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Enantioselective synthesis of (+)-8-hydroxy-8-methylidarubicinone ☆

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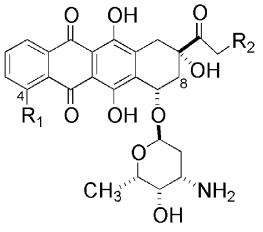
Abstract—An asymmetric Diels–Alder reaction methodology was employed to construct the tetracyclic structure of the anthracyclinone. A five-step sequence was needed to furnish the target (+)-8-hydroxy-8-methylidarubicinone.

1. Introduction

Anthracyclines are antitumour antibiotics that were originally obtained from the cultures of different *Streptomyces* species.[1] Daunorubicin **1** and doxorubicin **2**, the most famous anthracyclines, were isolated in the 1960s, and since that time, more than 300 new compounds were produced biosynthetically and more than 2000 analogues were synthesized.[2] These differed from the parent drugs either in the tetracyclic structure or in the sugar moiety, or in both. Of the most interesting analogues, which showed advances over the parent drugs, is idarubicin **3** (Fig. 1).[3] Since its discovery, several research groups showed interest in manipulating its structure to further enhance its activity and/or to diminish its toxicity. Arcamone et al. for example, prepared the 8- and 10-fluoro derivatives.[4]

We started a research to synthesize derivatives of idarubicinone that have a hydroxyl group at C-8 of the tetracyclic structure either alone or in the presence of an alkyl group at the same position. We envisaged that such addition will provide an additional hydrogen bonding capability to the drug and thus add to the stability of the drug–DNA complex, as suggested by the intercalation theory.[5] The effect of these additions on the cytotoxic activity compared to that of the parent compound against A2780 tumour cell line (ovarian cancer) was also scheduled.



1 R_1=OCH_3, R_2=H: Daunorubicin
2 R_1=OCH_3, R_2=OH: Doxorubicin
3 R_1=H, R_2=H: Idarubicin

Figure 1.

The synthetic methodology is based on a strategy developed in the group and has been in use for 20 years.[6] It is based on an asymmetric Diels–Alder reaction between an oxirane serving as the dienophile and a diene bearing a tetraacetate glucose auxiliary. In this article we wish to report the total synthesis of (+)-8-hydroxy-8-methylidarubicinone **4**.

2. Results and discussion

Synthesis of the title compound is outlined in Scheme 1. Reaction of the readily available oxirane[7] **5** and diene **6**[8] in acetonitrile afforded the cycloadduct **7** as a single diastereoisomer in 67% yield after crystallization.[9] The diastereoselectivity of this cycloaddition was attributed to the fact that the diene **6** reacted only by way of the *s-cis* conformer and the oxirane **5** underwent *endo*-addition preferentially at the least-hindered top face of the *s-cis* conformer.[8]

☆ The work presented in this article was carried out at UMIST.

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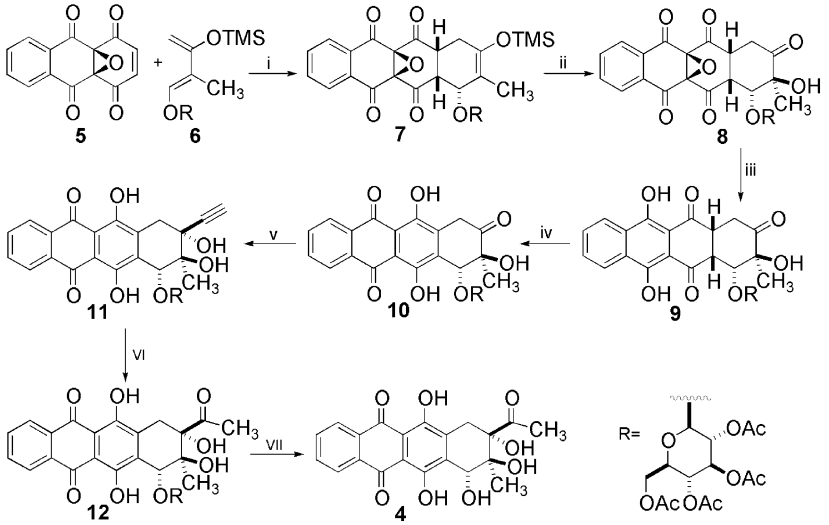


