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TOTAL SYNTHESIS OF THE ELEMANOLIDES (±) ZEMPOALIN A and B

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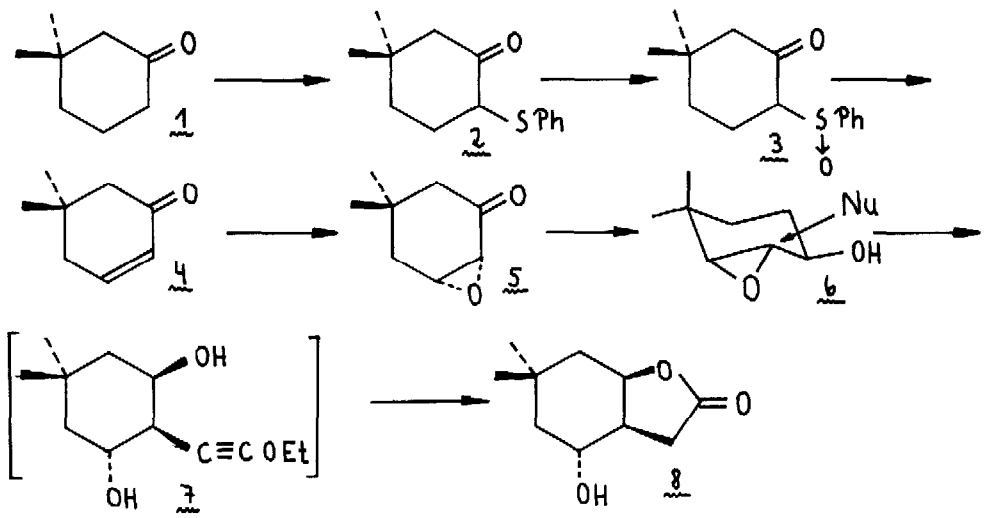
Abstract - Starting with a suitable trisubstituted cyclohexanone derivative two further substituents were introduced via an epoxy ketone which after reduction was reacted with the diethylaluminium derivative of ethoxyacetylene. The resulting dihydroxyester afforded the corresponding cis-lactone which could be transformed to (±) zempoalin A and B in the usual way via selenium chemistry.

Among other classes of sesquiterpene lactones also the elemanolides are widespread in the family Compositae[1,2]. Starting with the cyclohexanone derivative 9 several of the naturally occurring derivatives have been synthesized[2]. We now describe a regio and stereo controlled total synthesis of the elemanolides zempoalin A (18) and B (19) which have been isolated from a Verbesina species[3]. Retrosynthetic considerations led to the proposal that the divinyl cyclohexane 9 again should be a suitable starting material as via the corresponding α,β-unsaturated ketone the formation of an epoxide should be possible, which could be used for the introduction of the missing hydroxy group at C-6 and a C_2-unit at C-7. The transformation of the ketone 9 into the conjugated ketone 10 was achieved via the α-phenylsulfide derivative which by oxidation with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide gave the sulfoxide which after elimination gave in high yield the desired ketone 10.

