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A Steroselective Synthesis of (22R, 23R)-Methylenecholesterol

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Abstract □ The marine sterol (22R, 23R)-methylenecholesterol **1** has been synthesized from readily available C-22 steroidal ester **2** utilizing an intermolecular acyclic ester enolate alkylation as the key step.

Keywords □ Synthesis, marine sterol, (22R, 23R)-methylenecholesterol, intermolecular acyclic ester enolate alkylation

The marine sterol (22R, 23R)-methylenecholesterol (**1**) was isolated by Djerassi from various marine organisms such as *Dysidea* and *Xestospongia* species (Porifera) and *Siphonoborgia* species (Alcyonacea) and its structure was fully characterized by spectroscopic methods and synthesis of all four possible stereoisomers[1,2]. The occurence of the sterol in nature provides strong evidence that bioalkylation of the Δ^{22} double bond of a sterol side chain is possible in the absence of a C-24 substituent. Reported herein is a stereoselective construction of the marine sterol **1** from C-22 steroidal ester **2** based upon a stereoselective acyclic ester enolate alkylation at the C-22 position of a flexible steroidal side chain[3], as shown in the following scheme.

Treatment of the known 22-carbethoxy ester **2**[3,4], derived from stigmasterol, with LDA in THF followed by allyl bromide in the presence of HMPA yielded monoallylated ester **4** and its C-22 epimer (75% total yield) in an 87 : 13 ratio, probably by the preferential attack of the electrophile on the less hindered face of the more stable *'H-eclipsed'* conformation **3** of the acyclic lithio ester enolate[3,5].

Conversion of the major isomer **4** to cyclopropyl aldehyde **7** was carried out in a five-step sequnence in 57% overall yield as follows[6]: DIBAL reduction of **4** and mesylation of the resulting alcohol under standard conditions produced mesylate **5** in 96% overall yield. Osmylation of **5** followed by oxidative cleavage of the resulting diol with $NaIO_4$ furnished γ-mesyl aldehyde **6** which underwent spontaneous cyclization upon exposure to potassium t-butoxide to give (E)-cyclopropyl aldehyde **7** as the isolabe sole product in 59% yield in the three steps.

Wittig reaction of alddehyde **7** with the isopropylidene ylide produced olefin **8** in 82% yield. Not surprisingly, catalytic hydrogenation of vinyl cyclopropane **8** with Pd/C as catalyst resulted in facile cleavage of the cyclopropane ring. However, upon treatment with diimide, generated from 2,4-6-triisopropylbenzenesulfonylhydrazine (TPSH)[7] and triethylamine in refluxing THF, vinyl cyclopropane **8** underwent a very sluggish but clean reduction to give a 78% yield of the desired compound **9** based upon recovered starting material (50% conversion). Finally, unravelling of the i-ether moieity of **9** by a known procedure[1,8] afforded the marine sterol **1** in 84% yield, which was spectroscopically identical to the natural products[9].

In summary, (22R, 23R)-methylenecholesterol (**1**) has been synthesized from readily available C-22 steroidal ester **2** in nine steps in 20% overall yield utilizing a stereoselective intermolecular acyclic ester enolate alkylation, Ikekawa's cyclopropanation protocol[6], and a diimide reduction of a hindered vinyl cyclopropane system as the key steps.