Scheme 1. (i) CH_3CN, rt, overnight; (ii) DMDO, acetone, rt, overnight; (iii) Zn, AcOH, CH_2Cl_2, −20 °C, 1 h; (iv) $Pb(OAc)_4$, AcOH, rt, 15 h; (v) HC≡CMgCl, THF, 0 °C, 1 h; (vi) HgO, H_2SO_4, acetone, reflux, 0.5 h; (vii) HCl, C_2H_5OH, reflux, 25 h.

The cycloadduct **7** was treated with an acetone solution of dimethyldioxirane[10] (DMDO) to give, after crystallization, the epoxyalcohol **8** in 95% yield. The epoxyalcohol **8** underwent reduction by the action of zinc in a 2:1 mixture of dichloromethane and acetic acid at −20 °C to provide the trihydroxytrione **9** in 57% yield after crystallization. Lead (IV) acetate oxidation of the trihydroxytrione **9** in a 1:1 mixture of acetic acid and dichloromethane afforded the anthracycline **10** in 78% yield after crystallization. An ice-cold tetrahydrofuran solution of compound **10** was treated with a large excess of ethynylmagnesium chloride[11] to give after work-up the ethynyltetraol **11**, which was produced in 44% yield after crystallization. It is believed that the ethynylating reagent approached the ketone moiety at C-9 from the least-hindered top face of the ketone away from the bulky sugar auxiliary to give the desired *R* configuration. This could be stressed by the fact that the ethynyltetraol **11** did not react with either 2,2-dimethoxypropane or phenylboronic acid in the presence of a catalytic quantity of *p*-toluenesulfonic acid to produce a cyclic acetal or a boronate ester, respectively, in both cases the starting reactant was recovered.

When a mixture of the ethynyltetraol **11**, mercury (II) oxide and 7% sulfuric acid was heated in acetone, the ketone **12** was produced along with a small amount of an unidentified compound. As it was not possible to purify it by crystallization, crude ketone **12** was refluxed in a 1:1 mixture of ethanol and 1 M hydrochloric acid to afford, after work-up and crystallization, the target (+)-8-hydroxy-8-methylidarubicinone **4** in 57% yield.

3. Conclusion

A new, ring-A modified, idarubicinone was synthesized. The synthetic methodology allows the preparation of similar compounds having different alkyl or aryl groups at position-8 in addition to the hydroxyl group at the same position. A preliminary cytotoxic activity study for the intermediates of this synthesis against A2780 tumour cell line showed encouraging results.[12] The following ID_{50} values were obtained: 10.0, 7.19, 1.00, 0.78, 10.18 and 2.65 μM for compounds 7, 8, 9, 10, 11 and 4, respectively.

4. Experimental

4.1. Preparation of the cycloadduct 7

A mixture of the oxirane **5** (2.515 g, 9.89 mmol) and the diene **6** (4.97 g, 9.89 mmol) in acetonitrile (100 mL) was stirred in the dark overnight. The mixture was then evaporated, the residue triturated with diethyl ether and filtered. The precipitate thus obtained was crystallized from chloroform–diethyl ether–hexanes to give the pure cycloadduct **7** (5.01 g, 67%) as an off-white solid; mp 180–182 °C (with dec), $[\alpha]_D$ +170 (1% in CH_2Cl_2), IR (KBr): ν_{max} 1755, 1740, 1695 and 1590 cm^{-1}. UV (EtOH): λ_{max} (ε $M^{-1}\,cm^{-1}$) 203 (23,000), 235 (24,700), 262 (7400) and 309 (2800) nm.

