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A SHORT AND EFFICIENT SYNTHESIS OF 11-DEOXYANTHRACYCLINONES: STRONG BASE-INDUCED CYCLOADDITION OF THE SUITABLY SUBSTITUTED TETRAHYDROHOMOPHTHALIC ANHYDRIDE

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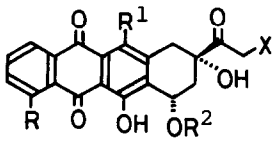
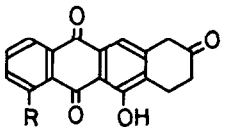
Summary: The preparation and use of the suitably substituted tetrahydrohomophthalic anhydride (17) as a common intermediate for a short regiospecific synthesis of 11-deoxyanthracyclinones, 11-deoxydaunomycinone (11), 11-deoxycarminomycinone (12), and 4-demethoxy-11-deoxydaunomycinone (13) is described.

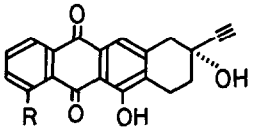
Because of the clinical effectiveness, the total synthesis of natural and unnatural anthracyclines, daunomycin (1), adriamycin (2), carminomycin (3), and 4-demethoxydaunomycin (4) has been the subject of intense study since the middle of 1970.[1] The 11-deoxy analogues (5-7) have been shown[2] to have a significant anticancer activity and less cardiotoxicity than the ordinary anthracyclines (1-4). As a part of our study[3] on the strong base-induced cycloaddition of homophthalic anhydrides and related compounds, we reported a brief and regiospecific synthesis of the late-stage intermediates (8-10) to 11-deoxyanthracyclinones (11-13).[4] There remains, however, the need for some improvements since the reported[5] side-chain elaboration of 9-keto group of 8 by using ethynylmagnesium bromide is inadequate in yield. All other existing methodologies for the homologation of 8 using acyl anion equivalents such as 1-lithio-1-methoxyethene, 2-lithio-2-methyl-1,3-dithiane, and trimethylsilylethynyl lithium did not give any satisfactory results probably due to the ready base-catalyzed enolization of 8.[6] Therefore, our attention was focused on the synthesis of the previously functionalized tetracyclic intermediates (14-16) by using our cycloaddition method for the suitably substituted tetrahydrohomophthalic anhydride (17). We report here a facile preparation of the starting anhydride (17), strong base-induced cycloaddition of 17 leading to 14-16, and conversion of 14-16 into 11-deoxyanthracyclinones, 11-deoxydaunomycinone (11), 11-deoxycarminomycinone (12), and 4-demethoxy-11-deoxydaunomycinone (13).



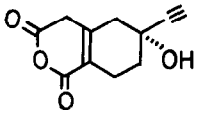
1; R=OMe,R^1=OH,R^2=Daunosaminyl,X=H
2; R=OMe,R^1=X=OH,R^2=Daunosaminyl
3; R=R^1=OH,R^2=Daunosaminyl,X=H
4; R=X=H,R^1=OH,R^2=Daunosaminyl
5; R=OMe,R^1=X=H,R^2=Daunosaminyl
6; R=OH,R^1=X=H,R^2=Daunosaminyl
7; R=R^1=X=H,R^2=Daunosaminyl
11; R=OMe,R^1=R^2=X=H
12; R=OH,R^1=R^2=X=H
13; R=R^1=R^2=X=H



8; R=OMe
9; R=OH
10; R=H



14; R=OMe
15; R=OH
16; R=H



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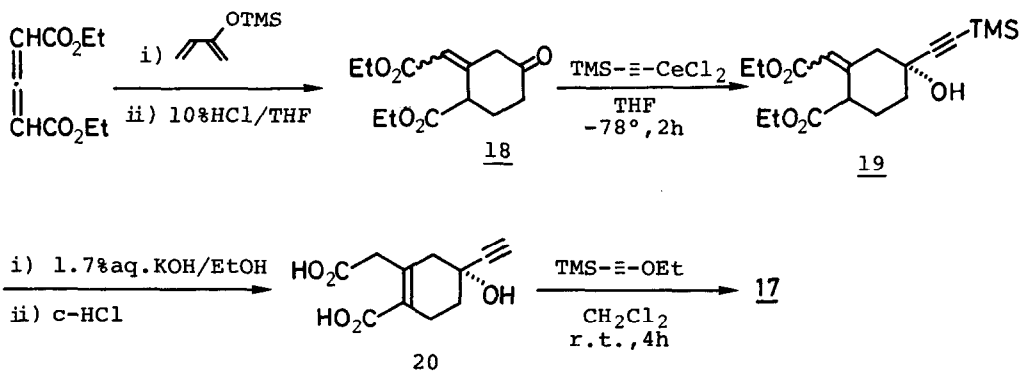
SYNTHESIS OF 6-ETHYNYL-6-HYDROXY-5,6,7,8-TETRAHYDROHOMOPHTHALIC ANHYDRIDE (17)

