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STEREOSELECTIVE ESTER ENOLATE ALKYLATION AND HYDROXYLATION AT C-22 OF A STEROID SIDE CHAIN

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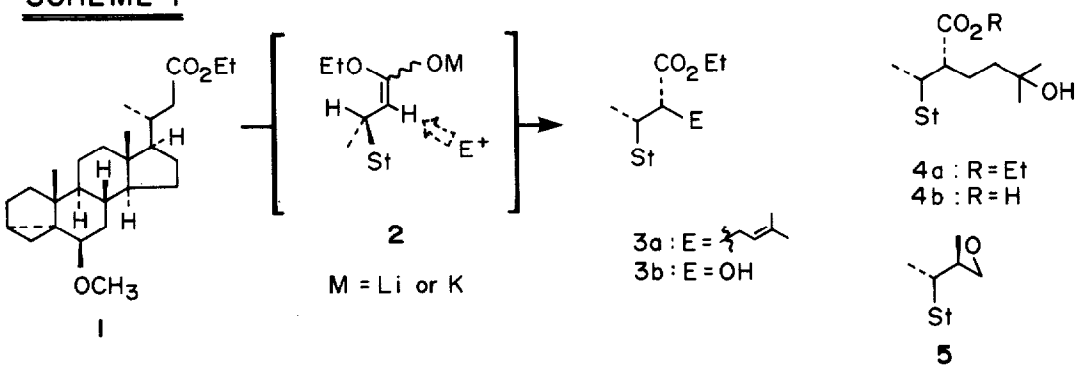
Summary: Reactions of steroidal acyclic ester enolate **2** with 4-bromo-2-methyl-2-butene and Davis' oxaziridine reagent proceeded with high diastereoselectivity to afford esters **3a** and **3b**, respectively.

Stereoselective construction of flexible steroid side chains still remains a formidable challenge to synthetic chemists.[1] As a part of our research program directed towards total synthesis of steroids,[2] we describe herein a stereoselective route to steroid side chains based upon acyclic ester enolate alkylation and hydroxylation as shown in SCHEME I.

SCHEME I



The starting 22-carbethoxy steroids are readily available from the corresponding 17(20)-(Z)-ethylidene derivatives by Trost's organopalladium methodology[3] or Midland's hydroboration-cyanomethylation protocol[4]. In the present study, however, key substrate **1** was conveniently prepared from stigmasterol in seven conventional steps.[5] Treatment of ester **1** with LDA in THF at -78 °C for 1 h followed by 4-bromo-2-methyl-2-butene in the presence of HMPA at -78 to -20 °C furnished an 87 : 13 mixture of mono-alkylated ester **3a** and its C-22 epimer in 75% yield.[6] The methyl ester corresponding to **3a** was used by Trost in a formal synthesis of α-ecdysone.[3] Likewise, hydroxylation of the potassium enolate generated from **1** [KHMDS/THF/-78 °C, 1 h] with Davis' oxaziridine reagent[7] at -78 °C for 2 h yielded a 3 : 1 mixture of hydroxylated ester **3b** and its epimer in 70% yield.[6]

In order to prove the structure of ester **3a** , especially the configuration at C-22, the major isomer was converted to hydroxy ester **4a** by an oxymercuration-demercuration procedure [$Hg(OAc)_2$, THF-CH_3CN-H_2O, rt, then $NaBH_4$, rt, 77%]. Compound **4a** was identical to an authentic sample made from known[3] hydroxy acid **4b** by treatment with Triton B and ethyl iodide. The C-22 configuration of **3b** was established by conversion to known epoxide **5** , a versatile steroidal intermediate, in three straigtforward steps [LAH, ether; TsCl, pyr; NaH, ether-HMPA].[1]

The stereochemical outcome of the alkylation and hydroxylation reactions can best be rationalized by postulating electrophilic attack on the less hindered face of the preferred 'H-eclipsed' conformation of the ester enolate as depicted in **2** .[8] It should be noted that the diastereoselective alkylations recently reported for some steroidal precusors at C-11 and C-20 involve systems which are more sterically biased than the present case.[9]

In summary we believe our C-22 stereoselective alkylation and hydroxylation method has considerable potential in the synthesis of structurally diverse side chains of physiologically active steroids.

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6. The ratio of stereoisomers of **3** was determined by HPLC (Shimpak-CLC-SIL, 5 μm, 6.0 mm i.d. x 15 cm, 1.5 ml/min, 4% EtOAc in n-hexane, RID). Compound **3a** : IR (neat) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 80MHz) δ 0.75(s, 3H), 0.97(d, J=7Hz, 3H), 1.02(s, 3H), 1.32(t, J=7Hz, 3H), 1.64(s, 6H), 2.75(m, 1H), 3.32(s, 3H), 4.12(q, J=7Hz, 2H), 5.04(t, J=7Hz, 1H): ^{13}C NMR ($CDCl_3$, 20.15MHz) δ 12.06, 13.02, 14.20, 14.62, 17.66, 19.14, 21.35, 22.69, 22.86, 23.99, 24.87, 25.62, 28.09, 30.47, 33.30, 35.02, 35.17, 37.98, 40.25, 42.77, 43.29, 47.95, 48.86, 53.72, 56.40, 56.60, 59.74, 82.27, 123.05, 131.95, 175.39. C-22 epimer of **3a** : ^1H NMR ($CDCl_3$, 80MHz) δ 0.72(s, 3H), 0.97(d, J=7Hz, 3H), 1.02(s, 3H), 1.25(t, J=7Hz, 3H), 1.61(s, 3H), 1.68(s, 3H), 2.75(m, 1H), 3.32(s, 3H), 4.12(q, J=7Hz, 2H), 5.03(t, J=7Hz, 1H). Compound **3b** : ^{13}C NMR ($CDCl_3$, 20.15MHz) δ 12.11, 12.68, 12.96, 14.11, 19.09, 21.31, 22.63, 23.90, 24.80, 27.62, 30.46, 33.23, 34.98, 35.11, 39.20, 39.97, 42.41, 43.23, 47.86, 51.73, 56.28, 56.34, 61.31, 73.09, 82.24, 175.30,
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