^1H NMR (300 MHz, $CDCl_3$): δ 0.23 (9 H, s, $SiMe_3$), 1.67 (3H, t, *J* 2 Hz, 8-Me), 1.76, 1.85, 1.97 and 2.07 (each 3H, s, 4×$MeCO_2$), 2.01–2.10 (1H, m, 10Hβ), 3.03 (1H, dd, *J* 9 and 3 Hz, 6aH), 3.08–3.16 (1H, m, 10Hα), 3.52–3.57 (1H, m, 5′H), 3.98–4.10 (3H, m, 10aH and 6′H_2), 4.39 (1H, d, *J* 8 Hz, 1′H), 4.51–4.57 (2H, m, 2′ and 7H), 4.89 (1H, t, *J* 10 Hz, 4′H), 5.06 (1H, t, *J* 9.5 Hz, 3′H) and 7.78–7.90 and 8.13–8.20 (each 2H, m, 1, 2, 3 and 4H), FABMS 795 (MK^+, 38%), 431 (38), 387 (66), 192 (61) and 137 (100). Found: C, 56.9; H, 5.1; Si, 3.9. $C_{36}H_{40}O_{16}Si$ requires C, 57.14; H, 5.33; Si, 3.71%.

4.2. Preparation of the epoxyalcohol 8

The cycloadduct **7** (3.00 g, 3.96 mmol) was treated with an acetone solution of DMDO (~0.1 M, 78 mL,

7.8 mmol) and the mixture stirred overnight. Evaporation left a residue that was crystallized from dichloromethane–diethyl ether to afford the epoxyalcohol **8** (2.65 g, 95%) as a white solid; mp 218–220 °C (with dec), $[\alpha]_D$ −133 (0.4% in CH_2Cl_2), IR (KBr): ν_{max} 3480, 1760, 1740, 1720, 1695 and 1595 cm^{-1}. UV (EtOH): λ_{max} (ε $M^{-1}\,cm^{-1}$) 202 (10,700) and 235 (15,200) nm.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s, 8-Me), 1.90, 1.94, 2.01 and 2.09 (each 3H, s, 4×$MeCO_2$), 2.36 (1H, dd, J 14.5 and 6.5 Hz, 10Hβ), 2.64 (1H, br s, 8-OH), 3.31 (1H, dd, J 14.5 and 11.5 Hz, 10Hα), 3.71–3.77 (1H, m, 5′H), 3.82 (1H, dd, J 12 and 2 Hz, 6aH), 4.05–4.18 (1 H, m, 10aH), 4.21–4.22 (2H, m, 6′H_2), 4.74 (1H, d, J 2 Hz, 7H), 4.76–4.85 (2H, m, 1′ and 2′H), 4.98–5.10 (2H, m, 3′ and 4′H) and 7.87–7.90 and 8.17–8.25 (each 2H, m, 1, 2, 3 and 4H), FABMS 739 (MK$^+$, 21%), 192 (59), 154 (100) and 136 (78). Found: C, 56.9; H, 4.7. $C_{33}H_{32}O_{17}$ requires C, 56.6; H, 4.6%.

4.3. Preparation of the trihydroxytrione 9

Activated zinc (11.2 g, 171.3 mmol) was added to a stirred solution of epoxyalcohol **8** (2.00 g, 2.85 mmol) in dichloromethane (200 mL) and acetic acid (100 mL) at −20 °C. The mixture was stirred for 1 h at −20 °C then filtered through Celite. The filtrate was washed with water, saturated aq sodium hydrogen carbonate (×2) and water, dried ($MgSO_4$) and evaporated. Crystallization of the crude product from dichloromethane–diethyl ether afforded the trihydroxytrione **9** (1.11 g, 57%) as a bright yellow solid; mp 194–196 °C (with dec), $[\alpha]_D$ +57 (0.52% in CH_2Cl_2), IR (KBr): ν_{max} 3480, 1770, 1745, 1730, 1645, 1610 and 1585 cm^{-1}. UV (EtOH): λ_{max} (ε $M^{-1}\,cm^{-1}$) 238 (26,600), 254 (24,800), 279 (23,050), 399 (12,600) and 419 (12,100) nm.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, s, 8-Me), 1.74, 1.87, 1.94 and 2.12 (each 3H, s, 4×$MeCO_2$), 2.75 (1H, s, 8-OH), 2.95 (1H, dd, J 14 and 8 Hz, 10Hβ), 3.32 (1H, dd, J 14 and 6 Hz, 10Hα), 3.44–3.49 (1H, m, 5′H), 3.58–3.64 (1H, m, 10aH), 3.74 (1H, dd, J 9 and 2 Hz, 6aH), 4.09–4.15 (2H, m, 1′ and 6′H), 4.21 (1H, dd, J 12 and 5 Hz, 6′H), 4.65–4.71 (2H, m, 7 and 2′H), 4.77 (1H, t, J 9 Hz, 4′H), 4.93 (1H, dd, J 10 and 9 Hz, 3′H), 7.82–7.86 and 8.46–8.57 (each 2H, m, 1, 2, 3 and 4H), and 13.24 and 14.08 (each 1H, s, 5- and 12-OH), FABMS 709 (MNa$^+$, 4%), 687 (MH$^+$, 22%), 686 (M^+, 46), 331 (55) and 169 (100). Found: C, 57.7; H, 4.9. $C_{33}H_{34}O_{16}$ requires C, 57.7; H, 5.0%.