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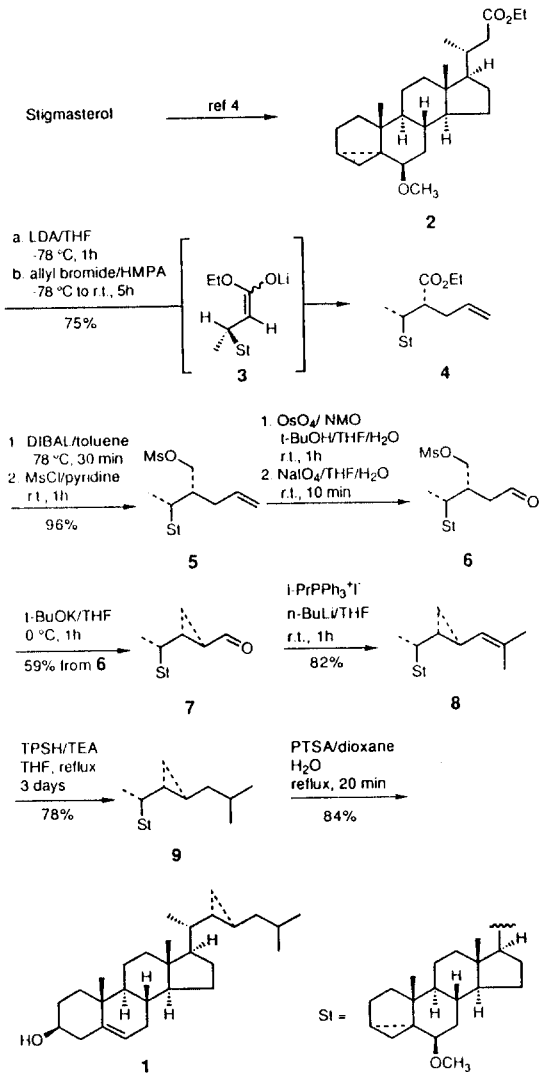

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5. All compounds gave satisfactory IR, ^{1}H and ^{13}C NMR spectral data. Compounds **4**: IR (film) 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.01 (m, 2H), 4.12 (q, J=7.2 Hz, 2H), 3.33 (s, 3H), 2.77 (br t, 1H), 1.02 (s, 3H), 0.75 (s, 3H), 0.67-0.64 (m, 1H), 0.46-0.43 (m, 1H); ^{13}NMR (20 MHz, $CDCl_3$) δ 178.5, 137.4, 115.4, 82.1, 59.9, 56.6, 56.5, 53.7, 48.3, 48.0, 43.3, 42.8, 40.3, 37.8, 35.2, 35.0, 33.3, 30.5, 28.4, 28.0, 24.9, 24.0, 22.7, 21.4, 19.1, 14.6, 14.2, 13.0, 12.2. Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.05 (m, 2H), 4.17 (dd, J=9.6, 4.8 Hz, 1H), 4.05 (t, J=9.4, 1H), 3.32 (s, 3H), 2.99 (s, 3H), 2.77 (br t, 1H), 1.02 (s, 3H), 0.74 (s, 3H), 0.66-0.63 (m, 1H), 0.45-0.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 116.7, 82.3, 71.0, 56.5, 56.4, 53.1, 48.0, 43.3, 42.8, 40.3, 39.9, 37.2, 35.3, 35.0, 34.9, 33.3, 30.5, 29.6, 28.0, 24.9, 24.0, 22.8, 21.5, 19.2, 13.2, 13.0, 12.2. Compound **7**: IR (film) 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, J=5.62 Hz, 1H), 3.32 (s, 3H), 2.77 (t, J=2.7 Hz, 1H), 1.01 (s, 3H), 0.67 (s, 3H), 0.45-0.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 82.3, 57.4, 56.5, 56.2, 48.0, 43.4, 43.0, 40.0, 39.3, 35.2, 35.1, 33.3, 30.6, 30.5, 28.8, 27.9, 24.9, 24.1, 22.7, 21.4, 19.5, 19.2, 16.8, 13.1, 12.3. Compound **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.55 (d, J=13.8 Hz, 1H). 3.32 (s, 3H),2.77 (t, J=4.0 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.02 (s, 3H), 0.67 (S, 3H), 0.49-0.45 (m, 3H). Compound **9**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.32 (s, 3H), 2.77 (br t, 1H), 1.01 (s, 3H), 0.99 (d, J=6.7 Hz, 3H), 0.90 (t, J=6.7 Hz, 6H), 0.66 (s, 3H), 0.45-0.38 (m, 4H), 0.22-0.18 (m, 3H).
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