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A HIGHLY CONVERGENT STRATEGY FOR THE SYNTHESIS OF 4-DEMETHOXYDAUNOMYCINONE AND DAUNOMYCINONE: A NOVEL SYNTHESIS OF C4-ACETOXYLATED HOMOPHTHALIC ANHYDRIDES

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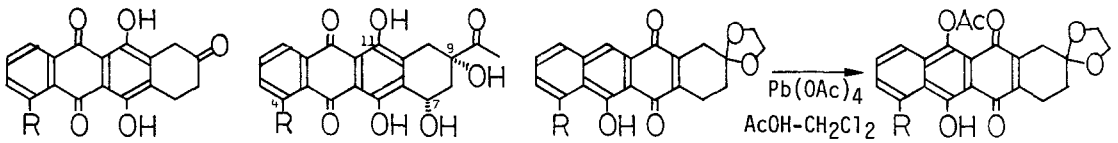
Summary: The C4-acetoxyl derivatives of homophthalic anhydrides were prepared by a convenient α-acetoxylation of homophthalic acid followed by a dehydrative cyclization. The anhydrides have been converted into 4-demethoxydaunomycinone and daunomycinone in excellent overall yields.

Recently, we reported a brief and regiospecific synthesis of the late-stage intermediates (1 and 2) to 4-demethoxydaunomycinone (3) and daunomycinone (4) using a strong base induced cycloaddition of homophthalic anhydrides to 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal.[1] However, the yields of the oxidation step of the cycloadducts (5 and 6) into the para-acetoxylated products (7 and 8) with $Pb(OAc)_4$/AcOH-CH_2Cl_2 are quite variable (25-79%) according to the reaction conditions, especially purity of the reagent itself, reaction temperature, and the scale of the reactions.[2] Here we report that the yields and generality for the key intermediates (1 and 2) can be extremely improved by using the cycloaddition of the previously C4-acetoxylated homophthalic anhydrides (9 and 10) and the intermediates can be efficiently converted into the anthracyclinones (3 and 4).



1; R=H
2; R=OCH_3

3; R=H
4; R=OCH_3

5; R=H
6; R=OCH_3

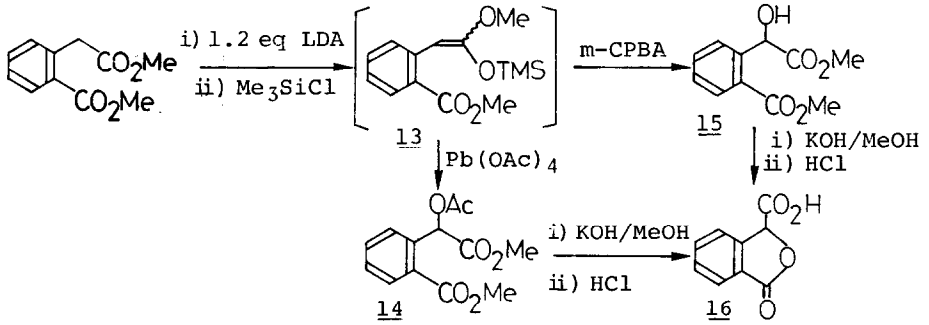
7; R=H
8; R=OCH_3

The 2'-acetoxyhomophthalic acids (11 and 12) seem to be the favorable starting materials for the C4-acetoxylated homophthalic anhydrides (9 and 10). Initially, dimethyl homophthalate was converted into 2'-acetoxyhomophthalate (14) via the ketene silyl acetal intermediate (13) by using $Pb(OAc)_4$[3] as an oxidizing agent. Similarly, dimethyl homophthalate was converted into 2'-hydroxyhomophthalic acid (15) via 13 by oxidation with m-CPBA.[4] Attempts to obtain 2'-acetoxyhomophthalic acid (11) or 2'-hydroxyhomophthalic acid from 14 or 15 by alkaline hydrolysis followed by careful acidification gave an unfavorably cyclized product, phthalide-3-carboxylic acid (16) [mp 151-153° (AcOEt), lit.[5] 149-150°], selectively in each case (Scheme 1). After several unsuccessful attempts, 2'-acetoxyhomophthalic acids (11 and 12) were obtained from homophthalic acids by the most straightforward method: Homophthalic acid was converted into the tri-anion with 3.2 equiv of LDA in THF at -78° for 0.5 h, which was reacted with Me_3SiCl at -78° for 1.5 h and at r.t. for 0.5 h to give the ketene silyl acetal intermediate (17). Oxidation of 17 with 1.1 equiv of $Pb(OAc)_4$ in dry benzene at r.t. for 2 h yielded a quantitative yield of 2'-acetoxylated homophthalic acid (11). 2'-Acetoxy-6-methoxyhomophthalic acid (12) was similarly prepared from 6-methoxyhomophthalic acid in a quantitative yield.