4.4. Preparation of the anthracycline 10

A mixture of the trihydroxytrione **9** (1.09 g, 1.59 mmol) in dichloromethane (27.5 mL) and acetic acid (27.5 mL) was treated with lead (IV) acetate (0.777 g, 1.75 mmol). The mixture was stirred for 15 h then diluted with dichloromethane, washed with water, saturated aq sodium hydrogen carbonate (×2) and water. Evaporation of the dried ($MgSO_4$) organic phase left a red residue, which was crystallized, from dichloromethane–diethyl ether to give the anthracycline **10** (0.85 g, 78%) as a bright orange-red solid; mp 205–207 °C (with dec), $[\alpha]_D$ +78 (0.5% in CH_2Cl_2), IR (KBr): ν_{max} 3380, 1755, 1740, 1720, 1630 and 1590 cm^{-1}. UV (EtOH): λ_{max} (ε $M^{-1}\,cm^{-1}$) 207 (22,400), 251 (34,200), 257 (32,300) 287 (9000) and 483 (8600) nm.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (3H, s, 8-Me), 1.72, 1.94, 2.00 and 2.16 (each 3H, s, 4×$MeCO_2$), 3.40 (1H, d, J 22 Hz, 10Hβ), 3.68–3.73 (1H, m, 5′H), 4.02 (1H, d, J 22 Hz, 10Hα), 4.23 (1H, dd, J 12 and 3 Hz, 6′H), 4.29 (1H, dd, J 12 and 5 Hz, 6′H), 4.60 (1H, d, J 8 Hz, 1′H), 4.88 (1H, dd, J 9 and 8 Hz, 2′H), 5.06–5.09 (2H, m, 3′ and 4′H), 5.47 (1H, s, 7H), 7.87–7.90 and 8.35–8.40 (each 2H, m, 1, 2, 3 and 4H) and 13.16 and 13.47 (each 1H, s, 6- and 11-OH), FABMS 723 (MK$^+$, 6%), 685 (MH$^+$, 7), 684 (M^+, 9), 331 (99), 295 (95) and 169 (100). Found: C, 58.1; H, 4.9. $C_{33}H_{32}O_{16}$ requires C, 57.9; H, 4.7%.

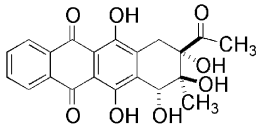
4.5. Preparation of the ethynyltetraol 11

