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A TOTAL SYNTHESIS OF (±) STEGANACIN VIA THE MODIFIED ULLMANN REACTION

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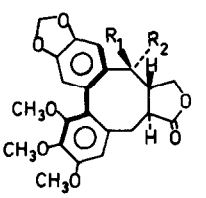
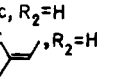
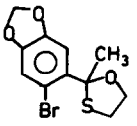
Steganacin (1a) and steganangin (1b), two antileukemic agents which occur along with steganone (1c) and steganol (1d) in *Steganotaenia araliacea* Hochst, were isolated by Kupchan in 1973.[2] Three of these natural products (1a, 1c, and 1d) have been synthesized.[3,4] As a consequence of our recently developed method[5] which permits the Ullmann reaction to be conducted regiospecifically at room temperature, we wish to report a new synthesis of members of this class of compounds.



1a, R_1=OAc, R_2=H
b, R_1=O_2C  , R_2=H
c, R_1,R_2=O
d, R_1=OH, R_2=H
e, R_1=H, R_2=OH

The 1,3- thiadioxolane 2, mp 64-66°C, was prepared in 50% overall yield from 6-bromo piperonal by successive treatment with methyl magnesium bromide (Et_2O-THF, 20h), pyridinchlorochromate (CH_2Cl_2, 25°C, 24h),[6] and β-mercaptoethanol (azeotrope, PhH, p-TSOH, 3h). Metal-halogen exchange of 2 (n-BuLi, THF, N_2, -78°C, 15 min) provided organolithium 3a as a pale yellow solution, which, upon treatment with solid CuI·$(C_2H_5O)_3P$ complex, produced a homogeneous orange solution of the organocopper reagent 3b. The organometallic intermediate was coupled with 2-iodo-3,4,5-trimethoxybenzaldehyde cyclohexylimine[7] (-78°→25°C, 20h) to provide the crude imine 4a, which was directly hydrolyzed (CH_2Cl_2/20% aq.HOAc, 12h, 25°C) to the aldehyde 4b, mp126-127°C, in 82% overall yield. The aldehyde 4b exists as a mixture of diastereomers (NMR($CDCl_3$) δ9.45 and 9.50, 1:3, CHO) due to the asymmetry of the thiadioxolane and the restricted rotation of the hindered biphenyl.



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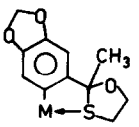
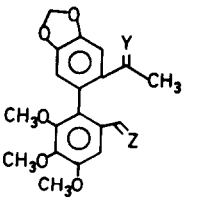
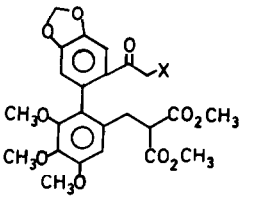


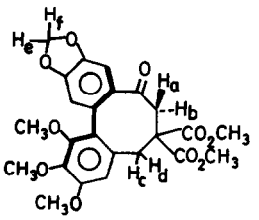
3a, M=Li
b, M=Cu←$P(OC_2H_5)_3$



4a, Y=SCH_2CH_2O, Z=NC_5H_{11}
b, Y=SCH_2CH_2O, Z=O
c, Y=SCH_2CH_2O, Z=$C(CO_2CH_3)_2$
d, Y=O, Z=$C(CO_2CH_3)_2$



5a, X=H
b, X=Br



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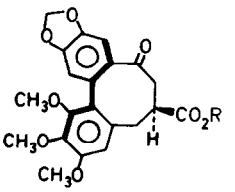
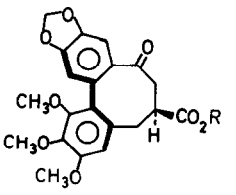
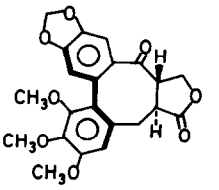


7a, R=H
b, R=CH_3



8a, R=H
b, R=CH_3



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The aldehyde was transformed (dimethyl malonate, PhH, $C_5H_{11}N$(cat.), reflux, 10h) into the malonylidene derivative 4c, mp 123-124°C, in 87% yield. Subsequent removal of the thiadioxolane group was readily achieved[8] (CH_3I, aq. acetone, reflux, 12h) giving rise (91%) to the ketodiester 4d: mp 120-122°C; NMR($CDCl_3$) δ2.12, 3.57, 3.72, 3.76, 3.82, 3.88 (6x3H,s), 6.04(2H,s), 6.58, 6.72, 7.25, and 7.32 (4x1H,s); IR($CHCl_3$) 1730 and 1682 cm^{-1}. Reduction (Ni(R), H_2, C_2H_5OH atm. pressure, 25°C) of the double bond provided the ketodiester 5a, mp 97-98°C, in 95% yield. Bromination ($C_5H_6NBr_3$, CH_2Cl_2-TFA(cat), 3.5h, 25°C) resulted in the formation of phenacyl bromide 5b, mp 123-124°C in 85% yield.

The critical intramolecular alkylation was effected by the slow addition (THF soln) of the phenacyl bromide to *tert*-BuOK (1.1 equiv. *tert*-BuOH/THF, N_2, 45 min, 25°C) followed by stirring for an additional 45 minutes, affording the ketodiester 6[9] in 73% yield: mp 143-144°C; NMR ($CDCl_3$, 270 MHz) δ2.76 ($1H_a$, d, J_{ab} = 14Hz), 3.06 ($1H_b$, d, J_{ab} = 14Hz), 3.20 ($1H_c$, d, J_{cd} = 14Hz), 3.32($1H_d$, d, J_{cd} = 14Hz), 3.56, 3.74, 3.79, 3.85, 3.91 (5x3H,s), 6.05

(1H_e, d, J = 2Hz), 6.08 (1H_f, d, J = 2Hz), 6.44, 6.64, and 7.56(3x1H,s); IR($CHCl_3$) 1732 and 1660 cm^{-1}. The significant upfield shift of H_a is due to its orientation over the shielding cone of the trimethoxybenzene ring.

The diester 7 was saponified and decarboxylated as previously described[3] to provide a nearly equal mixture of acids 7a and 8a, which was directly converted to ketoester 7b, mp 133-134°C, (lit[4] mp 133-134°C), and ketoester 8b, mp 128-130°C (lit[4] 127-129°C), respectively, with ethereal diazomethane. Further confirmation of these assignments was obtained by achieving the thermal equilibration, A $\rightleftarrows$ B (ca.1:1, xylene, reflux) of each ketoester.[4,10]

The mixture of monoacids 7a and 8a was sequentially treated with 40% formalin-5% aq. KOH and Jones reagent to provide from the neutral fraction (50%) a mixture of steganone 1c and isosteganone 9. Thermal biphenyl inversion was achieved in refluxing xylene to provide (±) steganone, mp 228-230°C (lit.[3] mp 229-230°C, 227-229°C[4]), whose 270 MHz NMR spectrum was identical with a sample of natural (-) steganone.[11] Reduction ($NaBH_4$, CH_3OH, 0°C)[2] of steganone gave a mixture (ca 1:1) of steganol (1d) and episteganol (1e). Whereas LiAl(tert-OBut)$_3$H affords a 2.5/1 (90%) ratio of 1d/1e,[4] we have observed that Li-sec-Bu_3BH (L-Selectride) provides episteganol in 70% yield with no apparent sign of 1d(HPLC).

Acetylation (Ac_2O, pyr, 4h, 25°C) of steganol provided (±) steganacin, mp 215-216°C, (lit[4] 214-217°C), whose 270 MHz NMR spectrum was identical with a sample of naturally occurring (-) steganacin.[11]

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