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Ireland–Claisen rearrangement of steroidal Δ^{23}-22-alcohols: an application to $\Delta^{22,25}$-24-alkyl steroid synthesis

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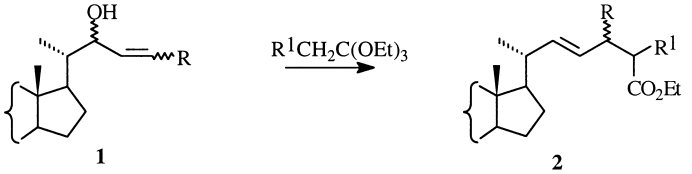
Abstract

A new method for the preparation of a 1,4-diene system in the steroid side chain, providing the possibility of stereocontrol at C-3 has been described. Its usefulness has been examined for $\Delta^{22,25}$-24-alkyl steroid synthesis. The proposed approach is based on the Ireland–Claisen rearrangement of Δ^{23}-22-alcohols followed by C-25 silylation of the formed ester and Peterson olefination as the final step.

Keywords: Ireland–Claisen rearrangement; steroids and sterols; silicon and compounds; Peterson olefination; 1,4-dienes.

The present study has been initiated by our interest in Δ^{22}-steroids bearing an alkyl substituent at C-24. Pericyclic processes have proved to be very effective for the stereoselective preparation of these compounds,[1] which are of great interest as convenient intermediates in synthetic approaches to biologically important steroids.[2] The possibility of realizing transfer of stereochemistry from the starting material **1** (Eq. (1)) to the product **2** in a predictable manner has attracted the attention of many chemists. Thus, the Claisen rearrangement has been used for the preparation of vitamin D,[3] brassinosteroids,[4] sterols,[5] and oogoniol.[6] The substituent R may be either a terminal isopropyl fragment[7] or a C-24 alkyl group,[8] which opens additional possibilities for the preparation of various types of side chain and their further transformation.



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A more difficult task is the preparation of related sterols with side chains **3**–**5** containing an additional Δ^{25}-double bond (Fig. 1). They are known as constituents of algae,[9] plants,[10] and marine organisms.[11]

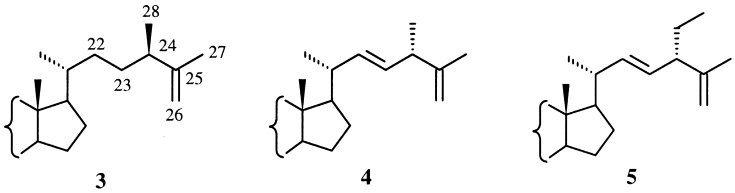
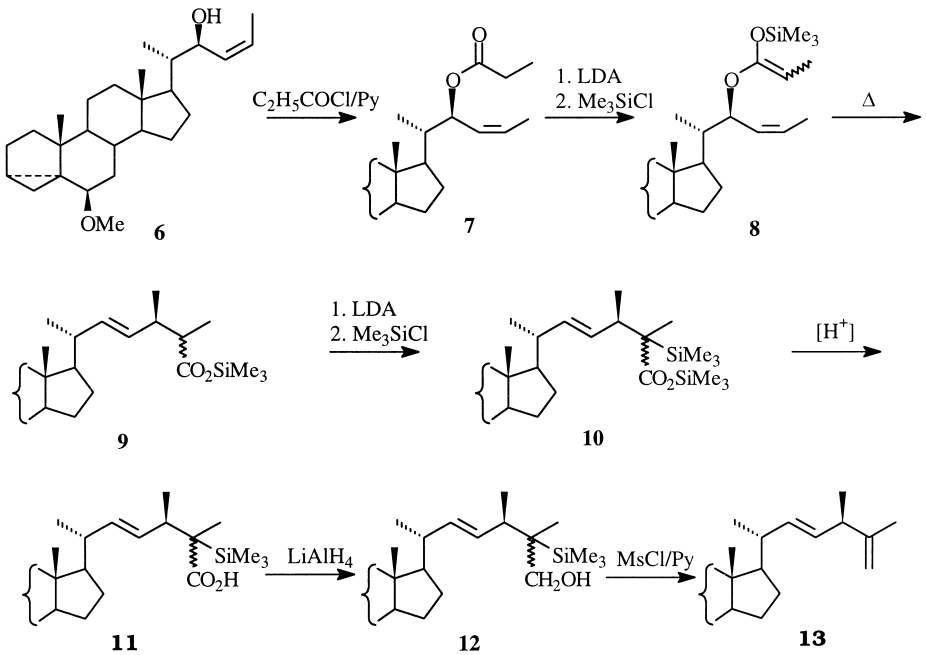


Figure 1. Structures of side chains of some natural Δ^{25}-steroids

The synthesis of such compounds implies the construction of a 1,4-diene system having an alkyl substituent at C-3 with defined configuration. Here we report the first application of the Ireland ester enolate variant of the Claisen rearrangement[12] to the preparation of these 1,4-dienes, in particular, to the synthesis of $\Delta^{22,25}$-24-alkyl steroids (Scheme 1) from the allylic alcohol **6**[13] (available in four steps from stigmasterol).



Scheme 1. A synthetic route towards $\Delta^{22,25}$-steroids based on an Ireland–Claisen rearrangement

Treatment of the propanoyl ester **7** with an excess of base and silylating agent led first to the product **9** of the Ireland–Claisen rearrangement which underwent further C-25 silylation to give the silane **10**. Its hydrolysis afforded the acid **11**. The synthetic sequence from the ester **7** to the acid **11** could be carried out in one pot, without isolation of intermediates.[14]

The final part of the synthetic route to $\Delta^{22,25}$-olefins was rather straightforward. Hydride reduction of the acid **11** gave the corresponding alcohol **12**. Its mesylation initiated the Peterson olefination reaction affording the desired $\Delta^{22,25}$-24-methyl derivative **13**.[15]

Acknowledgements

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14. The following procedure is representative. To a solution of $^{i}Pr_2NH$ (1.1 ml, 7.85 mmol) in THF (3 ml) at 0°C a 1.6 M solution of BuLi (2.6 ml, 4.16 mmol) was added. The mixture was left at this temperature for 10 min, then it was cooled down to –70°C and a solution of propanoyl ester **7** (630 mg, 1.42 mmol) in THF (4.5 ml) was added. The mixture was stirred for 8 min, then $(CH_3)_3SiCl$ (0.6 ml, 4.73 mmol) was added. Stirring was continued for 10 min at –70°C, then the reaction mixture was allowed to warm to room temperature and refluxed for a further 3 h. After cooling to room temperature it was treated with AcOH (3 ml), diluted with brine and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on SiO_2 with hexane–EtOAc (70:1→8:1) to give the starting ester **7** (220 mg) and the acid **11** (345 mg, 50% isolated yield) as a mixture (1:3) of less polar and more polar isomers.
15. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.69 s (3H, 27-Me), 2.78 m (1H, C_6-H), 3.33 s (3H, OMe), 4.71 br. s (2H, C_{26}-H), 5.19–5.30 m (2H, C_{22}- and C_{23}-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.1, 13.8, 19.7, 20.0, 21.5, 22.2, 23.4, 24.9, 25.7, 29.4, 30.4, 31.2, 34.1, 35.8, 36.0, 40.8, 40.9, 43.4, 44.1, 44.4, 48.8, 56.9, 57.2, 83.1, 109.3, 132.0, 137.0, 150.5.