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TOTAL SYNTHESIS OF (±)-AVENACIOLIDE VIA THE β-VINYLBUTENOLIDE ANNULATION

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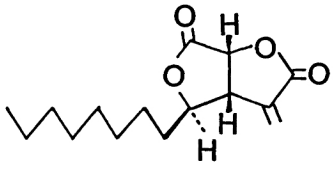
Annulation reaction of α-formylcaprylate (5) with 2,5-dihydro-3-phenylthio-4-vinylfuran-2-one (2), followed by dehydration, oxidation, and rearrangement, provided an epimeric mixture of 2,4,5,6-tetrahydro-6-hexyl-4-hydroxy-6-methoxycarbonylbenzofuran-2-ones (8a and 8b). From both the products, 2,3,3aβ,4,6,6aβ-hexahydro-4β-octylfuro[2,3-c]-furan-2,6-dione (4b), the known synthetic precursor of (±)-avenaciolide (1) was obtained.

Many synthetic efforts[1] have concentrated on avenaciolide (1),[2] an antifungal mold metabolite produced by Aspergillus avenaceus, because of its characteristic, fused dilactone structure as well as the eminent biological activity.



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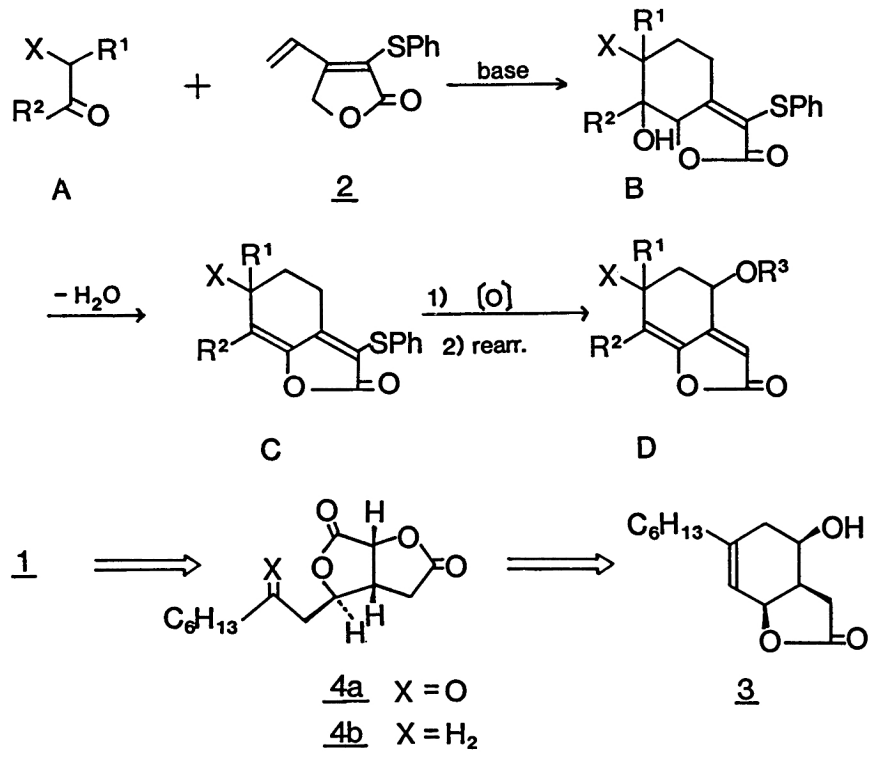
Recently, the novel annulation reaction using α-phenylthio-β-vinylbutenolide (2) has been developed in this laboratory for the synthesis of 4-oxygenated perhydrobenzofuran-2-ones.[3] The synthesis consists of the following steps; annulation product (B), obtained by the reaction of a carbonyl compound (A) (X = acyl, cyano, or alkoxycarbonyl) and 2, is dehydrated to give α,β,γ,δ-unsaturated lactone (C). The lactone (C) is then oxidized to afford sulfoxide, which on treatment with pyridine-water (or pyridine-acetic anhydride), provides hydroxy (or acetoxy) lactone (D) (R^3 = H or Ac).

