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Synthesis of 4-demethoxyadriamycinone utilizing ruthenium-catalyzed oxidation of allyl acetates

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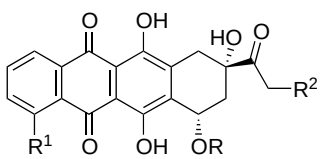
Abstract—A new method for the construction of the side chain of anti-cancer drugs adriamycins is demonstrated by the synthesis of 4-demethoxyadriamycinone. The key step is the ruthenium-catalyzed oxidation of allyl acetates to the corresponding α-hydroxyketones.

Anthracyclines are of extreme importance in chemical anti-cancer therapy; daunomycin (**1a**) and adriamycin (**1b**) provide a broad range of activity towards different types of tumors, and hence many methods for synthesis of natural and non-natural anthracyclines have been reported.[1] Among modified anthracyclines, 4-demethoxyanthracyclines[2] such as idarubicin (**1c**)[3] and annamycin (**1d**)[4] are of interest because of higher potency, particularly in the latter case of strongly decreased cardiotoxicity and activity against some normally anthracyclin-resistant cancer cell lines. Introduction of a functional group of α-ketol to the A ring would be the most important problem involved in the synthesis of aglycons of anthracyclines.

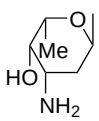
We wish to report synthesis of 4-demethoxyadriamycinone based on a process which includes ruthenium-catalyzed oxidation of trisubstituted alkenes to the corresponding α-ketols.[5] The reported method for introduction of the α-ketol group is limited to the hydration of tertiary propargyl alcohol with an excess of environmentally destructive mercury oxide under strongly acidic conditions.[6]

First, we examined synthesis of α-ketol quinone (**9**) as shown in Scheme 1. Diels–Alder reaction of benzoquinone with diene **2** in THF,[7] followed by hydrolysis with a 0.1 M HCl solution gave the adduct **3**. Acetylation of **3** upon treatment with acetic anhydride in the presence of triethylamine in THF gave the diacetate **4** (mp 118°C) (88%). Addition of vinyl magnesium bromide to a solution of **4** in THF gave no desired product due to enolization; however, in the presence of cerium chloride the reaction occurred smoothly under the strict reaction conditions.[8] Thus, use of dry $CeCl_3$ is crucial.[9] Quenching the reaction mixture with acetic anhydride at −78°C, the acetate **5** (mp 108°C) was obtained in 62% yield after recrystallization. Treatment of **5** with a catalytic amount of $PdCl_2(MeCN)_2$ in toluene gave the rearranged allyl acetate **6** (97%).[10] The oxidation of **6** with peracetic acid in acetonitrile/water (1:1) in the presence of a ruthenium chloride catalyst afforded a mixture of diastereomers (**7**+**8**) (1:7).[11] The desired *cis* isomer **8** (mp 138°C) was isolated in 60% yield.[12] Transformation of **8** to the benzoquinone **9** was quite difficult. The best result was obtained upon treatment with zinc dust in methanol, followed by oxidation of



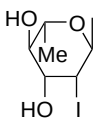
1a) R^1 = OMe, R^2 = H
1b) R^1 = OMe, R^2 =OH
1c) R^1 = H, R^2 = H

R =



1d) R^1 = H, R^2 = OH

R =



Keywords: 4-demethoxyadriamycinone; anthracyclinone; α-ketol; ruthenium-catalyzed oxidation.

