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TOTAL SYNTHESIS OF DEOXYVERNOLEPIN

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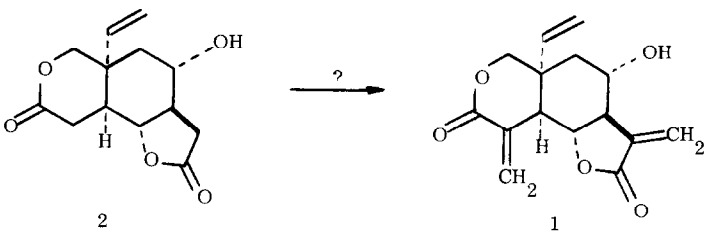
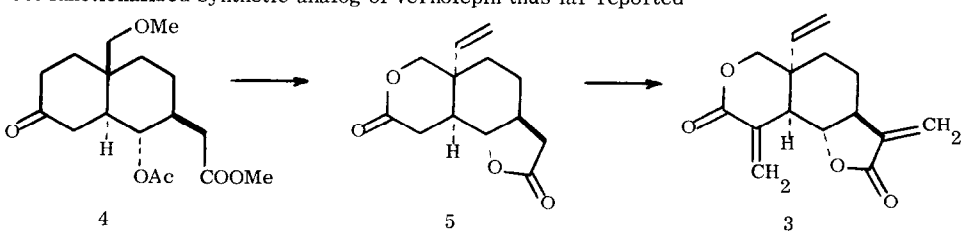
To date model studies directed toward the total synthesis of the sesquiterpene dilactone vernolepin(1)[2] have concentrated on the synthesis of the novel cis-fused α-methylene-δ-valerolactone AB-ring system[3-7] with no attention being devoted to either relevant functionality in the B-ring or to construction of bis-α-methylene dilactone systems An important simplification in the design of a total synthesis is possible if it can be assumed that the technology which we and others[8] have developed for the α-methylenation of lactones can be applied in a concurrent fashion for the simultaneous introduction of both α-methylene units of vernolepin(e g 2 → 1) Furthermore it would be useful if this operation could be postponed for the last



2 1

stage of the synthesis Our results described below indicate that such planning is realistic We demonstrate for the first time the feasibility of bis-α-methylenation in the context of the total synthesis of deoxyvernolepin (3), the most functionalized synthetic analog of vernolepin thus far reported



4 5 3

Initially our attention focused on the preparation of decalone 4 from the ketal olefin 6[9] Hydroboration of the methyl ether of octalone 6 followed by Collins oxidation[10] afforded ketone 7[11] Introduction of the acetic acid side chain at C-7(steroid numbering) in 7 was accomplished in a straight forward manner a) carbomethoxylation, b) alkylation with methyl bromoacetate, and c) decarboxylation using barium hydroxide[12] Reduction(sodium/isopropanol) and esterification of keto acid 8(mp 143-144°) provided in 55 % overall yield the crystalline hydroxy ester 9, mp 94-95° Acetylation and deketalization of 9 generated the desired decalone 4, mp 120° nmr[11a] ($CDCl_3$) δ 2 00(s, 3H, CH_3CO-), 3 34(s, 3H, CH_3O-), 3 53(ABq, 2H, -CH_2O-, J = 9 Hz, $\Delta\nu_{AB}$ = 15 6 Hz), 3 59(s, 3H, CH_3OCO-), 4.75(t, 1H, J = 10 Hz, -CHO-)

With the stereochemical and synthetic aspects of this sequence for the formation of 4 assured, attention was turned to the transformation of 4 to the required tricyclic dilactone 5 Formation of hydroxy ester 11 via specific cleavage of the C-2, C-3 carbon-carbon bond was accomplished by a) conversion of 4 to the Δ^2-enol acetate 10, mp 119-120°, b) ozonolysis with a reductive workup, and c) esterification Conversion of 11 to its corresponding mesylate followed by treatment with boron tribromide at -78° provided the valerolactone 12 Treatment of 12 with o-nitrophenylselenium anion afforded selenide 13 which upon oxidation-elimination[13], acetate cleavage, and lactonization was smoothly converted to the desired tricyclic dilactone 5 ir ($CHCl_3$) 5 59, 5 75, 6 10 μ, nmr[11a] ($CDCl_3$) δ 3 98(t, J = 10 Hz, 1H), 4 78(ABq, 2H, J = 11 Hz, $\Delta\nu_{AB}$ = 30 0 Hz), 5 3 - 5.8(ABC pattern, 3H, -CH=CH_2)

α-Hydroxymethylation[14] of dilactone 5 in tetrahydrofuran containing 10 % hexamethylphosphoramide gave a bis-α-hydroxymethyl derivative which when subjected to mesylation and β-elimination in pyridine afforded, in 32 % overall yield from 5, crystalline deoxyvernolepin(3), mp 169-170° ir ($CHCl_3$) 5 65, 5 82 μ, nmr[10a] ($CDCl_3$) δ 6 74(s, 1H), 6 20(d, J = 2 5 Hz, 1H), 5 95(s, 1H), 5 53(d, J = 2 5 Hz, 1H), 5 3 - 5 8 (typical vinyl pattern, 8 lines, 3H), 4 43(ABq, 2H, J = 12 Hz, $\Delta\nu_{AB}$ = 81 2 Hz), 4 00(t, 1H, J = 11 Hz)