The requisite anhydride (17) was prepared from the known ketone (18)[4] in three steps with a 75% overall yield according to Scheme I. Trimethylsilylethynylation of 18 with 2-trimethylsilylethynylcerium(III) reagent, which was prepared from 2-trimethylsilylethynyl lithium and cerium(III) chloride in THF,[7,9] at -78° for 2 h gave an 82% yield of the trimethylsilylethynyl alcohol (19) [syrup, δ ($CDCl_3$) 0.17 (s, 9H), 1.31 (t, 6H, J=7 Hz), 1.95-2.2 (m, 4H), 3.1-3.4 (m, 3H), 4.17 (q, 4H, J=7 Hz), 5.81 (br s, 1H); ν_{max} ($CHCl_3$) 3000, 2950, 1725 cm^{-1}], although treatment of 18 with trimethylsilylethynyl lithium instead of the cerium(III) reagent at -78° for 3 h gave only an 11% yield of 19 together with a 73% yield of recovered ketone (18).[10] Treatment of 19 with 1.7% aqueous KOH in refluxing ethanol for 8 h followed by acidification with c-HCl caused saponification, desilylation, and exo-endo olefin isomerization at the same time to give a quantitative yield of the diacid (20) [syrup, δ (acetone-d_6) 1.8-2.1 (m, 2H), 2.39 (s, 1H), 2.45-2.7 (m, 4H), 2.84 (s, 1H), 3.51 (s, 2H); ν_{max} (neat) 3400-2850, 1720-1640 cm^{-1}], which was cyclized with a powerful dehydrating reagent, trimethylsilylethoxyacetylene[11] in CH_2Cl_2 at room temperature for 4 h to give the desired anhydride (17) in 92% yield [syrup, δ ($CDCl_3$) 1.8-2.1 (m, 2H), 2.39 (s, 1H), 2.45-2.6 (m, 4H), 3.29 (br s, 2H); ν_{max} ($CHCl_3$) 3300, 3025, 2950, 1800 sh, 1740 cm^{-1}].

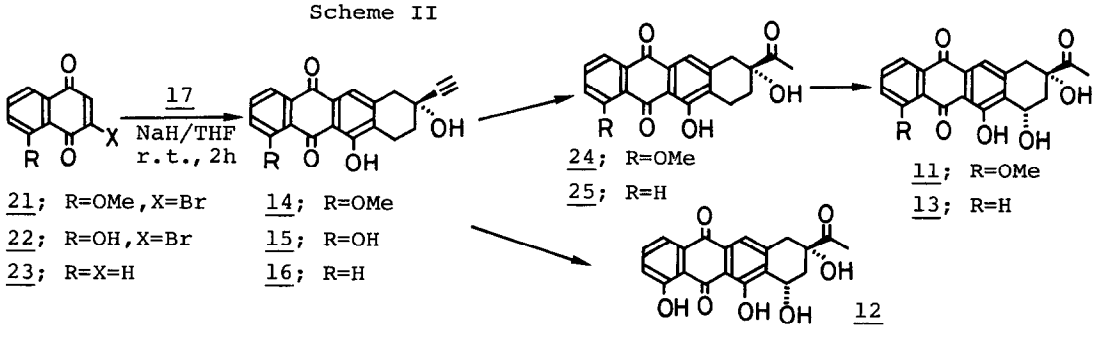
Scheme I



SYNTHESIS OF 11-DEOXYANTHRACYCLINONES (11-13) BY USING A STRONG BASE-INDUCED CYCLOADDITION OF 17 TO 1,4-NAPHTHOQUINONES (21-23)

