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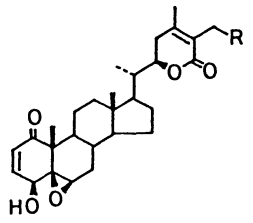
SYNTHESIS OF THE STEROIDAL LACTONE MOIETY OF WITHANOLIDES[1]

Masao HIRAYAMA,† Keiji GAMOH, and Nobuo IKEKAWA*

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

A facile synthesis of the steroidal α,β-disubstituted α,β-unsaturated-δ-lactones with 22R-configuration, withanolide side-chain lactones, was described.

Withanolides, a group of naturally occurring C_{28} steroids isolated from the plants of the Solanaceae family, have been paid a special attention for their biological activity, e.g. antitumor and insect antifeedant.[2] Most compounds of them possess an unsaturated-δ-lactone with 22R-configuration in the side chain. Previous attempts to synthesize the side-chain moieties were based on the aldol type condensation with the 22-aldehydes, so that they were resulted in the formation of stereoisomeric 22S-lactones.[3]



1a : R = OH

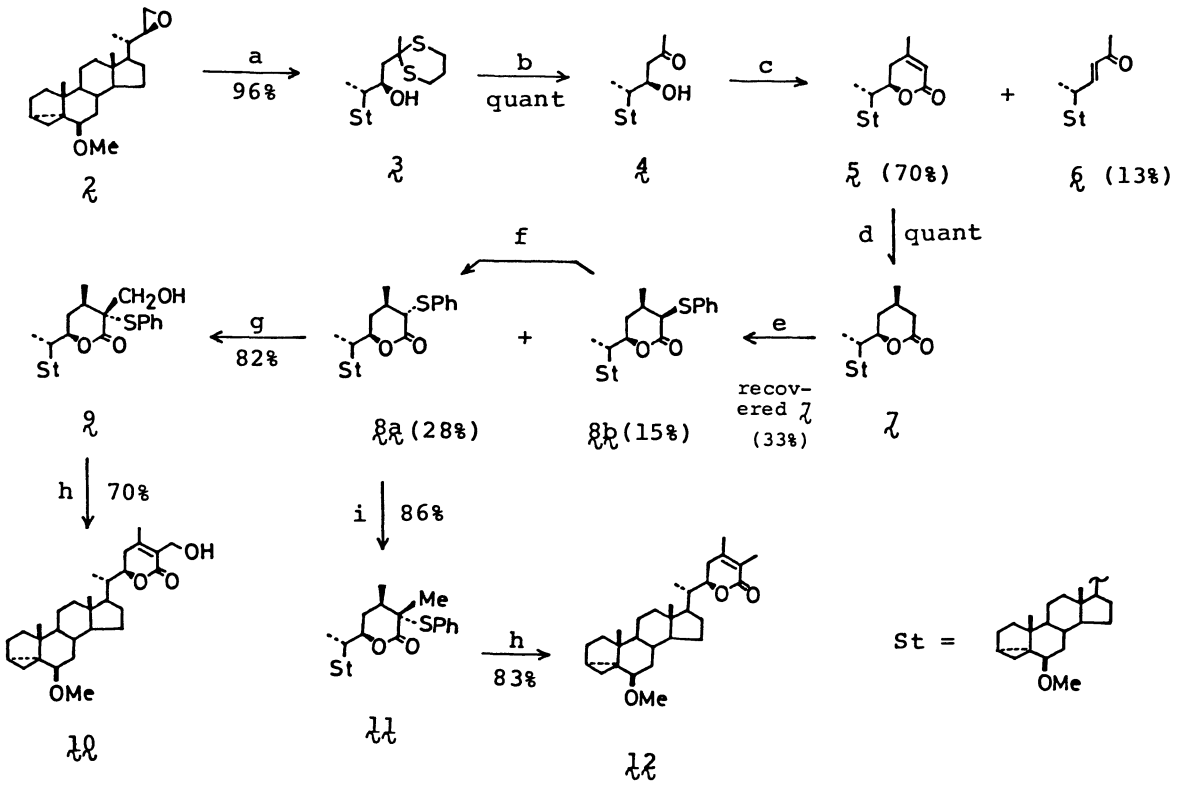
1b : R = H

In continuation of the synthetic studies of the 22R-steroidal side chain,[4] we have now extended our studies to the development of a facile synthesis of the 22R-lactone, which led us to the first synthesis of both side-chain lactones of withaferin A (1a) and 27-deoxywithaferin A (1b).[5] According to this route, the correct configuration at C-22 was secured by utilizing the chiral center of a steroidal (22S)-22,23-epoxide 2 and the function at C-25 was introduced into the enolate of α-phenylthio lactone 8a, the C-25 anion equivalent of 5 (Scheme I).

The key intermediate is the (22R)-25-phenylthio-δ-lactone 8a, prepared from

(22S)-22,23-epoxy-6β-methoxy-3,5-cyclo-24-norcholane (2).[4,6] The chiral epoxide 2 was subjected to alkylative opening of the epoxide ring with 2-methyl-1,3-dithiane anion and the resulting 22-hydroxydithioketal 3 was treated with mercuric oxide-boron trifluoride etherate[7] to give the (22R)-22-hydroxy-24-one 4, mp 102-104°C, in high yield. According to the strategy developed by McMorris[8] for the synthesis of 23-deoxyantheridiol, acylation of 4 with bromoacetyl bromide followed by Arbusov reaction with triethylphosphite gave the corresponding diethylphosphonate. The subsequent intramolecular Wittig-Horner reaction afforded the α,β-unsaturated-δ-lactone 5, mp 138-139°C, [NMR δ 4.37(1H, dt, J=4, 12 Hz, C_{22}-H) and 1.98(3H, s, C_{24}-Me)], in good yield, accompanied by small amount of the elimination product 6. The R-configuration at C-22 was determined by the positive Cotton effect at 250 nm (Δε +3.52) in agreement with those of withanolides.[9]