With the acids (11 and 12) in hand, we next examined our excellent anhydride formation[6] from the acids followed by the strong base induced cycloaddition[1] with the chloroquinone acetal: The acids (11 and 12) were treated with 1.3 equiv of trimethylsilylethoxyacetylene in CH_2Cl_2 at r.t. for 4 h to give a quantitative yield of 4-acetoxyhomophthalic anhydrides (9 and 10), respectively. Treatment of sodium salt generated from 9 or 10 and 1.1 equiv of NaH in THF at r.t. for 15 min with 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal at r.t. for 18-20 h gave the regiospecific naphthacenedione (18 or 19) in 75 or 62% yield, respectively [18; mp 225-228° (CH_2Cl_2-MeOH), 19; mp 248-253° (CH_2Cl_2-EtOH), both compounds were identical with the authentic samples prepared earlier by us[1b]], which is known to give 1 or 2, respectively in 95% yield by the treatment with CF_3CO_2H-H_2O at 50° for 3 h.[1b] Trimethylsilylethynylation of 1 with 20 equiv of trimethylsilylethynylcerium(III) reagent,[7] which was prepared from trimethylsilylethynyllithium and cerium(III) chloride in THF, at -78° for 3 h gave a 77% yield of the 9-trimethylsilylethynyl alcohol (20) [mp 193-195° ($CHCl_3$-n·hexane), lit.[8] —], which was hydrolyzed with HgO-d·H_2SO_4 in THF at 70° for 1.5 h to give (±)-4-demethoxy-7-deoxydaunomycinone (22) [mp 211-213.5° (CH_2Cl_2-n·hexane), lit.[8] 212.5-214.5°, lit.[9a] 160-162°. lit.[9b] 210-212°, lit.[9c] 216-218°, lit.[9d] 210-211°, lit.[9e] 202-203°, lit.[9f] 214-216°, lit.[9g] 213-215°] in 87% yield. Similarly, the triketone (2) was treated with trimethylsilylethynylcerium(III) chloride to give a 69% yield of the 9-trimethylsilylethynyl alcohol (21) [mp 262-264.5° ($CHCl_3$)], which was hydrolyzed with HgO-d·H_2SO_4 to give (±)-7-deoxy-

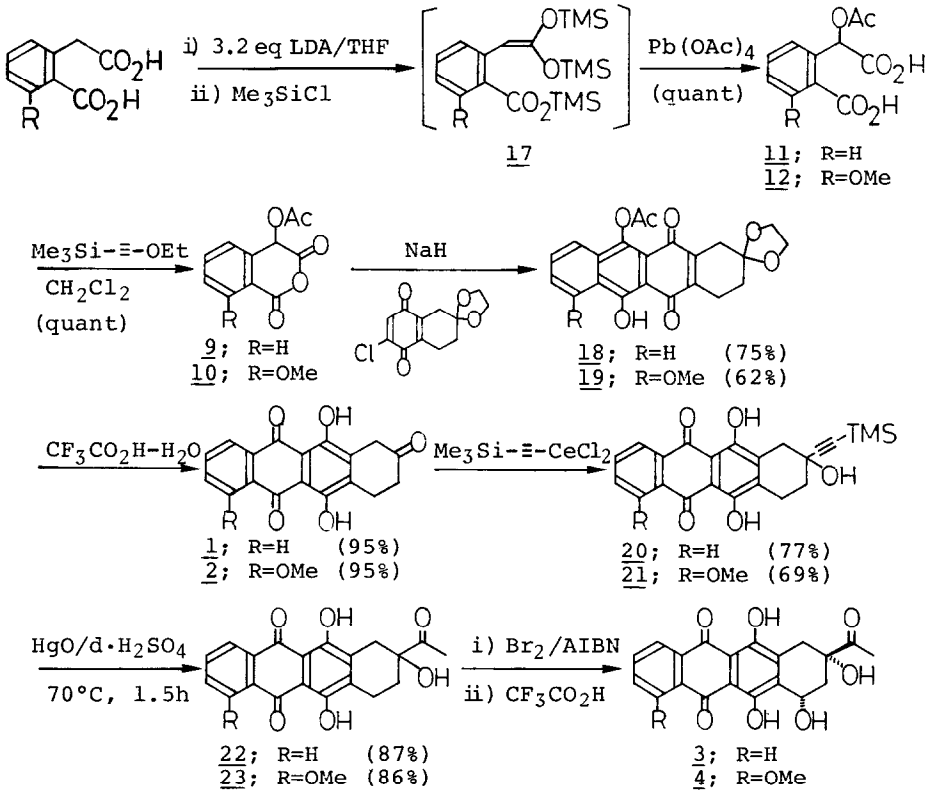
daunomycinone (23) [mp 229-233.5° (AcOEt-THF), lit.[10a] 229-231°, lit.[10b] 230-232°, lit.[10c] 228-230°, lit.[10d] 228-229°] in 86% yield. As the conversion of 22 or 23 into 3 or 4 by convenient methods has already been described,[8,9c,10b,c,11] our approach constitutes a highly convergent synthesis of 3 and 4 (Scheme 2).

