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Enantioselective Synthesis of (+)-4-Demethoxy-1,4-Dimethyldaunomycinone

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Abstract—(+)-4-Demethoxy-1,4-dimethyldaunomycinone **1** was synthesized using a convergent approach. Here, the key tetracyclic compound **10** was assembled by way of a Diels–Alder reaction using the sugar-based diene **8** and the quinizarin-related dienophile **7**.

Introduction

The anthracycline antibiotics such as daunomycin and adriamycin are clinically useful in the treatment of a wide range of human cancers.[1] However, their dose-dependent side effects such as cumulative cardiotoxicity, myelosupression and nephrotoxicity often present a serious problem. Consequently, various analogues have been prepared to decrease the side effects in these compounds and to improve their activity profiles by appropriate structural modifications. For example, 4-demethoxyanthracyclines are much more potent than the ordinary anthracyclines. The relationship between chemical structure and biological activity is of considerable importance for the establishment of the molecular requirements for action, and therefore for the development of new analogues. It is also known that the C-ring quinone moiety of anthracyclines play an important role in structure–activity relationships. The B- and/or D-ring modification of the chromophore is also known to influence the C-ring quinone moiety. In this respect, several D-ring hetero anthracyclines were prepared with the hope of producing analogues having higher anticancer activity and/or lower cardiotoxicity.[2] As part of ongoing studies on synthetic anthracyclines, we wish to report the total synthesis of (+)-4-demethoxy-1, 4-dimethyldaunomycinone **1**[3] (Fig. 1).

Results and Discussion

The synthesis of (+)-4-demethoxy-1,4-dimethyldaunomycinone **1** requires the oxirane **7** as the BCD-ring synthon. This dienophilic building block is available from 2,5-dimethylfuran **2** and maleic anhydride **3** by the route shown in Scheme 1. In diethyl ether at ambient temperature, 2,5-dimethylfuran **2** reacted with maleic anhydride **3** to give the crystalline cycloadduct **4** in 96% yield. Concentrated sulfuric acid converted the cycloadduct **4** into the crystalline anhydride **5** (56% yield).[4] The anhydride reacted with hydroquinone in a melt of aluminum chloride–sodium chloride to yield the quinizarin **6** in 36% yield after crystallization.[5] When treated with lead (IV) acetate in acetic acid followed by *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane, the quinizarin **6** was converted into the oxirane **7** (mp 240–242 °C decomp, 53% yield).

The oxirane **7** was transformed into (+)-4-demethoxy-1,4-dimethyldaunomycinone **1** by the route shown in Scheme 2. The diene **8** prepared from D-glucose in five steps according to the earlier report[6] was reacted with the oxirane **7** in acetone at room temperature to give mainly the cycloadduct **9**. Then, the adduct was immediately subjected to the action of dilute hydrochloric acid in tetrahydrofuran (THF), following recrystallization, the epoxy-pentaone **10** (mp 205–206 °C) was obtained in 44% yield. It was crucial to use the diene **8** and the oxirane **7** in a pure state for the success of this reaction.

Previously, zinc–acetic acid and sodium dithionite–methanol have been employed with more or less equal

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efficiency to effect reductions of the type **10** to **11**.[6] However, in the present work, incomplete reduction was always observed when compound **10** was treated with the latter reagent. This may have been due to poor solubility of the oxirane **10** in methanol. Although zinc–acetic acid reduction at room temperature proceeded in the desired manner, the product was contaminated with unwanted aromatized material which could not be separated by recrystallization. Attempts to isolate compound **11** in a pure state by chromatography were also unsuccessful due to instability. After considerable experimentation, it was found that replacing the solvent by a 1:5 mixture of acetic acid and dichloromethane and lowering the temperature to 0 °C provided a quantitative yield of compound **11** (mp 150–155 °C).

