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PREPARATION OF (9Z,11Z) - VITAMIN A

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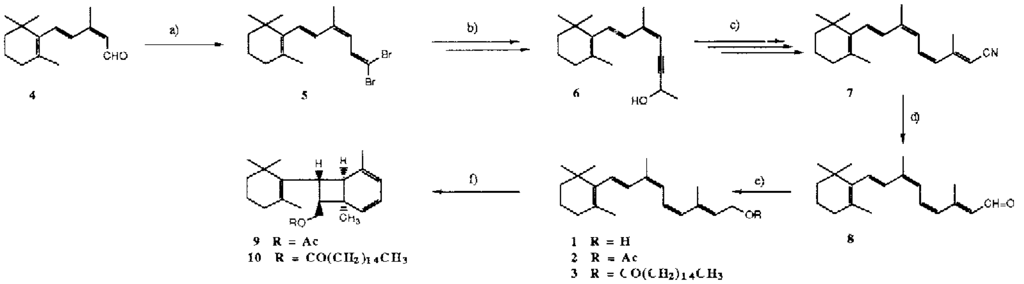
Summary : Starting from (7E,9Z)-C_{15}-aldehyde **4**, the syntheses of (9Z,11Z)-vitamin A acetate and palmitate are reported. The construction strategy is based on treatment of **4** with Zn-PPh_3/CBr_4, addition of acetaldehyde followed by a Wittig-Horner reaction to give the (9Z,11Z)-C_{20}-nitrile **7** which was reduced with DIBAH to the corresponding aldehyde **8** and then to the title compound **1**. The thermal instability of **1** is discussed.

Although all mono- and dicis-isomers of retinal are well known[1], some of the corresponding retinols have not yet been described. Here, we report on the syntheses of (9Z,11Z)-retinol **1**[2], its acetate **2** and palmitate **3** which were required for the determination of their biological activity.[3]

Starting from a mixture of the (7E,9E)- and (7E,9Z)-isomers of the C_{15}-aldehyde **4**, Liu et al[4] achieved the synthesis of the (11Z)- and (9Z,11Z)-retinals which then were separated by preparative hplc.

In contrast, we treated pure (9Z)-aldehyde **4**[4,5] with Zn-PPh_3/CBr_4[6] and obtained the dibromide **5** in 97% yield and a purity of 86% (hplc). After sequential treatment of this dibromide with n-BuLi in THF at -60°C and acetaldehyde at -5°C, the (9Z)-propargylic alcohol **6**, isolated in 79% yield, was transformed in three steps by analogy with ref[4] to the (9Z,11Z)-nitrile **7** in 37% overall yield. The main byproduct, the (9E)-isomer of **7**, could be removed by flash chromatography. Subsequent crystallization from hexane provided isomerically pure (9Z,11Z)-nitrile 7 (hplc 99%).



a). Zn-PPh_3/CBr_4, dichloroethane, rt, b). 1. BuLi, THF, -60°C, 2. acetaldehyde, THF, -5°C, c). 1. MnO_2, hexane, 10°C, 2. H_2/Lindlar cat., EtOAc, -25°C; 3. $OP(OEt)_2CH_2CN$/BuLi, ether, -60°C->rt; d) 1. DIBAH, hexane, -55°C; 2. moist THF, aqueous formaldehyde , e) 1. DIBAH, hexane, -55° C, 2. moist THF· f) hexane, rt

DIBAH reduction of the nitrile **7** in hexane at -50° C, careful workup of the resulting imine with moist THF followed by transimination using aqueous formaldehyde furnished the crude (9Z,11Z)-retinal **8** which was purified by flash chromatography to give **8** in almost quantitative yield and a purity of greater than 99% (hplc) Reduction of the purified aldehyde **8** with DIBAH in hexane at -55° C followed by workup at -35° C with moist THF yielded crude (9Z,11Z)-retinol **1** which was not isolated but directly transformed at -55^{o} -> -30^{o} C into either the acetate **2** or the palmitate **3** by treatment with the corresponding acid chlorides in the presence of pyridine. The final purifications were performed by flash chromatography at -25^{o} C to give the acetate **2**[7] in 50% and the palmitate **3**[7] in 38% yield. Both esters are very unstable at room temperature and in hexane solution, they gradually cyclized overnight to the cyclobutane derivatives **9** (65%) and **10** (78%yield). The thermal instability of conjugated tetraenes with similar geometry is well known[8]. An initial thermally allowed eight electron conrotatory cyclization is followed by a disrotatory six electron ring closure to give the bicyclo[4,2,0]-octadienes. Okamura et al.[9] described the isolation of the free hydroxyl-derivative of **9** from a thermally induced sigmatropic rearrangement of a vinyl allene precursor. (9Z,11Z)-retinol **1** was postulated to be an intermediate in this case.

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