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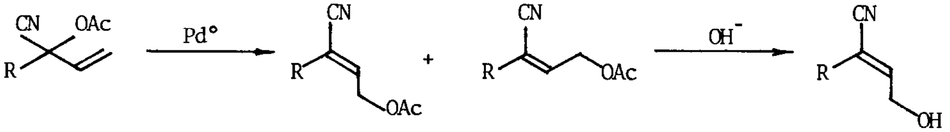
A NEW TOTAL SYNTHESIS OF DL-SIRENIN

T. Mandai, K. Hara, M. Kawada, and J. Nokami
Okayama University of Science, Ridai-cho, Okayama 700, Japan

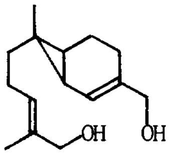
Summary: A new total synthesis of dl-sirenin (1) has been effectively accomplished by employing the acetate 4a obtained by the stereoselective rearrangement of the acetate 3 using a palladium catalyst.

In a previous paper,[1)] we reported a general synthetic method for γ-acetoxy-α,β-unsaturated nitriles by the palladium catalyzed allylic rearrangement of α-cyanoallylic acetates. In our study on the palladium catalyzed rearrangement of I, we have found the stereochemical outcome of the resulting γ-acetoxy-α,β-unsaturated nitriles II is considerably dependent on the reaction temperature and that IIa (Z isomer) is obtained predominantly at a lower temperature. In addition, we have found that only IIa can be easily transformed to the allyl alcohol III by alkaline hydrolysis because the cyano group in IIb (E isomer) is further attacked, being probably converted to a carboxylic acid.

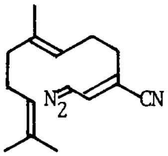


I IIa IIb III

We now wish to report a new total synthesis of sirenin (1),[2)] a sperm attractant produced by female gametes of water mold, *Allomyces*,[3)] by employing a key intermediate 5d easily obtained by the sequence of these reactions. Our synthetic route is depicted in the scheme.



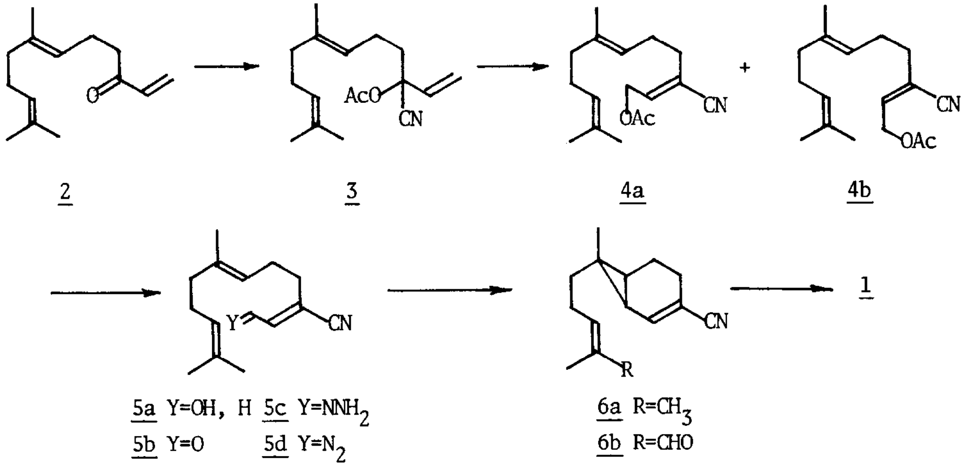
sirenin (1)



5d

Successive treatment of the readily available vinyl ketone 2[4)] with Me_3SiCN-cat. KCN-18-crown-6 complex[5)] and with 1N HCl in acetone gave a crude cyanohydrine which was converted to the acetate 3 (92% from 2) by reaction of Ac_2O-Py in the presence of a catalytic amount of 4-dimethyl aminopyridine. The stereoselective allylic rearrangement of 3 by use of $Pd(PPh_3)_4$ (5 mol%) in THF at 0 °C-30 °C for 2 h gave a mixture of 4a and 4b (85%-89%). The ratio of 4a/4b is largely dependent on the reaction temperature, i.e., 4a/4b=7:3 at 0 °C and 4a/4b=4:6 at 30 °C. Careful hydrolysis of a mixture,4a and 4b,(7:3) by dioxane-0.5N NaOH at room temperature provided the Z alcohol 5a (94% from 4a) as a sole product. The corresponding E alcohol could not be isolated.

Scheme



The alcohol 5a was oxidized to the aldehyde 5b (91%) by CrO_3-Py complex. Conversion of 5b to the bicyclonitrile 6a was carried out according to the reported procedures.[2b)] The aldehyde 5b was transformed to the hydrazone 5c by reaction with H_2NNH_2-Et_3N (each 4 eq) in EtOH, and thence to diazo nitrile 5d by oxidation with MnO_2 in CH_2Cl_2. Slow addition of the crude 5d (9.1 mmol) in THF (50 ml) to a stirred suspension of CuI (10 eq) in THF (150 ml) at room temperature for 3 h afforded 6a (45% from 5b). Oxidation of 6a by SeO_2[2a)] in dioxane-water (95:5) at reflux for 1 h gave the E aldehyde 6b (53%)[2a,6)] as a sole product. Reduction of 6b by $^{i}Bu_2AlH$ in ether at 0 °C provided a crude hydroxy aldehyde which was again reduced by the same procedure to afford 1 (56%). The IR and NMR spectra of 1 were fully identical with those reported.[2a)]

References and Notes

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Protection of the vinyl olefin in 2 is essential to the reaction of Me_3SiCN-cat. ZnI_2 because of decomposition of the geranyl moiety. Thanks are due to the reviewer for suggestion of this process.
6) The chemical shift of the E aldehyde proton has been clearly established.
cf: K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, J. Org. Chem., 33, 3382 (1968).

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