Satisfactory analytical and spectral results were obtained[12] for all new compounds (9-12, 14, 15, and 21).



13 15 14 16

Scheme 1



17

11; R=H
12; R=OMe

9; R=H
10; R=OMe

18; R=H (75%)
19; R=OMe (62%)

1; R=H (95%)
2; R=OMe (95%)

20; R=H (77%)
21; R=OMe (69%)

22; R=H (87%)
23; R=OMe (86%)

3; R=H
4; R=OMe

Scheme 2

References and Notes

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2 Scale-up of the reaction extremely decreases the yields of the para-acetoxylated products (7 and 8).

3 Introduction of an α-OAc group of esters with $Pb(OAc)_4$ via ketene silyl acetals, see: G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve, Jr., and C. W. Kim, J. Org. Chem., 48, 4940 (1983) and references cited therein.

4 Introduction of an α-OH group of esters with m-CPBA via ketene silyl acetals, see: G. M. Rubottom and R. Marrero, Synth. Commun., 11, 505 (1981); R. Z. Andriamialisoa, N. Langlois, and Y. Langlois, J. Org. Chem., 50, 961 (1985).

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12 Spectral data for all new compounds (9 - 12, 14, 15, and 21) are given.
9: νmax($CHCl_3$) 1805, 1765, 1600 cm^{-1}; δ ($CDCl_3$) 2.31 (s, 3H, $OCOCH_3$), 6.53 (s, 1H, CH), 7.3-7.9 (m, 3H, ArH), 8.05-8.3 (m, 1H, ArH)
10: νmax($CHCl_3$) 1815, 1765, 1600 cm^{-1}; δ ($CDCl_3$) 2.32 (s, 3H, $OCOCH_3$), 4.00 (s, 3H, OCH_3), 6.51 (s, 1H, CH), 6.9-7.2 (m, 2H, ArH), 7.70 (t, 1H, ArH)
11: νmax(KCl) 3070, 3020, 2920, 2850, 2630, 1755, 1720, 1675, 1600, 1580 cm^{-1}; δ (acetone-d_6) 2.12 (s, 3H, $OCOCH_3$), 6.8 (br s, 2H, CO_2H×2), 7.18 (s, 1H, CH), 7.2-7.8 (m, 3H, ArH), 7.9-8.15 (m, 1H, ArH)
12: νmax($CHCl_3$) 3300-2800, 1760-1710 cm^{-1}; δ (acetone-d_6) 2.09 (s, 3H, $OCOCH_3$), 3.87 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 6.30 (br s, 2H, CO_2H×2), 6.95-7.55 (m, 3H, ArH)
14: νmax($CHCl_3$) 1740, 1720 cm^{-1}; δ ($CDCl_3$) 2.17 (s, 3H, $OCOCH_3$), 3.72 (s, 3H, CO_2CH_3), 3.91 (s, 3H, CO_2CH_3), 7.3-7.65 (m, 3H, ArH), 7.85-8.1 (m, 1H, ArH)
15: νmax($CHCl_3$) 3030, 2960, 2900, 2400, 1740, 1720, 1600, 1580 cm^{-1}; δ ($CDCl_3$) 3.48 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 5.97 (s, 1H, CH), 7.0-7.85 (m, 4H, ArH)
21: νmax($CHCl_3$) 1605, 1580 cm^{-1}; δ ($CDCl_3$) 0.16 (s, 9H, Me_3Si), 2.13 (br t, 2H, C8-CH_2), 3.02 (br t, 2H, C7-CH_2), 3.15 (br s, 2H, C10-CH_2), 4.10 (s, 3H, OCH_3), 7.38 (dd, 1H, C3-H), 7.76 (t, 1H, C2-H), 8.04 (dd, 1H, C1-H), 13.48 (s, 1H, OH), 13.85 (s, 1H, OH)

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