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MARSCHALK REACTION APPROACH FOR A SIMPLE SYNTHESIS OF (±)4-DEMETHOXYDAUNOMYCINONE

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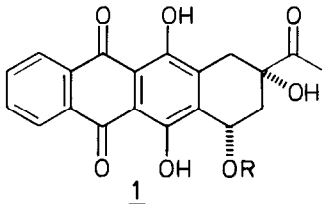
SUMMARY - Marschalk reaction of leucoquinizarin 2 with levulinic (oxo-ketal) aldehyde 3 gave 2-(4'-oxo-n-pentane)-quinizarin 4b, which on formylation followed by second Marschalk reaction led to (±)-4-demethoxy-7,9-dideoxydaunomycinone 6, which is further exploited for the synthesis of (±)-4-demethoxydaunomycinone 1b.

During the recent past, the anthracycline antibiotics such as adriamycin and daunomycin have emerged as effective drugs for cancer chemotherapy[1]. However, like other anti-cancer drugs, these compounds also display some side effects, the most serious being the cumulative dose dependent cardiotoxicity. To overcome this drawback, considerable efforts have been directed towards the synthesis of new derivatives such as (+)4-demethoxydaunomycin 1a, which is orally active and also shown to be 5 to 10 times more active than adriamycin and daunomycin[2].



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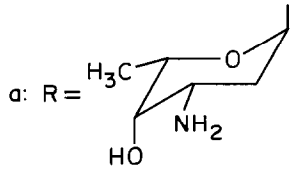


b: R = H

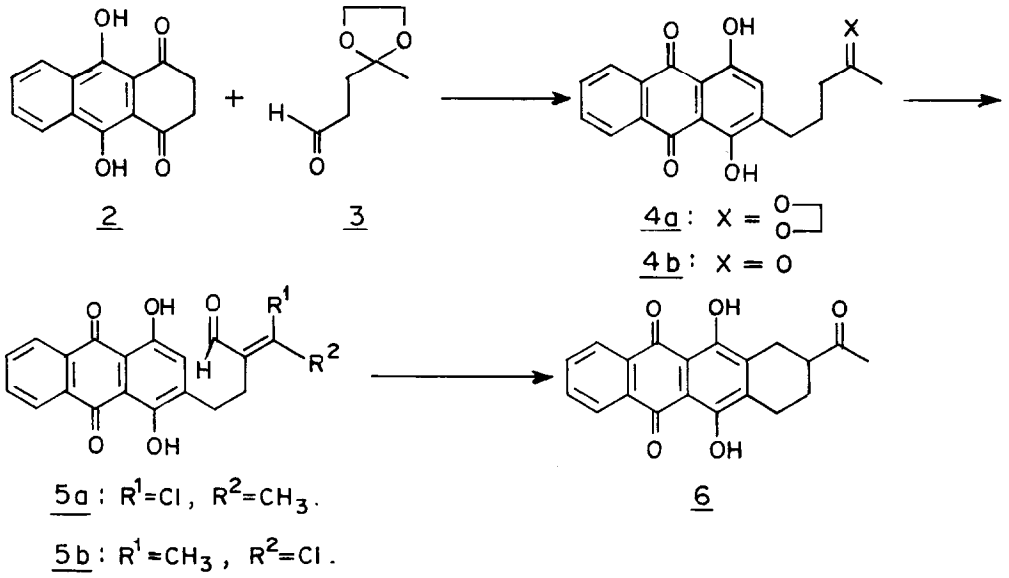
Our main efforts are directed towards the synthesis of the aglycone 1b, because 1a is not available by fermentation process and synthesis of L-daunosamine[3], and its coupling with the aglycone was already established[4].

Among the various approaches employed for the synthesis of 1b[5], the Marschalk reaction approach was relatively less explored[6]. Albeit, it remained as one of the promising approaches for the large scale synthesis of 1b. The recent report[7] for introducing the free formyl group α- to carbonyl function further prompted us to extend this methodology for the synthesis of 1b.

Our synthetic strategy therefore centred upon condensation of leucoquinizarin 2 (a commercial dyestuff intermediate) with the aldehyde 3, employing our modified Marschalk reaction conditions to get 4b, which on formylation, followed by second Marschalk reaction would give 6.

The aldehyde 3 was obtained in two steps from easily available methyl levulinate. Ketalization of methyl levulinate [$(CH_2OH)_2$, PTS acid, C_6H_6, 8 h azotropic reflux] afforded methyl (oxo-ketal) levulinate (80%), which on reduction (DIBAL, $C_6H_5CH_3$,-78°, 2 h] gave the aldehyde 3 (80%), b.p. (5 mm) 85-90°C.