Initially, the reaction of trione **11** with ethynylmagnesium bromide to generate **12** also presented problems. However, after several experiments, it was found that addition of compound **11** in THF to an ice-cold solution of ethynylmagnesium bromide (≈22 mol equiv) in THF was satisfactory. Treatment of the crude product with lead(IV) acetate in acetic acid gave the anthracycline **13** in 76% yield as a bright-red solid (mp 269–274 °C). The anthracycline **13** underwent hydrolysis in ethanolic hydrochloric acid to give, after silica-gel purification, compound **14** in 66% yield (mp 202–204 °C). Hydration of the acetylene **14** with mercury(II) oxide in boiling acetone-sulfuric acid gave (+)-4-demethoxy-1,4-dimethyldaunomycinone **1** (mp 120–125 °C) in 57% yield after chromatography.

Conclusion

In conclusion, the novel oxirane **7** was prepared from 2,5-dimethylfuran in five steps and reacted with sugar-based diene **8** to give Diels–Alder adduct **9** which was further extended to the synthesis of (+)-4-demethoxy-1,4-dimethyldaunomycinone **1**.

Experimental

Reaction of 5,8-dimethyl-1,4-dihydroxyanthraquinone 6 with lead(IV) acetate followed by *m*-CPBA oxidation. The dimethylanthraquinone **6** (5.7 g, 21.2 mmol) lead (IV) acetate (11.0 g, 24.8 mmol) and acetic acid (15 mL) were ground together in a mortar. The mixture was kept at room temperature for 2 h with occasional grinding and then diluted with water (100 mL) and filtered. The resulting solid was thoroughly washed with water and dried over P_2O_5. To the crude product (6.7 g) in dry dichloromethane (150 mL) at 0 °C was added 85% *m*-CPBA (4.7 g, 23.3 mmol) over a period of 10 min. The mixture was stirred at room temperature for 4 h and then filtered through a buchner funnel. The filtrate was concentrated under reduced pressure and the resultant solid was dissolved in ethyl acetate (150 mL). The ethyl acetate solution was washed quickly with saturated solution of $NaHCO_3$ followed by brine. Drying over $MgSO_4$ and removal of the solvent gave a crude product

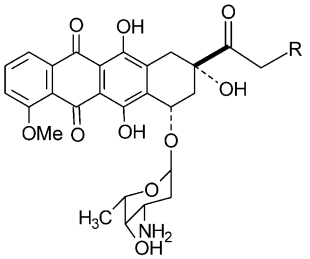
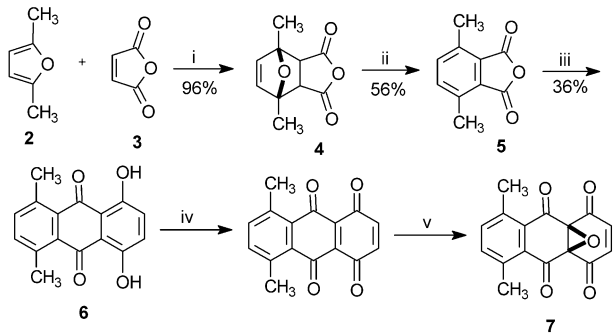
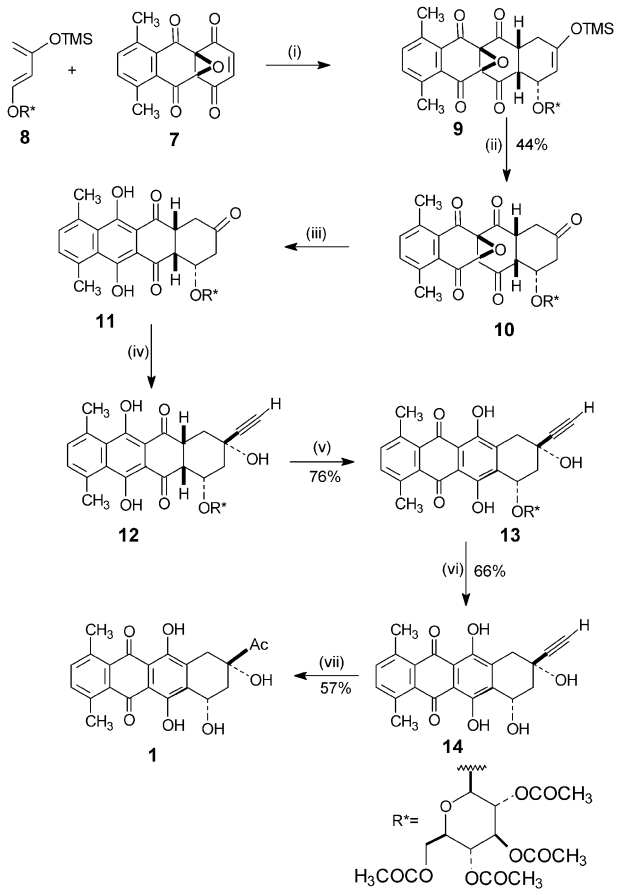