Scheme I



(a) 2-methyl-1,3-dithiane (BuLi), THF, -78°C, 2 h; (b) HgO-BF_3·OEt_2, aq THF, room temp, 15 min; (c) $BrCH_2COBr$, Py-ether, 0°C, 30 min / $(EtO)_3P$, 100°C, 50 min / NaH, THF, room temp, 30 min; (d) H_2 (10% Pd-C, 1 atm), $NaHCO_3$-dioxane, room temp; (e) LICHA (2 equiv), THF, -78°C, 30 min / $(PhS)_2$ (1 equiv), THF-HMPA, -78°C, 20 min; (f) LICHA, 0°C, 1 h; (g) LICHA, THF, -78°C, 1 h / CH_2O, -78°C, 30 min; (h) m-CPBA, $CHCl_3$, 0°C, 10 min / neat, 100°C; (i) LICHA, THF, -78°C, 1 h / MeI, -78°C, 1 h.

In order to introduce a relevant substituent at C-25 in 5, 5 was converted to its C_{25}-anion equivalent, i.e. the enolate of the saturated α-phenylthio lactone 8a. Hydrogenation of 5 proceeded stereospecifically to give the saturated lactone 7, mp 130-132°C, as a sole product. Spectral data[10] supported that 7 possessed the half-chair conformation with R-configuration at C-24. This result was agreement with that of the reported hydrogenation of withaferin A diacetate.[9b] Sulfenylation of 7 with diphenyl disulfide by inverse quench[11] yielded a mixture of two sulfides, which was chromatographed on silica gel to afford the major and less polar sulfide 8a, oil, [NMR δ 4.28(1H, dt, J=3,12 Hz, C_{22}-H) and 3.28(1H, d, J=8 Hz, C_{25}-H); IR 1735 cm^{-1}] and the minor and more polar sulfide 8b, oil, [NMR δ ca.4.40(1H, br s, C_{22}-H) and 3.72(1H, d, J=5 Hz, C_{25}-H); IR 1730 cm^{-1}] in the ratio 2 : 1. The C_{22}- and C_{25}-proton NMR signals of 8a and epimerization of 8b to 8a with lithium isopropylcyclohexylamide (LICHA) indicated that 8a was the thermodynamically stable (25S)-sulfide and 8b was the (25R)-isomer.

The enolate anion of the key intermediate 8a was treated with monomeric formaldehyde to afford the 25-hydroxymethyl compound 9 (syrup) as a sole product. The 25R-configuration of 9 was deduced by the success of the following dehydrosulfenylation, which required the stereochemical syn arrangement of the phenylthio unit and the hydrogen at C-24.[11∿13] Oxidation of 9 to the sulfoxide with m-CPBA followed by heating of the sulfoxide at 100°C gave the unsaturated lactone 10 (amorphus solid), the side-chain moiety of withaferin A, [NMR δ 4.42(1H, dt, J=4, 12 Hz, C_{22}-H), 4.36(2H, s, C_{27}-H_2), and 2.04(3H, s, C_{24}-Me); IR 1700 cm^{-1}; CD 254 nm (Δε +4.70); MS m/z 456.32497 (M^+)]. The structure of 10 was supported by the proton signals of C_{22}-H, C_{24}-Me, and C_{27}-H_2 showing a perfect agreement with those of withaferin A.[14] Furthermore, the strong positive peak in the CD spectrum indicated the R-configuration at C-22.[9a]

By the treatment with methyl iodide followed by dehydrosulfenylation, 8a was converted to the corresponding δ-lactone 12 (syrup), the side-chain moiety of 27-deoxywithaferin A, [NMR δ 4.36(1H, dt, J=4, 12 Hz, C_{22}-H) and 1.92(6H, s, C_{24}-Me and C_{25}-Me); IR 1710 cm^{-1}; CD 250 nm (Δε +3.33); MS m/z 440.33193 (M^+)]. The relevant spectral data including the positive Cotton effect showed good agreement with those of 27-deoxywithaferin A.[9b, 15]

Further studies of stereoselective synthesis of withaferin A and 27-deoxywithaferin A on the basis of this methodology are now in progress.

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† Present address; Central Research Laboratories, Meiji Seika Kaisha, Ltd., Morooka-cho, Kohoku-ku, Yokohama 222.

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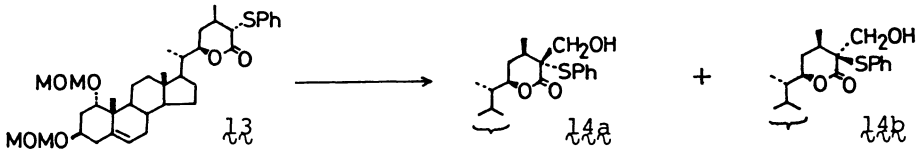
13) Similar hydroxymethylation of the 1,3-bis(methoxymethoxy)-5-ene derivative 13 gave a mixture of the corresponding (25R)-25-hydroxymethyl compound 14a and its (25S)-isomer 14b in the ratio 9 : 1. Dehydrosulfenylation of 14a successfully afforded the expected α,β-unsaturated lactone, which could not be obtained by the similar dehydrosulfenylation of 14b.



13 14a 14b

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