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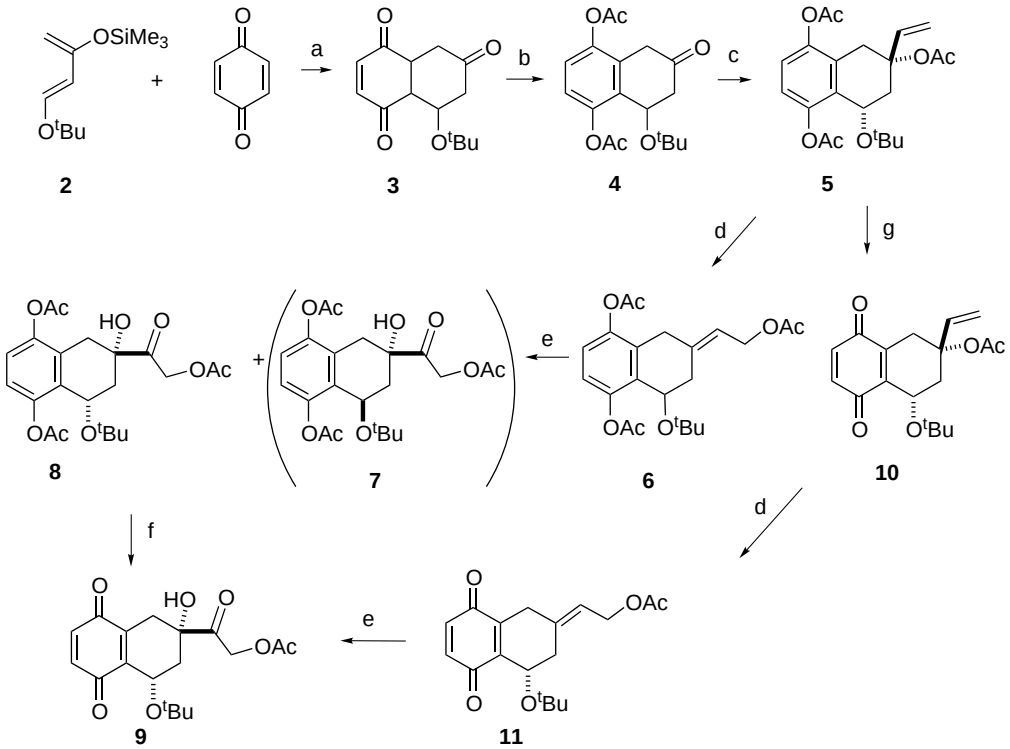
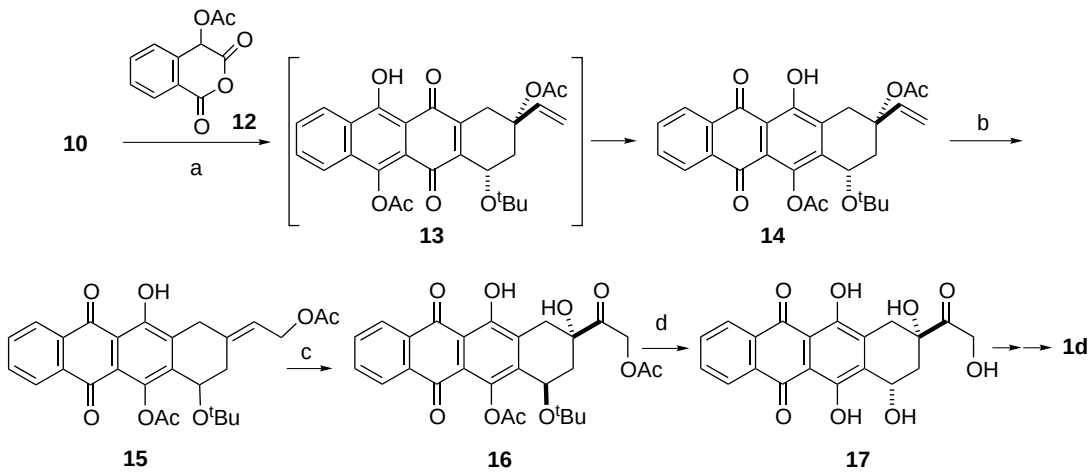


Scheme 1. Reagents: (a) i. THF, rt, 4 h; ii. 0.1 M HCl, THF, rt, 15 min, 74%. (b) Ac_2O, NEt_3, THF, 45°C, 5 h, 88%. (c) i. CH_2=CHMgBr, $CeCl_3$, THF, 1 h, −78°C; ii. Ac_2O, −78°C to rt, 1 h, 62%. (d) $PdCl_2(MeCN)_2$ cat., toluene, rt, 97% for **6**, 98% for **11**. (e) CH_3CO_3H, $RuCl_3$ cat., MeCN/H_2O, 60% for **8**, 30% for **9**. (f) i. Zn, MeOH, rt, 24 h; ii. CAN, MeCN/H_2O, 0°C, 15 min, 47%. (g) i. $NaBH_4$, THF/H_2O, 0°C, 38 h. ii. CAN, MeCN/H_2O, 0°C, 74%, 1 h.