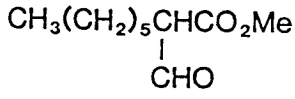
Our synthetic approach to 1 described herein can be outlined as follows; hydroxylactone 3, accessible from α-formylcaprylate 5 via the above annulation reaction and the subsequent transformation, was oxidatively cleaved at the cyclohexene double bond, followed by lactone ring formation, to give keto dilactone 4a. Upon reduction of the ketone carbonyl, 4a provided dilactone 4b well-established as the synthetic precursor of 1.



Methyl α-formylcaprylate (5), obtained from methyl caprylate (LDA, HCO_2Et; 74%), reacted with 2 (KF, DMSO-DME, room temperature; 62% yield) to give a diastereomeric mixture of annulation products, 6a, mp 108-109.5°C, and 6b in a ratio of 72:28.[4,5] The major product 6a gave 7 by dehydration ($SOCl_2$, pyridine, 0°C; 90% yield).[6] Oxidation of 7 with mCPBA (1 mol equiv., CH_2Cl_2, 0°C) and the subsequent rearrangement of the resulting crude sulfoxide in pyridine-water (8:2) at 35-37°C provided a 1:1 mixture of hydroxy lactones 8a and 8b,[7] mp 91-93°C (95% combined yield). The relative stereochemistry of the ester vs. hydroxyl group in these products was assigned by the fact that the latter lactone 8b formed dilactone 9 on acid treatment (TsOH, PhH, reflux; 42% yield).

After protection of the hydroxyl group in 8b as t-butyldimethylsilyl ether (t-$BuMe_2SiCl$, imidazole, DMF, 87% yield), hydrogenation (5% Pd-$SrCO_3$, EtOH) of the product proceeded with high stereoselectivity yielding γ-lactone 10a[8] (91% yield), whose ester group was then selectively hydrolyzed (n-PrSLi, HMPA; 85% yield). Carboxylic acid 10b thus obtained was oxidatively decarboxylated ($Pb(OAc)_4$, $Cu(OAc)_2 \cdot H_2O$, pyridine, PhH[9]) giving an inseparable mixture of olefins, 11a and 11b (57% combined yield), along with acetate 12 (33% yield). The olefin mixture was separable, after desilylation (n-Bu_4NF, THF), by chromatography to afford the desired olefinic alcohol 3[10] (72% yield) and its regioisomer 11c (23% yield).

On the other hand, the isomeric lactone 8a afforded butenolide 13[11] by reduction under alkaline conditions ($NaBH_4$, K_2CO_3, MeOH; 48% yield). After the hydroxyl group had been protected as t-butyldimethylsilyl ether, the olefinic double bond of the butenolide ring in 13 was reduced ($NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH[12]) to give saturated lactone 14 in quantitative yield from 13. By applying the same sequence of reactions as described



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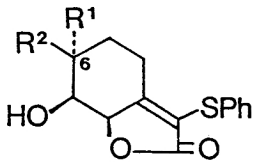
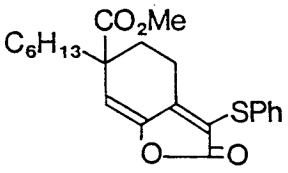


6a R^1= CO_2Me R^2 = C_6H_{13}
6b R^1= C_6H_{13} R^2 = CO_2Me



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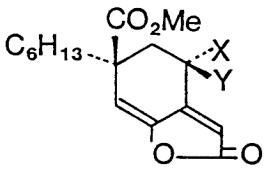
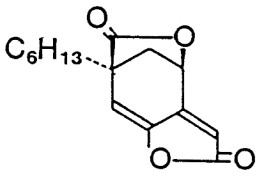