The synthesis of 11-13 was established by starting from the anhydride (17) in Scheme II. Treatment of sodio anion of 17 with 3-bromojuglone methyl ether (21) at room temperature for 2 h gave a 42% yield of 14[12] as the sole product [mp, 250-252° (CH_2Cl_2-MeOH); δ 2.17 (t, 2H, J=6.5 Hz), 2.31 (s, 1H), 2.47 (s, 1H), 3.03 (t, 2H, J=6.5 Hz), 3.10 (d, 1H, J=16.5 Hz), 3.32 (d, 1H, J=16.5 Hz), 4.07 (s, 3H), 7.35 (dd, 1H, J=7.5 and 1.5 Hz), 7.50 (s, 1H), 7.72 (t, 1H, J=7.5 Hz), 7.96 (dd, 1H, J=7.5 and 1.5 Hz), 13.39 (s, 1H); ν_{max} (KCl) 3460, 3260, 1660, 1620, 1580 cm^{-1}]. Similarly, the sodio anion of 17 was treated with 3-bromojuglone (22)[13] and 1,4-naphthoquinone (23) under the same conditions to give the corresponding tetracyclic compounds (15 and 16) in 32 and 38% yields, respectively [15; mp 261.5-263° ($CHCl_3$); (lit.[14] 260°); 16; mp 243-245.5° ($CHCl_3$); δ ($CDCl_3$); 2.16 (t, 2H, J=6.5 Hz), 2.48 (s, 1H), 3.03 (t, 2H, J=6.5 Hz), 3.10 (d, 1H, J=17.5 Hz), 3.34 (d, 1H, J=17.5 Hz), 7.57 (s, 1H), 7.7-7.85 (m, 2H), 8.2-8.35 (m, 2H), 13.04 (s, 1H); ν_{max} (KCl) 3550-3350, 3250, 1665, 1620, 1590, 1575 sh cm^{-1}]. None of the regioisomers was formed in these cycloadditions. Since the conversion of 15 into 11-deoxycarminomycinone (12) has already been described by a convenient method,[14] we examined the conversion of the other two carbinols (14 and 16) into the corresponding α-hydroxyketones (24 and 25). Hydration of 14 and 16 by the standard method[5] using HgO-c·H_2SO_4 in refluxing THF for several hours gave 24 and 25 in quantitative yields [24; mp 218-219.5° ($CHCl_3$); (lit.[5,15] 209-211°, lit.[16] 210-211°); δ ($CDCl_3$) 1.85-2.1 (m, 2H), 2.37 (s, 3H), 2.75 (d, 1H, J=17.5 Hz), 2.9-3.1 (m, 2H), 3.31 (d, 1H, J=17.5 Hz), 3.72 (s, 1H), 4.07 (s, 3H), 7.34 (dd, 1H, J=7.5 and 1.5 Hz), 7.47 (s, 1H), 7.72 (t, 1H, J=7.5 Hz), 7.94 (dd, 1H, J=7.5 and 1.5 Hz), 13.38 (s, 1H); ν_{max} ($CHCl_3$) 2925, 1715, 1670 sh, 1620, 1585 cm^{-1}; 25; mp 219-220° (CH_2Cl_2) (lit.[17] 208-214°, lit.[18] 213-215°); δ ($CDCl_3$) 1.9-2.15 (m, 2H), 2.37 (s, 3H), 2.78 (d, 1H, J=17.5 Hz), 2.9-3.15 (m, 2H), 3.32 (d, 1H, J=17.5 Hz), 3.72 (s, 1H), 7.56 (s, 1H), 7.7-7.85 (m, 2H), 8.2-8.4 (m, 2H), 13.04 (s, 1H); ν_{max} ($CHCl_3$) 3475, 1710, 1670, 1630, 1590 cm^{-1}]. As the conversions of 24 into 11-deoxydaunomycinone (11) and 25 into 4-demethoxy-11-deoxydaunomycinone (13) have been accomplished in high yields,[15-17,19] our approach constitutes a general and practical synthesis of 11-deoxyanthracyclinones (11-13).

Scheme II



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6) Very recently, an efficient elaboration method of the 9-keto group of 11-hydroxytetracyclic analogue has been reported by Terashima,[7] but the application of the method to the elaboration of 11-deoxy intermediate (8) met to failure probably due to an extraordinary high reactivity of the quinone carboryl group of 8 toward the organomagnesium and lithium compounds compared with the corresponding 11-hydroxy analogues. Similar result was observed by Boeckman in the Wittig reaction of the dihydronaphthacenetrione.[8]

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10) Due to the ready base-catalyzed enolization of 18, the yield of 19 never exceeded 20% even if a large excess of trimethylsilylethynyl lithium was used.

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12) The same compound (14) was reported[5] without any physical and spectral data.

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19) We have also performed the conversion of 24 into 11 in about 60% overall yield according to the reported three-step sequence.[15]

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