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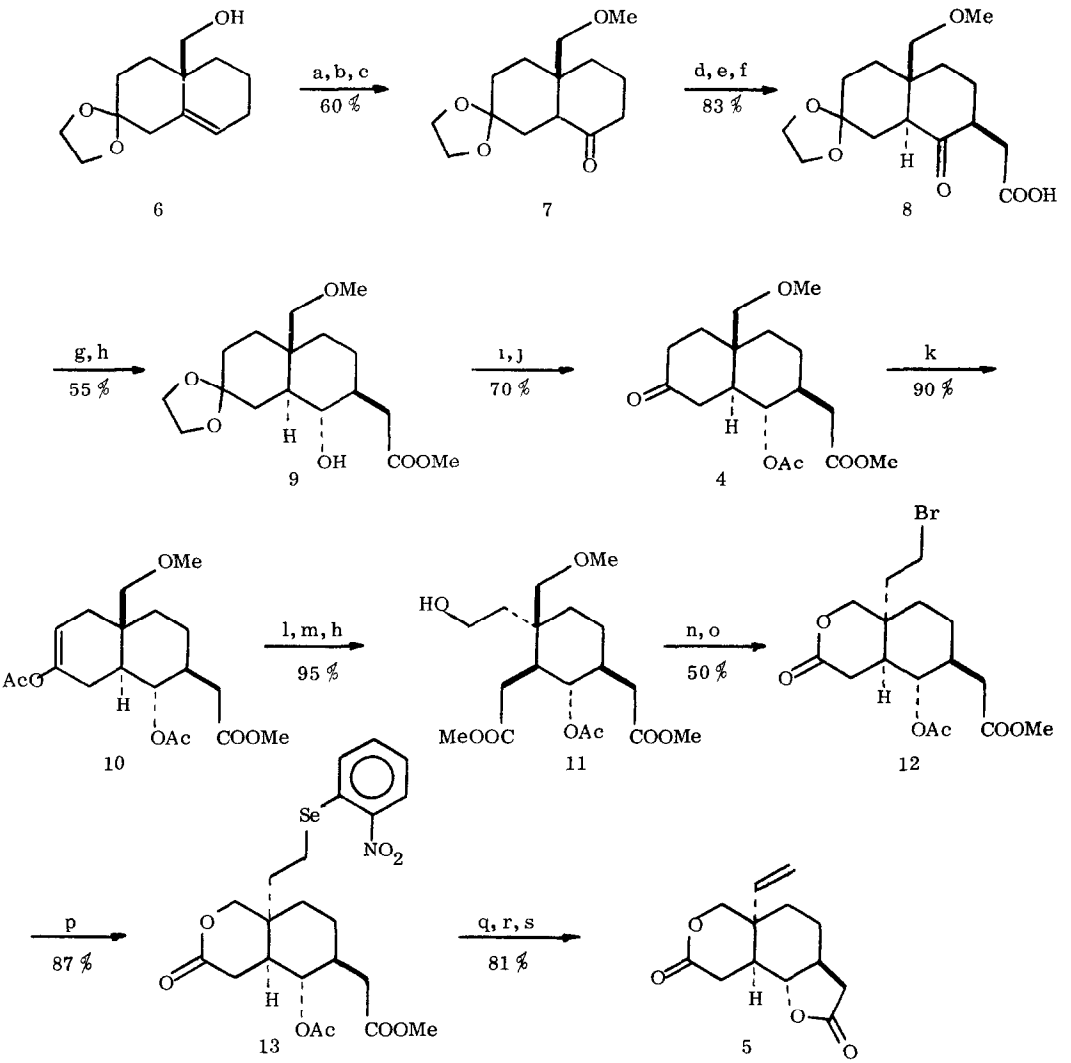

a, NaH, MeI, THF, b, BH_3 THF, OH^-, H_2O_2, c, CrO_3 2Py, CH_2Cl_2, d, NaH, $(MeO)_2CO$, dioxane, e, NaH, $BrCH_2COOMe$, dioxane, f, $Ba(OH)_2$ $8H_2O$, EtOH, reflux, g, Na, i-PrOH, h, CH_2N_2, Et_2O, i, $(CH_3CO)_2O$, Py, j, 5 % HCl, THF, k, $CH_2=C(OAc)CH_3$, TsOH, l, O_3, MeOH CH_2Cl_2(2 3), m, BH_4^-, OH^-, n, MsCl, Py, 0°, p, o-$O_2NC_6H_4SeCN$, BH_4^-, DMF, rt, o, BBr_3, CH_2Cl_2, -78°, q, 50 % H_2O_2, THF, r, K_2CO_3, MeOH, s, TsOH, C_6H_6, reflux

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