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SIMPLE SYNTHESIS OF 2-ACETYL-5,8-DIMETHOXY-3,4-DIHYDRONAPHTHALENE, A KEY INTERMEDIATE FOR THE SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLIONES

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2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene is synthesised easily starting from 2-acetyl-5,8-dimethoxytetralone.

Recent communication[1] on the synthesis of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (5) had prompted us to report our findings on its synthesis which was completed some time back. Earlier, we had reported a simple synthesis of (±) 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (6) which was then elaborated to (±)-4-demethoxydaunomycinone.[2] Compound 6 was originally synthesised in nine steps starting from 2,5-dimethoxybenzaldehyde[3] and the optically active (R)(-)-6 has been achieved by optical resolution.[4] Further synthetic routes from (R)(-)-6 to optical active anthracyclinones have been established.[5] An elegant and most rational approach for the synthesis of (R)(-)-6 making use of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (5) as a key intermediate has been reported recently by Terashima et al.[6] However, their synthesis of 5 is more tedious and not convenient for the preparation of 6 in gram quantities. We have achieved the synthesis of 5 in much shorter route and in better yields.

Our synthetic approach is shown in scheme I. 2-Acetyl-5,8-dimethoxytetralone (2) is made from 1 either by condensing with sodium and ethyl acetate or BF_3 etherate-Ac_2O[7] in 85% yield. The acetyl ketone group was then selectively protected ($HS-CH_2CH_2-SH$,HCl gas, $CHCl_3$, r.t., 10 hr) to give ketone 3[8], [PMR, CCl_4, δ 1.70 (s, 3H, CH_3), 1.90-2.80 (m, 5H, CH and 2 x CH_2), 2.90 (2, 4H, $-S(CH_2)_2S-$), 3.46 (s, 6H, 2xOMe), 5.96, 6.16 (dd, J=9 Hz, 2H, ArH)]. Compound 3 was subjected to reduction ($NaBH_4$, MeOH, r.t., 24 hr) followed by acid work up gave 4 in 76% yield, m.p. 95-97°, [PMR, CCl_4, δ 2.0 (s, 3H, CH_3), 2.53 (m, 4H, $2CH_2$), 3.36 (s, 4H, $-S(CH_2)_2S-$), 3.76 (s, 6H, 2xOMe), 6.43 (s, 2H, ArH), 6.83 (bs, 1H, vinylic C-H)]. Deketalization of 4 (NCS, $AgNO_3$, 80% aq.CH_3CN, r.t., 20 min) gave the desired 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (5) in 73% yield, m.p. 102-103° (Lit.[6,1] m.p. 104-105°, m.p. 102-103°) [PMR,CCl_4, δ 2.36, s, 3H, CH_3), 2.60 (m, 4H, 2xCH_2), 3.76, 3.83 (2s, 6H, 2 x OMe), 7.53, 7.76 (dd, J=9 Hz, 2H, ArH), 7.70 (bs, 1H, vinylic C-H)][9].

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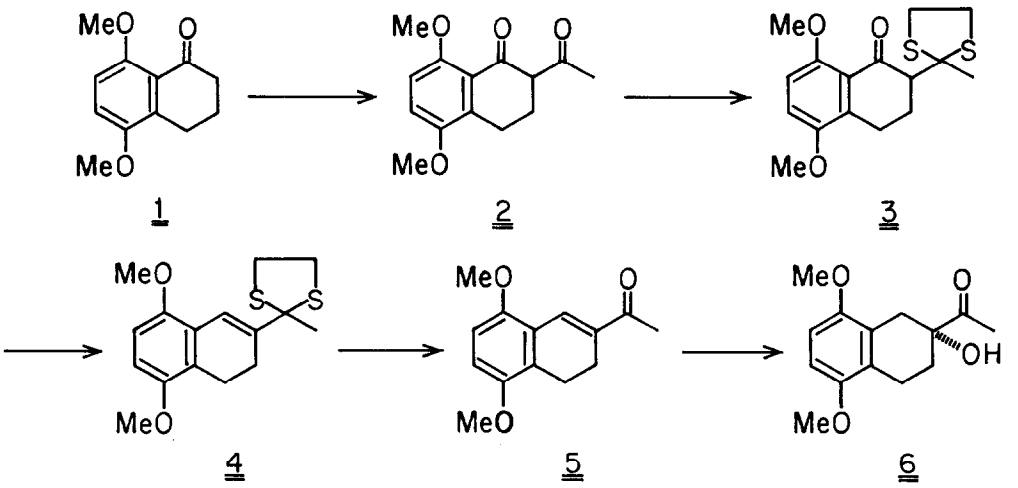
Scheme 1



This approach is being extended for the synthesis of optically active aklavinone, the aglycone of aclacinomycin A[10,11].

References and Notes

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8. Protection of 2 with ethylene glycol, PTSA cleaves the acetyl group to give 1 ketal. Although partial thioketalization of 2 proceeds smoothly to give 3 but often the product is not free from 1 thioketal which can be removed from 3 by silica gel chromatrography. The conditions for the exclusive formation of 3 are being optimised.

9. All the compounds gave satisfactory elemental analyses and spectroscopic data.

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