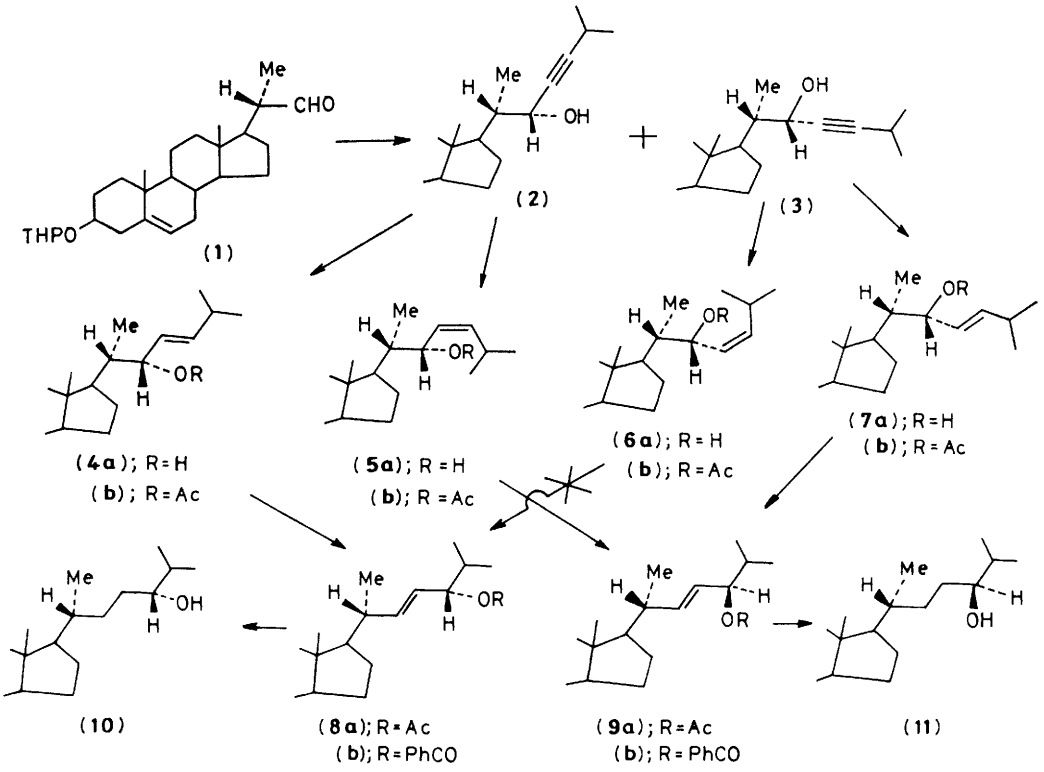
Chirality Transfer in the Cholesterol Side Chain; Synthesis of (24*R*)- and (24*S*)-24-Hydroxycholesterols

Suguru Takatsuto, Masaji Ishiguro, and Nobuo Ikekawa*

Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

Δ^{23}-22-Acetoxycholesterol derivatives can be converted into 24-hydroxycholesterol derivatives highly stereoselectively by 1,3-chirality transfer with bis(acetonitrile)palladium(II) dichloride.

The stereocontrolled introduction of hydroxy groups into steroidal side chains has been the subject of our recent investigation into the synthesis of biologically active steroids, such as withanolides, vitamin D metabolites, bile alcohols, and unusual marine sterols. Recently we reported an asymmetric reduction of the 24-carbonyl group on the cholesterol side chain leading to the stereoselective introduction of a hydroxy group into the 24-, 25-, or 26-position.[1] We report

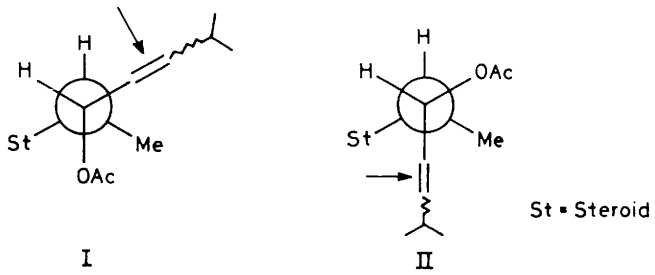


THP = tetrahydropyran-2-yl

another method for the stereocontrolled introduction of a hydroxy group using 1,3-chirality transfer by the palladium-catalysed rearrangement of allylic acetates. The stereoselective introduction of a hydroxy group at the C-22 position in the side chain has been well established in synthetic work on ecdysteroids and withanolides.[2-4] A new procedure in which the chirality at the C-22 position can be transferred into the C-24 position has now been developed.

