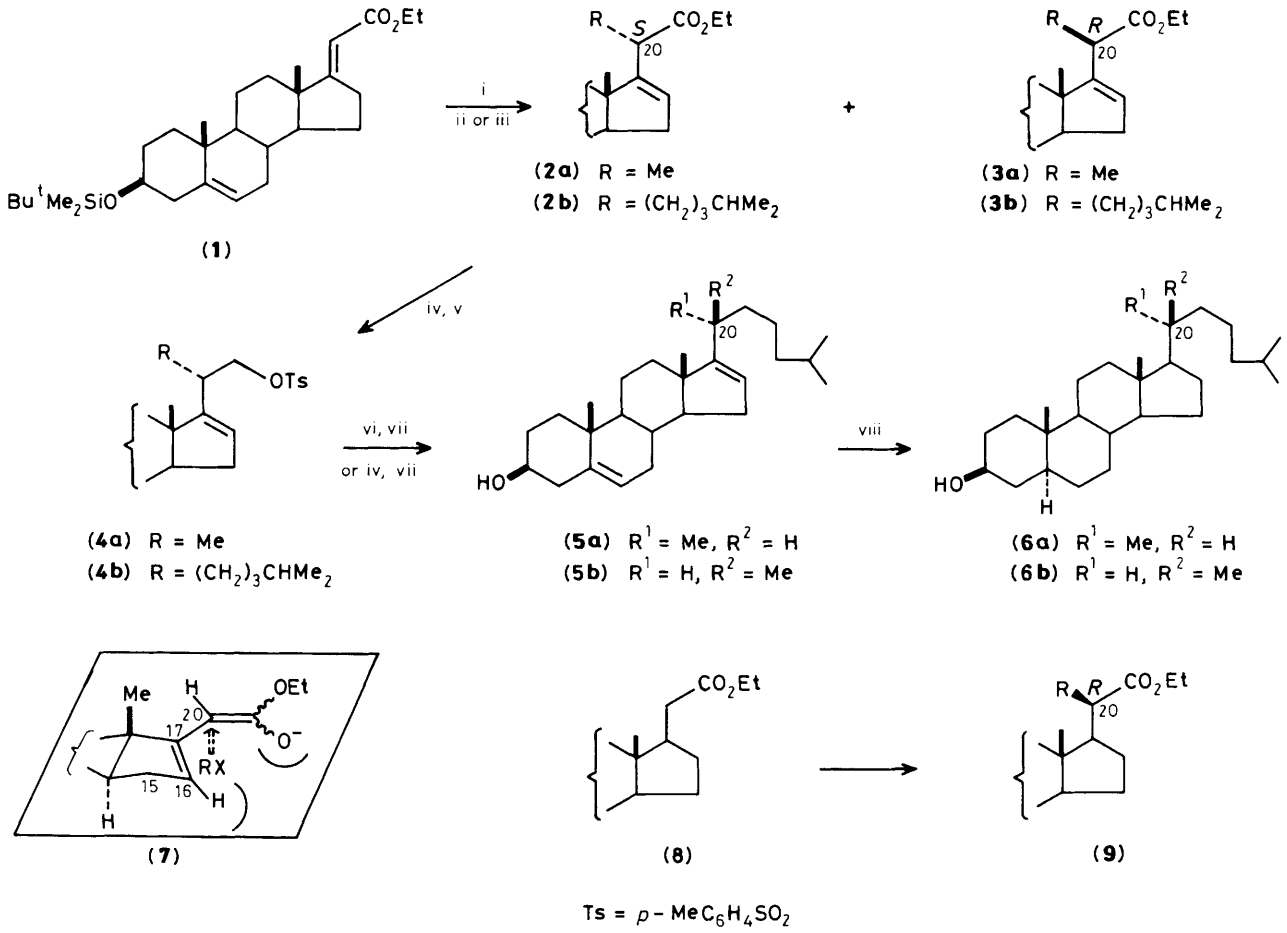
Reaction of (*E*)-ethyl 3β-t-butyldimethylsiloxypregna-5,17-dien-21-oate with lithium di-isopropylamide followed by alkyl halides results in the predominant formation of (20*S*)-alkylation products in >88% isolated yields; a synthetic application to both (20*R*)- and (20*S*)-steroidal side chains is also described.

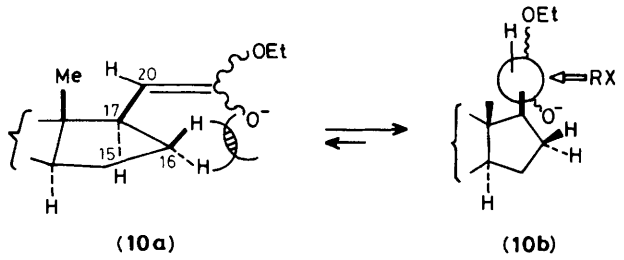
Recent isolation of many biologically important sterols with modified (20*R*) ('natural') and (20*S*) ('unusual') side chains, such as the ecdysones, the metabolites of vitamin D, the brassinolides, and the marine sterols, have stimulated the development of newer methods to introduce side chains onto readily available steroidal starting materials.[1] One of the problems is the practical and efficient stereocontrol of the C-20 chiral centre. Reported procedures for the construction of the C-20 chiral centre have involved the use of organocopper,[2] organopalladium,[3] and organoboron[4] reagents, the ene reaction,[5] and sigmatropic rearrangements.[6] We have now developed an efficient and simple synthetic route from readily available 3β-hydroxyandrost-5-en-17-one to (20*R*)- and (20*S*)-sterols with a double bond at the strategically important 16(17) position.