Figure 1. R = H, daunomycine; R = OH, adriamycine.



Scheme 1. (i) Δ; (ii) H^+ (iii) hydroquinone, $AlCl_3$, NaCl; (iv) $Pb(OAc)_4$; (v) *m*-CPBA.



Scheme 2. (i) Δ; (ii) H^+; (iii) Zn—AcOH, CH_2Cl_2; (iv) ethynylmagnesium bromide, H^+; (v) $Pb(OAc)_4$; (vi) H^+; (vii) HgO, H_2SO_4.

which was crystallized from ethyl acetate to give the pure oxirane **7** (3.2 g, 53%), mp 240–242 °C (decomp). IR (KBr): ν 1720, 1680 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 230 (23 400) nm, 325 (4 030) nm. ^1H NMR (220 MHz, $CDCl_3$): δ 2.50 (s, 6H), 6.72 (s, 2H), 7.40 (s, 2H). CIMS: *m*/*z* (relative intensity) 285 (MH_3^+, 19%), 284 (MH_2^+, 59%), 268 (37%), 254 (27%), 226 (25%), 201 (98%), 115 (63%), 103 (35%), 91 (27%), 82 (100%). Analysis for $C_{16}H_{10}O_5$: calcd C 68.09%; H 3.54%; found C 67.90%; H 3.60%.

Preparation of the epoxy-pentaone (10). To a solution of the diene **8** (0.827 g, 1.17 mmol) in dry acetone (35 mL) was added the oxirane **7** (0.478 g, 1.69 mmol). The resulting mixture was stirred at room temperature in the absence of light. After 2.5 days, the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether (insoluble material was removed by filtration). Concentration of the filtrate gave a foam (1.232 g) which was dissolved in THF (10 mL) and treated with 0.1 N HCl (2 mL). After stirring for 0.5 h, the mixture was filtered through a sintered funnel. The solid obtained was crystallized from ethanol to yield the compound **10** (0.525 g, 44%). Mp 205–206 °C. $[\alpha]_D^{25}$ −20 (1% in CH_2Cl_2). IR (KBr): ν 1750, 1720 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 330 nm (3914). ^1H NMR (300 MHz, $CDCl_3$): δ 1.82, 1.92, 2.00, 2.12 (s, each 3H), 2.32 (d, $J=18$ Hz, 1H), 2.35 (dd, $J=18$ and 3 Hz, 1H), 2.55 and 2.60 (s, each 3H), 2.95 (dd, $J=18$ and 2 Hz, 1H), 3.22 (dd, $J=10$ and 2 Hz, 1H), 3.36 (dd, $J=18$ and 7 Hz, 1H), 3.62–3.72 (m, 1H), 3.91–4.01(m, 1H), 4.10–4.22 (m, 2H), 4.58 (d, $J=8$ Hz, 1H), 4.75 (dd, $J=10$ and 8 Hz, 1H), 4.60–4.90 (m, 1H), 5.00 (t, $J=10$ Hz, 1H), 5.15 (t, $J=10$ Hz, 1H), 7.44 (s, 2H). CIMS: *m*/*z* (relative intensity) 406 (11%), 335 (34%), 334 (99%), 242 (35%), 241 (24%), 240 (100%). Analysis for $C_{34}H_{34}O_{16}$: calcd C 58.45%, H 4.87%; found C 58.10%, H 5.20%.