Ethynylmagnesium chloride (0.5 M, 80 mL, 40 mmol) was added to a stirred solution of compound **10** (0.94 g, 1.373 mmol) in THF (94 mL) at 0 °C. The resultant blue mixture was stirred for 1 h then poured onto a cold saturated aq ammonium chloride solution and extracted with dichloromethane (×2). The combined organic extracts were washed with water (×2), dried ($MgSO_4$) and evaporated to give a residue, which was crystallized from dichloromethane–diethyl ether to give the ethynyltetraol **11** (0.424 g, 44%) as a reddish-brown solid; mp 273–276 °C (with dec), $[\alpha]_D$ +260 (0.5% in CH_2Cl_2), IR (KBr): ν_{max} 3540, 3480, 3250, 1750 and 1625 cm^{-1}. UV (EtOH): λ_{max} (ε $M^{-1}\,cm^{-1}$) 204 (11,600), 251 (18,900), 287 (4500) and 485 (5100) nm.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (3H, s, 8-Me), 1.85, 2.00, 2.07 and 2.16 (each 3H, s, 4×$MeCO_2$), 2.37 (1H, s, C═CH), 3.10 (1H, d, J 19 Hz, 10Hβ), 3.45 (1H, d, J 19 Hz, 10Hα), 3.44 and 3.71 (each 1H, s, 8- and 9-OH), 3.89–3.96 (1H, m, 5′H), 4.17 (1H, dd, J 12 and 6 Hz, 6′H), 4.41 (1H, dd, J 12 and 2 Hz, 6′H), 5.00–5.19 (4H, m, 1′, 2′, 4′ and 7H), 5.33 (1H, t, J 9.5 Hz, 3′H), 7.83–7.86 and 8.35–8.38 (each 2H, m, 1, 2, 3 and 4H) and 13.28 and 13.76 (each 1H, s, 6- and 11-OH), FABMS 749 (MK$^+$, 5%), 192 (25) and 39 (100). Found: C, 59.25; H, 4.82. $C_{35}H_{34}O_{16}$ requires C, 59.16; H, 4.82%.

4.6. Hydration of the ethynyltetraol 11 and subsequent hydrolysis to the target (+)-8-hydroxy-8-methylidarubicinone 4

Red mercury (II) oxide (0.578 g, 2.67 mmol) and 7% sulfuric acid (50 mL) were added to a stirred solution of ethynylcarbinol **11** (0.385 g, 0.542 mmol) in acetone (50 mL). The resultant mixture was refluxed for 0.5 h then allowed to cool to ambient temperature. The mixture was diluted with 1 M hydrochloric acid (40 mL) and extracted with dichloromethane (×2). The combined organic extracts were washed with 0.1 M hydrochloric acid, dried ($MgSO_4$) and evaporated leaving a residue



4 (+)-8-Hydroxy-8-methylidarubicinone

Figure 2.

comprising mainly ketone **12** (0.386 g); ^{1}H NMR (200 MHz, $CDCl_3$): inter alia δ 2.49 (3H, s, MeCO), 3.09 (1H, d, J 19.5 Hz, 10Hβ), 3.25 (1H, d, J 19 Hz, 10Hα), 7.83–7.88 and 8.33–8.37 (each 2H, m, 1, 2, 3 and 4H) and 13.27 and 13.84 (each 1H, s, 6- and 11-OH).

The above residue was dissolved in ethanol (55 mL) and 1 M hydrochloric acid (55 mL) and the mixture refluxed for 25 h. After allowing to cool, the mixture was diluted with water and extracted with chloroform once and with ethyl acetate once again, and the combined organic extracts were washed with water. Evaporation of the dried ($MgSO_4$) organic phase left a residue, which was crystallized from dichloromethane–hexanes to give the target compound **4** (0.122 g, 57%) as a red solid (Fig. 2); mp 218–222 °C (with dec), $[\alpha]_D$ +103 (0.09% in CH_2Cl_2), IR (KBr): ν_{max} 3420, 1700 and 1630 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 206 (32,000), 286 (13,750), 462 (13,400), 484 (15,600) and 518 (10,350) nm.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (3H, s, 8-Me), 2.52 (3H, s, MeCO), 3.12 (1H, d, J 18 Hz, 10Hβ), 3.24 (1H, d, J 18 Hz, 10Hα), 3.29 (1H, br s, 8-OH), 3.71 (1H, d, J 6 Hz, 7-OH), 4.68 (1H, s, 9-OH), 4.73 (1H, d, J 6 Hz, 7H), 7.84 and 8.33 (each 2H, dd, J 6 and 3 Hz, 1, 2, 3 and 4H) and 13.27 and 13.55 (each 1H, s, 6- and 11-OH) (addition of D_2O caused the signals at δ 3.29, 3.71, 13.27 and 13.55 to disappear and that at δ 4.73 to collapse to a singlet), FABMS 399 (MH$^+$, 55%), 381 (83), 337 (100) and 39 (77).

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