the intermediate hydroquinone with CAN (47%).[13] The low yield is due to the high lability of **9**. An alternative method for the synthesis of **9** is as follows. Removal of the acetyl groups of **5** upon treatment with $NaBH_4$ in water/THF followed by oxidation with CAN gave **10** (74%), which underwent allylic rearrangement to give **11** as a quite stable yellow solid (mp 115°C) in 98% yield. However, the ruthenium-catalyzed oxidation of **11** gave the unstable **9** in low yield.

We examined a route which includes a coupling reaction of the CD ring as shown in Scheme 2. A solution of the compound **12** was treated with sodium hydride, to which was added a solution of **10** at −40°C according to the procedure of Kita et al.[14] Stirring at room temperature for an additional 3 h was necessary to allow the extrusion of carbon dioxide of **12**. The desired yellow tetracycle **14** (mp 168–173°C), in which the acetyl group at O-5 of **13** was shifted to O-6, could be



Scheme 2. (a) NaH, THF, −40°C to rt, 3 h, 70%. (b) $PdCl_2(MeCN)_2$ cat., toluene, rt, 24 h, 99%. (c) $RuCl_3$ cat., CH_3CO_3H, MeCN/CH_2Cl_2/H_2O, rt, 24 h, 60%. (d) 1.2 M HCl, *i*-PrOH, reflux, 2 h, 50%.

obtained in 70% yield as a single product.[15] Such migration of the acyl group takes place readily because of higher thermodynamic stability of the naphthacenedione **14** in comparison with its tautomer **13**.[16] The palladium-catalyzed allylic rearrangement of **14** gave the allyl acetate **15** (mp 187–189°C) in 99% yield.[17] Oxidation of **15** with CH_3CO_3H in the presence of $RuCl_3$ catalyst in a mixture of water, acetonitrile and dichloromethane (1:1:1) afforded **16** (mp 209–213°C) in 60% yield after crystallization.[18] The relative configuration between the *t*-BuO group at C-7 and the OH group at C-9 of **16** was determined to be *trans* using NOESY experiments. The stereochemistry is also deduced by measuring the width of the 7-H proton signal at half height; a very broad signal (18.3 Hz) indicates *trans* configuration.[19] Strong temperature dependence of the shift of this peak also indicates an intramolecular hydrogen bonding with the OH group at C-9, which is only possible for the *trans* isomer. The presence of an acetoxy group at C-5 in the compound **6** seems to affect the stereochemistry of the oxidation products **8**, making them *cis* because of the attractive interaction of the acetoxy group with the ruthenium, while the oxidation of **15** affords *trans*-**16**. Deprotection and epimerization at C-7 was readily achieved in one step by heating **16** with diluted hydrochloric acid in isopropanol/water to yield 4-demethoxyadriamycinone (**17**), which showed the same spectroscopic data to those reported.[20,21] Conventional treatment of **17**, including oxyiodination with L-rhamnal diacetate in the presence of *N*-iodosuccinimide, gave **1d**, where resolution of the racemic aglycon **17** took place to furnish the optically pure (7*S*,9*S*)-4-demethoxy-7-*O*-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)adriamycinone (**1d**) and its 7*R*,9*R* isomer.[3]

Our present approach using ruthenium-catalyzed oxidation of alkenes to the corresponding α-ketols can be also applied to the synthesis of other anthracyclinones.