Zinc-acetic acid reduction of the epoxy-pentaone (10). A stirred solution of epoxy-pentaone **10** (1.0 g, 1.43 mmol) in acetic acid (10 mL) and dichloromethane (50 mL) was treated with activated zinc (2 g, 30.7 mmol). After being stirred for 3 h at ice temperature, the mixture was filtered, diluted with water (50 mL) and extracted with dichloromethane (3×100 mL). The organic layer was washed with brine and dried over $MgSO_4$. Removal of solvent gave the trione **11** in quantitative yield. An analytical sample, prepared by a series of crystallization of the material (from ether–hexane, methanol, large amount of ether) possess the following properties. Mp 150–155 °C. $[\alpha]_D^{25}$ +139 (0.25% in CH_2Cl_2). IR (KBr): ν 3440, 1750, 1720, 1625 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 245 (36,440), 270 (23,430), 422 (13,275), 448 (13,535) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83, 1.88, 2.04 and 2.16 (s, each 3H), 2.46 (dd, $J=16$ and 10 Hz, 1H), 2.50 (dd, $J=16$ and 4 Hz, 1H), 2.95 and 2.99 (s, each 3H), 3.10 (br d, $J=16$ Hz, 1H), 3.42 (dd, $J=8$ and 3 Hz, 1H), 3.50–3.70 (m, 3H), 4.12 (dd, $J=13$ and 3 Hz, 1H), 4.16 (dd, $J=13$ and 5 Hz, 1H), 4.50 (d, $J=8$ Hz, 1H), 4.60 (t, $J=10$ Hz, 1H), 4.74–4.77 (m, 1H), 4.90–5.05 (m, 2H), 7.36–7.44 (m, 2H), 13.94 and 14.84 (s, each 1H). FAB: *m*/*z* 684 (M^+), 331, 169 (base peak), 109. Analysis for $C_{34}H_{36}O_{15}$: calcd C 59.65%, H 5.26%; found C 59.40%, H 5.20%.

Reaction of the dihydroxytrione (11) with ethynylmagnesium bromide followed by lead(IV) acetate (13). To a flame-dried three-neck flask (500 mL) equipped with a water condenser, pressure-equalized dropping funnel and nitrogen inlet were added freshly activated magnesium turning (12 g, 0.5 mmol) and dry THF (100 mL). Ethyl bromide (dried over $CaCl_2$) in dry THF (200 mL) was added to the magnesium turnings over a period of 2 h. After the formation of ethylmagnesium bromide was complete the mixture was transferred into a pressure equalizing funnel (500 mL) with the help of a double cannula. Dry THF (200 mL) was placed in a three-neck flask and acetylene (purified by passage through a trap cooled at −80 °C then through concd H_2SO_4 and finally through NaOH) was introduced through the gas inlet. Ethylmagnesium bromide was added over a period of 2.5 h while the acetylene bubbling was continued. After the addition was complete, passage of acetylene was continued till a white precipitate appeared. The solution of ethynylmagnesium bromide was stored at 0 °C.