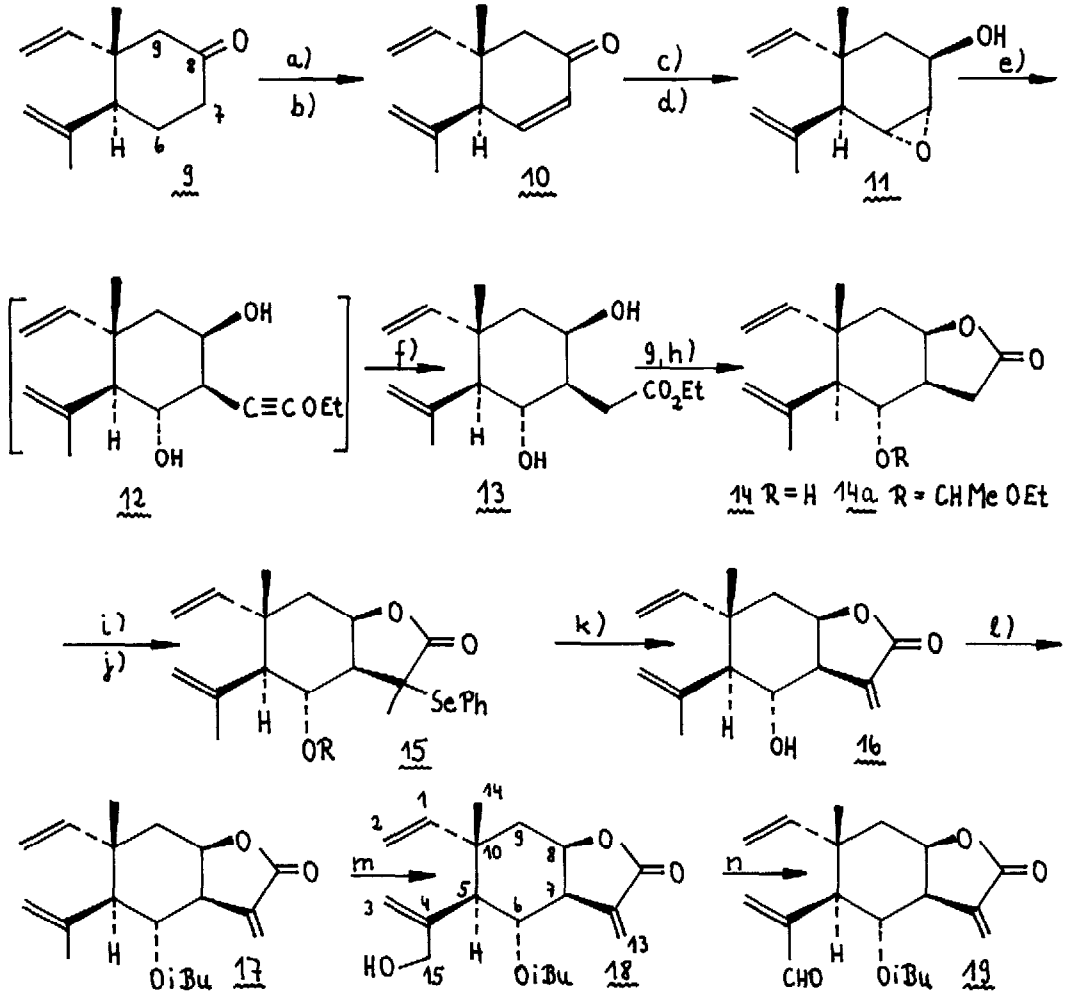
The regio and stereo controlled introduction of a hydroxy group at C-6 and an acetic acid moiety at C-7 was first studied with a model compound.

The readily available 3,3-dimethylcyclohexanone 1 was converted to the cyclohexenone 4 via the phenylsulfide 2 and the sulfoxide 3 and by epoxidation to the corresponding epoxide 5, colourless oil, ^{1}H NMR ($CDCl_3$): δ 4.17 dd (H-1, J = 7, 6 Hz), 1.66 dd (H-2, J = 14, 6), 1.18 dd (H-2', J = 14, 7), 1.77 d (H-4, J = 16), 1.62 dd (H-4', J = 16, 4), 3.25 dd (H-5, J = 4, 4), 3.13 d (H-6, J = 4), 0.91 s (H-7), 0.98 s (H-8). Boranate reduction in the



presence of $CeCl_3$ gave exclusively the β-hydroxyepoxide 6 which was useful for the introduction of the necessary C_2-unit. Reaction with the diethyl aluminium derivative of ethoxy acetylene[4,5] and acid treatment gave the corresponding cis-lactone 8 indicating that the nucleophilic attack of the epoxide occurred in the desired direction. Most likely this is due to a preferred conformation with an equatorial hydroxy group (s. Scheme).

Similarly epoxidation of 10 with hydrogen peroxide in the presence of sodium hydroxide gave by attack from the α-face the α-epoxide. Obviously due to the axial methyl group at C-10 an attack from the β-face was hindered. The stereospecific reduction again was achieved with sodium boranate in the presence of $CeCl_3$ affording the epoxy alcohol 11. For the regiospecific introduction of the C_2-unit also the diethylaluminium derivative of ethoxyacetylene was used. Surprisingly, in toluene no reaction occurred while in tetrahydrofuran a complete transformation of the epoxide 11 was observed. Usual work-up directly gave the ester 13 which on treatment with acid gave the desired cis-lactone 14 (mp. 76°, ^{1}H NMR ($CDCl_3$): δ 5.69 dd (H-1, J = 17, 11 Hz), 4.95 d (H-2, J = 17), 4.99 d (H-2c, J = 11), 4.79 and 5.17 br s (H-3), 1.96 d (H-5, J = 11), 3.71 dd (H-6, J = 11, 9.5), 2.37 dddd (H-7, J = 9.5, 6, 5, 2), 4.71 ddd (H-8, J = 5, 4.5, 2), 2.10 and 1.74 dd (H-9, J = 16, 2 and 16, 4.5), 2.75 m (H-11), 1.10 s (H-14), 1.79 br s (H-15); ^{13}C NMR ($CDCl_3$, C-1 - C-15): δ 147.4 d, 111.8 t, 114.2 t, 143.2 s, 57.6 d, 69.0 d, 43.0 d, 79.6 d, 39.2 t, 40.0 s, 35.9 t, 176.7 s, 18.8 q, 26.9 q). Accordingly, again the nucleophilic attack of the epoxide was regiospecific indicating a conformation of 11 with an equatorial hydroxy and an axial vinyl group. Introduction of the exomethylene group required protection of the 6-hydroxy group. The ether 14a was then transformed in the usual way via the phenylselenium derivative 15 into the lactone 16 (mp. 128°, ^{1}H NMR ($CDCl_3$): δ 5.78 dd