SCHEME 1



The Marschalk reaction of 2 with 3 either using Lewis condition[9] (^{i}PrOH, piperidinium acetate, refluxed 1 h) or in only 1% aqueous sodium hydroxide [1 h, 80°C, N_2]followed by acidification [$CHCl_3$, MeOH, HCl] gave 4b in 61% and 50% yield respectively (m.p. 121°C). Formylation of 4b [DMF, $POCl_3$, 60°C, 1/2 h] gave a separable mixture of geometrical isomers cis 5a (38%), m.p. 150-1°C and trans 5b (40%), m.p.166°C. Intramolecular Marschalk reaction[10] of both 5a and 5b (1% aq. NaOH, $Na_2S_2O_4$, RT 2 h) followed by acidification directly gave 4-demethoxy-7,9-dideoxy daunomycinone 6 (50%) m.p. 186-7°C, lit.[11] 186-7°C identical with authentic sample in all respects (m.p., IR, ^{1}H-NMR, MS)[12].

Since the introduction of C-9 and C-7 hydroxy groups in 6 was already known[13,14] this constitutes a simple and practical approach for the synthesis of (±)4-demethoxydaunomycinone 1b.

Acknowledgements - The authors are thankful to Dr.A.V.Rama Rao for the supply of the authentic sample of 6.

References and Notes

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8. Alternatively the aldehyde 3 could be obtained from methyl-(oxo-ketal) levulinate by reduction [LAH-Et_2O, R.T.,3 h](80%), followed by oxidation [PCC, CH_2Cl_2, NaOAc] (70%).
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12. The cyclization and replacement of chloro group with hydroxy and subsequent rearrangement to ketone took place simultaneously in both 5a and 5b, although the reaction rate of 5a was faster.
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15. All new compounds gave satisfactory elemental and spectral analysis.
    a) Levulinic (oxo-ketal) aldehyde 3: IR ν^{max}(Neat) 2710 and 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ1.2 (3H, s, δ-CH_3); 2.1(2H, m β-CH_2); 2.4 (2H, m,α-CH_2); 3.9 (4H, s,$(OCH_2)_2$ and 9.6 (1H, t, -CHO). MS: m/e = 144 (M^+).
    b) 2-(4'oxoketal-n-pentane) quinizarin 4a: IR ν^{max}(Nujol): 1620 and 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$):δ1.25 (3H, s, 5'-H); 1.7 (4H), m, 2'and 3'-H); 2.7 (2H, m, 1'-H); 3.8 (4H, s, $(OCH_2)_2$); 7.1 (1H, s, 3-H); 7.8 (2H, m, 6- and 7-H); 8.3 (2H, m, 5- and 8-H); 12.8 (1H, s, -OH) and 13.25 (1H, s, -OH). MS: m/e 368 (M^+).
    c) 2-(4'-oxo-n-pentane)quinizarin 4b: IR ν^{max}(Nujol): 1705, 1630and 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.3 (2H, m, 2'-H); 2.15 (3H, s, 5'-H); 2.5 (2H, m, 3'-H), 2.6 (2H, m, 1'-H); 7.1 (1H, s, 3-H); 7.8 (2H,m, 6- and 7-H; 8.3 (2H, m, 5- and 8-H). 12.9 (1H, s, -OH) and 13.3 (1H, s, -OH). MS m/e = 324 (M^+).

d) 2-(Cis-4'-chloro-3'-formyl-3'-pentene)quinizarin 5a: IR ν^{max}(Nujol): 2700, 1740, 1720 1665 and 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.4 (3H, s, 5'-H); 2.7 (4H, bs, 1'-and 2'-H); 7.1 (1H, s, 3-H); 7.9 (2H, m, 6- and 7-H); 8.35 (2H, m, 5- and 8-H); 10.0 (1H, s, -CHO); 12.9 (1H, s,-OH) and 13.35 (1H, s, -OH). MS m/e = 370 ($M^{\ddagger}$); 372 ($M^{\ddagger}$ +2).

e) 2-(Trans-4'-chloro-3'-formyl-3'-pentene)quinizarin 5b: IR ν^{max}(Nujol): 2700,1650, 1640, 1605 and 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$):δ2.25 (3H, s, 5'-H); 2.85 (4H, bs, 1'-and 2'-H). 7.1 (1H, s, 3-H); 7.9 (2H, m, 6- and 7-H); 8.4 (2H, m, 5- and 8-H). 10.0 (1H, s, CHO); 12.9 (1H, s, -OH) and 13.35 (1H, s, -OH). MS: m/e = 370($M^{\ddagger}$); 372 ($M^{\ddagger}$ +2).

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