8a X=OH, Y=H
8b X=H , Y=OH



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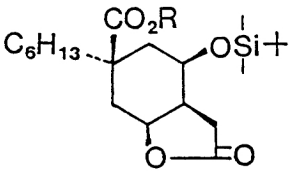
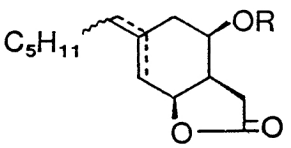
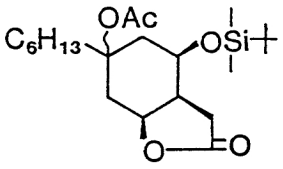


10a R=Me
10b R=H



11a endo olefin, R=t-$BuMe_3Si$
11b exo olefin, R=t-$BuMe_3Si$
11c exo olefin, R=H



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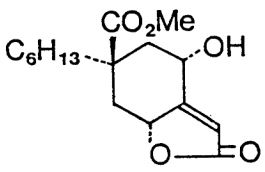

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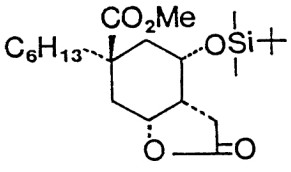

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for 10a (i, PrSLi, HMPA; ii, $Pb(OAc)_4$, $Cu(OAc)_2 \cdot H_2O$, pyridine, PhH; iii, Bu_4NF, THF), the key intermediate 3 was also obtained from 14 (24% yield).

The olefinic lactone 3 thus secured was ozonized and the product was oxidized (PCC[14]) to give 4a (73% yield). Reduction of the ketone carbonyl was performed by the modified Clemmensen reduction (Zn, ether saturated with dry HCl gas[15]), yielding the known precursor 4b of (±)-avenaciolide (1),[1a,1b,1d,1e,1f] which was identified in comparison with an authentic sample (IR and ^1H NMR).

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References

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4) The stereochemical assignments of these products at the C(6) positions were made by analogy with the C(6) methyl derivatives, i.e. in the major annulation product obtained from methyl α-formylpropionate and 2, a cis stereochemistry of the C(6)-methyl to the hydroxyl group was demonstrated by NOE measurements (unpublished results).

5) Chemical shift values shown below are given at 100 MHz unless otherwise stated. 6a; δ($CDCl_3$) 0.87 (t, 3H, J 6), 3.72 (s, 3H), 4.52 (t, 1H, J 4), 5.02 (d, 1H, J 4), 7.24 (m, 5H); 6b ($CDCl_3$) 0.89 (t, 3H, J 6), 3.68 (s, 3H), 4.50 (t, 1H, J 4), 5.00 (d, 1H, J 4), 7.26 (m, 5H).

6) Similar treatment of the mixture of 6a and 6b afforded 7 in 54% yield.

7) 8a; δ($CDCl_3$) 0.90 (t, 3H, J 6), 3.70 (s, 3H), 4.99 (br. m, 1H), 5.75 (d, 1H, J 2), 6.12 (t, 1H, J 2); 8b ($CDCl_3$) 0.89 (t, 3H, J 6), 3.77 (s, 3H), 4.96 (br. q, 1H, J 12 and 6), 6.07 (d, 1H, J 2), 6.14 (t, 1H, J 2).

8) δ($CDCl_3$) 0.06 (s, 6H), 0.86 (br. s, 12H), 3.68 (s, 3H), 4.04 (t of d, 1H, J 10 and 5.5), 4.66 (q of d, 1H, J 10, 8, and 6).

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10) δ($CDCl_3$) 0.90 (t, 3H, J 6), 4.07 (br. q, 1H, J 7 and 4), 4.96 (m, 1H), 5.71 (br. s, 1H).

11) δ($CDCl_3$) 0.89 (t, 3H, J 6), 3.75 (s, 3H), 4.67 (br. q, 1H, J 10 and 6), 4.92 (br. q, 1H, J 11 and 6), 5.98 (br. s, 1H).

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13) δ($CDCl_3$; 90 MHz) 0.04 (s, 3H), 0.06 (s, 3H), 0.88 (12H), 3.74 (s, 3H), 3.88 quint, 1H, J 6), 4.80 (t of d, J 11 and 7).

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