a) LDA, -78°, $PhSO_2SPh$, 77%; b) SeO_2/H_2O, 5°; $CaCO_3/C_6H_6$, 6 h reflux, 90%; c) $H_2O/NaOH$, 65%; d) $NaBH_4$, $CeCl_3$, MeOH, 55%; e) $Et_2AlC{\equiv}COEt$, THF, -30°, then 12 h, 20°; f) NaHCO , H_2O; g) EtOH, HCl, 12 h, 20°, Σ 39%; h) $(iPr)_2NEt$, ClCHMeOEt, 89%; i) LDA, PhSeCl, -78°, 63%; j) LDA, MeI, HMPT, -78°, 91%; k) H_2O_2, SeO_2, HOAc, 77%; l) iPrCOCl, DMAP, $(iPr)_2NEt$, 70%; m) tBu-OOH, SeO_2, 3 d, RT, 68%; n) MnO_2/Et_2O, 75%.

(H-1, J = 17, 11 Hz), 4.97 d (H-2, J = 17), 5.00 d (H-2c, J = 11), 4.76 and 5.14 br s (H-3), 2.02 d (H-5, J = 11.5), 3.73 dd (J = 11.5, 9), 2.86 ddt (H-7, J = 9, 6, 1.5), 4.68 ddd (H-8, J = 6, 5, 3), 2.03 and 1.82 dd (H-9, J = 16, 3 and 16, 5), 6.28 d (H-13, J = 1.5), 5.89 br s H-13'), 1.08 s (H-14), 1.79 br s (H-15); ^{13}C NMR ($CDCl_3$, C-1 - C-15): δ 147.8 d, 111.7 t, 114.2 t, 143.1 s, 57.1 d, 69.4 d, 47.1 d, 76.6 d, 39.3 t, 39.6 s, 138.9 s, 170.2 s, 123.4 t, 19.6 q, 26.8 q). Hydrolysis of the protection group and esterification with isobutyryl chloride in the presence of 4-dimethylaminopyridine gave the lactone 17 (mp. 74°, ^{1}H NMR ($CDCl_3$): δ 5.46 dd (H-1), 4.76 and 4.85 d (H-2), 2.11 d (H-5), 5.38 dd (H-6), 2.38 br dd (H-7), 3.94 ddd (H-8), 1.96 and 1.47 dd (H-9), 6.18 and 5.24 br s (H-13), 1.23 s (H-14), 1.86 br s (H-15); OCOR: 2.37 qq, 1.33 d, 1.225 d (J [Hz]: s. compound 16). Reaction of 17 with tert. -butylhydroperoxide in the presence of catalytic amounts of selenium dioxide in methylene chloride gave 18 (mp. 103°, ^{1}H NMR ($CDCl_3$): δ 5.68 dd (H-1), 4.99 and 6.01 d (H-2), 2.24 d (H-5), 5.32 dd (H-6), 3.00 br dd (H-7), 4.68 ddd (H-8), 2.14 and 1.83 dd (H-9), 6.19 and 5.54 d (H-13), 1.19 s (H-14), 4.01 and 3.92 br d (H-15, J = 14 Hz); OCOR: 2.48 qq, 1.12 d, 1.13 d (J [Hz]: s. compound 16); ^{13}C NMR ($CDCl_3$, C-1 - C-15): δ 146.1, 112.6, 113.6, 144.3, 50.6, 70.3, 46.4, 76.5, 38.9, 40.1, 138.2, 169.3, 122.8, 18.9, 67.3; OCOR: 175.8, 34.1, 19.0 (2 x). Lactone 18 was stirred with manganese dioxide in ether yielding the aldehyde 19 (mp. 121°, ^{1}H NMR ($CDCl_3$): δ 5.54 dd (H-1), 4.84 and 4.91 d (H-2), 3.16 d (H-5), 5.37 dd (H-6), 3.03 br dd (H-7), 4.70 ddd (H-8), 2.16 and 1.89 dd (H-9), 6.31 and 6.12 br s (H-13), 1.12 s (H-14), 9.37 s (H-15); OCOR: 2.14 qq, 1.05 d, 1.03 d (J [Hz]: s. compound 16); ^{13}C NMR ($CDCl_3$, C-1 - C-15): δ 145.5, 113.0, 136.9, 145.8, 43.5, 69.3, 46.3, 76.7, 38.7, 40.4, 138.1, 169.2, 122.9, 17.5, 193.9; OCOR: 175.7, 33.9, 19.0, 18.8. Direct comparison of the data with those of zempoalin A and B were not possible as no samples could be obtained. The ^{1}H NMR data agree with reported ones[3].

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