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9. Cerium chloride heptahydrate was dried in a Schlenk flask under vacuum (0.1 Torr) for 24 h at 70°C, for 24 h at 80°C, for 48 h at 90°C, for 12 h at 100°C, for 12 h at 120°C and finally for 100 h at 140–145°C.
10. A NOESY experiment confirmed the configuration at the double bond of **6**. The ratio of the isomers was 91:7.
11. A NOESY experiment with the minor oxidation product **7** proved indirectly the configuration of the major product **8**.
12. Selected data for **8**. Mp 138°C; ^{1}H NMR ($CDCl_3$) δ 7.03 (d, $J=10$ Hz, 1H), 7.01 (d, $J=10$ Hz, 1H), 5.23 (d, $J=18$ Hz, 1H), 5.06 (d, $J=18$ Hz, 1H), 4.91 (dd, $J=4$ and 3 Hz, 1H), 3.48 (s(br), 1H), 3.31 (d, $J=15$ Hz, 1H), 2.67 (d, $J=15$ Hz, 1H), 2.58 (dd, $J=15$ and 3 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.85 (ddd, $J=15$, 4, and 1 Hz, 1H), 1.17 (s, 9H).
13. Selected data for **9**. Mp 126–131°C; ^{1}H NMR ($CDCl_3$) δ 6.76 (d, $J=13$ Hz, 1H), 6.72 (d, $J=13$ Hz, 1H), 5.17 (d, $J=17$ Hz, 1H), 4.98 (d, $J=17$ Hz, 1H), 4.97, (t, $J=5$ Hz, 1H), 3.64 (s(br), 1H), 3.08 (d, $J=19$ Hz, 1H), 2.57 (d, $J=19$ Hz, 1H), 2.32 (dd, $J=14$ and 5 Hz, 1H), 2.17 (s, 3H), 2.08 (ddd, $J=14$, 5, and 1 Hz, 1H), 1.24 (s, 9H).
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15. Selected data for **14**. Mp 168–173°C (decomp.); ^{1}H NMR ($CDCl_3$) δ 13.53 (s, 1H), 8.23 (m, 2H), 7.76 (m, 2H), 6.16 (dd, $J=17$ and 11 Hz, 1H), 5.17 (d, $J=17$ Hz, 1H), 5.14 (d, $J=11$ Hz, 1H), 4.94 (s(br), 1H), 3.48 (d, $J=18$ Hz, 1H), 3.40 (d, $J=18$ Hz, 1H), 2.97 (d, $J=16$ Hz, 1H), 2.54, (s, 3H), 2.04 (dd, $J=16$ and 4 Hz, 1H), 2.00 (s, 3H), 1.31 (s, 9H).
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17. Selected data for **15**. Mp 187–189°C (decomp.); ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 2H), 7.76 (m, 2H), 5.77 (t, $J=7$ Hz, 1H), 5.01 (s(br), 1H), 4.68 (d, $J=20$ Hz, 1H), 4.64 (d, $J=20$ Hz, 1H), 3.81 (d, $J=20$ Hz, 1H), 3.68 (d, $J=20$ Hz, 1H), 3.04 (dd, $J=16$ and 2 Hz, 1H), 2.55 (s, 3H), 2.23 (d, $J=16$ Hz, 1H), 2.06 (s, 3H), 1.25 (s, 9H).
18. Preparation of **16**: To a mixture of 30 ml of acetonitrile, 30 ml of dichloromethane and 30 ml of water was added 450 mg (0.914 mmol) of **15** and ruthenium trichloride (10 mg, about 0.048 mmol) at room temperature, together with peracetic acid (30% solution in ethyl acetate, 2 equiv.). The mixture was stirred for 12 h. After 4 and then 8 h another 2 equiv. of peracetic acid was added. Mp 209–213 (decomp.); ^{1}H NMR ($CDCl_3$) δ 13.42 (s, 1H), 8.23 (m, 2H), 7.76 (m, 2H),

5.26 (d, $J=17$ Hz, 1H), 5.09 (d, $J=17$ Hz, 1H), 5.02 (m, 1H), 3.50 (s(br), 1H), 3.34 (d, $J=16$ Hz, 1H), 3.28 (d, $J=16$ Hz, 1H), 2.66 (dd, $J=15$ and 4 Hz, 1 H), 2.54 (s, 3H), 2.18 (s, 3H), 1.88 (dd, $J=15$ and 4 Hz, 1H), 1.22 (s, 9 H). Anal. calcd for $C_{28}H_{28}O_8$: C, 64.14; H, 5.38. Found: C, 64.12; H, 5.31.

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