The requisite α,β-enoate (**1**) was readily prepared in 97% yield from commercially available 3β-hydroxyandrost-5-en-17-one *via* t-butyldimethylsilylation followed by treatment with triethyl phosphonoacetate–sodium ethoxide in the usual way.[7] Metallation of the enoate (**1**) with lithium di-isopropylamide (LDA), followed by alkylation with methyl iodide, gave a mixture of the β,γ-enoates (**2a**) and (**3a**). A single recrystallization from Et_2O–MeOH (1 : 5) gave the diastereoisomerically pure β,γ-enoate (**2a**) {m.p. 126 °C, $[\alpha]_D^{30}$ −18.9° ($CHCl_3$)} in 79% yield. Thin-layer mesh silica gel flash column chromatographic separation of the mother liquor gave the minor product (**3a**) {5.4% yield, m.p. 44—45 °C, $[\alpha]_D^{25}$ −49.0° ($CHCl_3$)} and (**2a**) (9.6% yield). Thus, the total yield of the major product (**2a**) amounts to *ca.* 88%. Evidence for the stereochemical assignment of the C-20 chiral centre in the major product (**2a**) was obtained by its conversion to the known steroids, cholesta-5,16-dien-3β-ol (**5a**)[8a] (m.p. 167—169 °C) and 5α-cholestan-3β-ol (**6a**)[8b] (m.p. 141—142 °C) through the sequence of steps (**2a**) → (**4a**) → (**5a**) → (**6a**), as shown in Scheme 1. *X*-Ray analysis of the major product (**2a**) confirmed the (20*S*)-stereochemistry.†

† All synthesized compounds have been fully characterized spectroscopically and have correct elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis. *X*-Ray data for (**2a**) will be presented in a full paper.



Scheme 1. *Reagents and conditions:* i, Pr^i_2NLi, THF, −78 °C, 1 h; ii, MeI, THF, hexamethylphosphoric triamide (HMPA), −78 °C (2 h) to −40 °C (1 h), 93%; iii, $Me_2CH(CH_2)_3I$, THF, HMPA, −78 °C (2 h) to −40 °C (1 h), 98%; iv, $LiAlH_4$, Et_2O, reflux, 1 h, 97—98%; v, toluene-*p*-sulphonyl chloride/pyridine, room temp., overnight, 93—98%; vi, $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4, THF, 30 °C, 5 h, 81%; vii, Me_2CO–Et_2O–H_2O–HF (48 : 48 : 1 : 1), room temp., 1 h, 91—95%; viii, H_2/PtO_2, EtOAc, 98—99%.



Scheme 2

In a similar manner, the α,β-enoate (**1**) was treated with LDA followed by 1-iodo-4-methylpentane to yield the (20*S*)-product (**2b**) [92% yield, m.p. 76—77 °C, $[\alpha]_D^{34}$ −29.0° ($CHCl_3$)] accompanied by small amounts of the diastereoisomer (**3b**) {6% yield, syrup, $[\alpha]_D^{27}$ −26.8° ($CHCl_3$)}. The (20*S*)-stereochemistry in the major product (**2b**) was assigned on the basis of the following chemical evidence. Successive treatment of (**2b**) with $LiAlH_4$, toluene-*p*-sulphonyl chloride–pyridine, $LiAlH_4$, and aqueous 1% hydrogen fluoride yielded (20*S*)-20-isocholesta-5,16-dien-3β-ol (**5b**) {m.p. 40—42 °C, $[\alpha]_D^{27}$ −60.0° ($CHCl_3$)}, which was converted into the known (20*S*)-5α,20-isocholestan-3β-ol (**6b**)[8,9] {m.p. 161—162 °C, $[\alpha]_D^{25}$ +6.50° ($CHCl_3$)} by catalytic hydrogenation over PtO_2 in ethyl acetate.

The above facts indicated that the alkylation occurred predominantly from the more exposed 'α-face' of the lithium dienolate (**7**) to yield (**2a**) or (**2b**) as the major product. Interestingly, the (20*S*)-stereochemistry of the major alkylation products (**2a**) and (**2b**) is opposite to the (20*R*)-stereochemistry of the major product (**9**) derived from the saturated ester (**8**) under similar conditions.[7,10] There is severe steric congestion in the enolate (**10a**) derived from the saturated ester (**8**), though a similar congestion between –C=C–H and O is released in the dienolate (**7**). Accordingly, the alkylation of the saturated ester (**8**) presumably takes place in the conformation (**10b**) which has minimal steric interaction of the C-17 chain with the C-13 methyl group and C-16 hydrogen atoms leaving the *Re* face at C-20 open to reaction; the *Si* face is shielded by the C-13 methyl group, producing the (20*R*)-product (**9**).[11]

The present process represents a short and efficient method for attaching both (20*R*)- and (20*S*)-side chains to the readily available 17-keto-steroids. Furthermore, by chemical manipu-

lations the ester group in (**2a**) and (**2b**) can be transformed into a wide variety of useful derivatives.†

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