Reaction of the 22-aldehyde 3-tetrahydropyran-2-yl (THP) ether (**1**) with 3-methylbut-1-ynyl-lithium in tetrahydrofuran at −78 °C afforded, in almost quantitative yield, a 3:2 mixture of the 22-alcohols (**2**), m.p. 154—155 °C, $[\alpha]_D$ −21.2° (*c* 1.59),† and (**3**), m.p. 129—130 °C, $[\alpha]_D$ −46.6° (*c* 0.84), which could be separated by recrystallization from methanol. The configurations at C-22 of (**2**) (22*R*) and (**3**) (22*S*) were established by conversion into the known (22*S*)- and (22*R*)-22-hydroxycholesterols, respectively. Compounds (**2**) and (**3**) were partially hydrogenated (H_2, Lindlar catalyst, EtOH–Et_2O), in quantitative yield, to give the (22*S*,23*Z*)-22-ol (**5a**), m.p. 156—158 °C, $[\alpha]_D$ −42.9° (*c* 0.468), and the (22*R*,23*Z*)-22-ol (**6a**), amorphous, $[\alpha]_D$ −20.7 °(*c* 1.24), respectively. When the compounds (**2**) and (**3**) were reduced with $LiAlH_4$ in refluxing tetrahydrofuran (THF) for 1 h, the (22*S*,23*E*)-22-ol (**4a**), m.p. 167—169 °C, $[\alpha]_D$ −41.0° (*c* 1.50), and the (22*R*,23*E*)-22-ol (**7a**), m.p. 138—139.5 °C, $[\alpha]_D$ −36.6° (*c* 1.10) were obtained respectively, in 65% yield. These compounds [(**4a**), (**5a**), (**6a**), and (**7a**)] were converted into their 3,22-diacetates by successive treatment with 2 M HCl in methanol and acetic anhydride in pyridine, giving (**4b**), m.p. 170—171 °C, $[\alpha]_D$ −47.9° (*c* 1.00), (**5b**), m.p. 135—137 °C, $[\alpha]_D$ −74.6° (*c* 1.25), (**6b**), oil, $[\alpha]_D$ −64.2° (*c* 1.12), and (**7b**), m.p. 141—143 °C, $[\alpha]_D$ −36.4° (*c* 1.13).

Treatment of (**4b**) with bis(acetonitrile)palladium(II) dichloride $[PdCl_2(MeCN)_2]$[5,6] (0.05 equiv.) in tetrahydrofuran (THF) at room temperature for 4 h gave, *via* a [3,3]sigmatropic type transition state, the (22*E*,24*R*)-24-ol acetate (**8a**), m.p. 86—88 °C, $[\alpha]_D$ −29.4° (*c* 1.07) in 86% yield with highly stereoselective (96:4) transfer of chirality from C-22 to C-24. Similarly, when (**5b**) was treated with the palladium complex for 15 h, the rearranged product, the (22*E*,24*S*)-24-ol acetate (**9a**), m.p. 146—147 °C, $[\alpha]_D$ 73.1° (*c* 1.01) was obtained in 92% yield with 95% selectivity. In the case of (**7b**), a longer reaction time (35 h) was necessary to complete the reaction giving rise to the same rearrangement product (**9a**) (90% yield) with 95% selectivity. However, the (22*R*,23*Z*)-22-ol acetate (**6b**) did not undergo the rearrangement under these conditions.



This difference in the reactivity can be attributed to the different conformation of the side chains of the 22-hydroxycholesterol derivatives. As reported in our previous paper,[7] the hydroxycholesterol may have different conformations depending on the configuration at the C-22 position; thus, the (22*S*)-compounds (**4b**) and (**5b**) should have the conformation (I) and the (22*R*)-compounds (**6b**) and (**7b**) the conformation (II). In order to initiate the rearrangement reaction, the palladium complex, as the first step, has to co-ordinate with the π-electrons of the double bond from the side opposite to the acetoxy group. The conformation (II) clearly indicates that the large steric hindrance of the steroidal nuclei inhibits the reaction and so this reaction demonstrates the confor-

† Optical rotations were determined in chloroform solution at 20 °C.

mational differences between the 22-substituted sterol side chains.

The structures of compound (**8a**) and (**9a**) were confirmed by alternative syntheses from the 22-*trans*-Δ^{22}-24-oxocholesterol acetate.[8] When the acetate was reduced with sodium borohydride in methanol–THF, a separable mixture of 24-alcohols (2:1) was obtained; the more polar major product had m.p. 121—123 °C, $[\alpha]_D$ −78.4° (*c* 0.80) and the less polar one m.p. 126—128 °C, $[\alpha]_D$ −56.3° (*c* 1.10). The acetylated products of each compound were completely identical with (**8a**) and (**9a**), respectively.

The configurations of (**8a**) and (**9a**) were determined by transformation into the known 24-hydroxycholesterols. Thus, (**8a**) and (**9a**) were saponified with 5% KOH–MeOH and treated with benzoyl chloride in pyridine to give the dibenzoates, (**8b**), m.p. 175—176 °C, $[\alpha]_D$ −11.6° (*c* 1.35) and (**9b**), m.p. 143—145 °C, $[\alpha]_D$ −30.7° (*c* 1.25), respectively. Hydrogenation of the dibenzoates with 5% Pd–C gave (24*R*)-24-hydroxycholesterol, m.p. 178—180 °C and (24*S*)-24-hydroxycholesterol, m.p. 139—141 °C, respectively.[9,10] Thus, the chirality transfer of the (22*S*,23*E*)-22-alcohol (**4a**) gives the (24*R*)-24-alcohol (**10**), while the (22*S*,23*Z*)-22-alcohol (**5a**) and the (22*R*,23*E*)-22-alcohol (**7a**) give the (24*S*)-24-alcohol (**11**).

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