To a stirred solution of ethynylmagnesium bromide (25 mL, 22.7 mol equiv) was added the ketone **11** (0.760 g, 1.1 mmol) in dry THF (60 mL) at ice temperature. The reaction mixture was stirred for 1.5 h, poured into an ice cold saturated aqueous solution of ammonium chloride and extracted with dichloromethane (3×100 mL). The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent gave the crude product **12** (0.74 g, 94%) which was dissolved in acetic acid (15 mL) and treated with lead(IV) acetate (0.55 g, 1.24 mmol). After being stirred for 60 h at room temperature, the mixture was diluted with water (30 mL) and filtered. The solid obtained **13** (0.60 g, 76%) was dried and crystallized from methanol. An analytical sample, prepared by passing the sample through a short silica gel column, possessed the following properties. Mp 269–274 °C. $[\alpha]_D^{25}$ +134 (0.25% in CH_2Cl_2). IR (KBr): ν 3500, 3300, 1750, 1610 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 252 (65 560), 285 (77 000) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83, 1.98, 2.04 and 2.16 (s, each 3H), 2.38 (d, $J=16$ and 5 Hz, 1H), 2.54 (s, 1H), 2.80 and 2.81 (s, each 3H), 2.92 (dt, $J=16$ and 3 Hz, 1H), 2.96 (d, $J=19$ Hz, 1H), 3.56 (dd, $J=19$ and 4 Hz, 1H), 3.82–3.89 (m, 2H), 4.28–4.31 (m, 2H), 4.91 (dd, $J=10$ and 8 Hz, 1H), 5.10 (t, $J=10$ Hz, 1H), 5.11 (d, $J=8$ Hz, 1H), 5.25–5.31 (m, 2H), 7.44 (s, 2H), 13.41 and 13.80 (s, each 1H). CIMS: *m*/*z* 342 (3.4%), 115 (16%), 60 (100%). Analysis for $C_{36}H_{36}O_{15}$: calcd C 61.01%; H 5.08%; found C 60.70% H 4.90%.

Hydrolysis of the anthracycline (13). To a suspension of compound **13** (0.17 g, 0.24 mmol) in ethanol (35 mL) was added 1N HCl (35 mL). The mixture was heated under reflux for 48 h and was concentrated and filtered. The residue was purified by silica gel chromatography (ethyl acetate–hexane, gradient elution) to give compound **14** (0.06 g, 66%). An analytical sample was obtained by crystallization from methanol. Mp 202–

204 °C. $[\alpha]_D^{25}$ +85 (0.25% in CH_2Cl_2). IR (KBr): ν 3400, 3290, 1610 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 230 (26,360), 252 (35,810), 286 (8950), 352 (2984). ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (dd, $J=15$ and 5 Hz, 1H), 2.59 (s, 1H), 2.65 (ddd, $J=15$, 4 and 3 Hz, 1H), 2.82 (s, 6H), 3.01 (d, $J=19$ Hz, 1H), 3.46 (dd, $J=19$ and 3 Hz, 1H), 3.62 (s, 1H), 3.70 (d, $J=4$ Hz, 1H), 5.29–5.33 (m, 1H), 7.46 (s, 2H), 13.44 and 13.82 (s, each 1H). CIMS: m/z 378 (M^+, 8%), 360 (12%), 343 (25%), 342 (95%). HRMS for $C_{22}H_{18}O_6$: calcd 378.1103; found 378.1070.

Hydration of the ethynyldione (14). To a solution of compound **14** (0.1 g, 0.26 mmol) in acetone (25 mL) was added red mercury (II) oxide (0.3 g, 1.38 mmol) in 7% sulfuric acid (25 mL). The mixture was heated under reflux for 5 h and the cooled solution was diluted with 1 N HCl (20 mL) and extracted with chloroform (2×30 mL). The organic layer was washed with water, dried over $MgSO_4$ and evaporated. Purification of the crude product by chromatography on a short silica gel column gave the anthracycline **1** (0.06 g, 57%). Mp 120–125 °C. $[\alpha]_D^{25}$ +66 (0.11% in CH_2Cl_2). IR (KBr): ν 3420, 1710, 1610 cm^{-1}. UV (EtOH): λ_{max} (ε M^{-1} cm^{-1}) 526 (5065), 492 (9670), 470 (10,040), 353 (2880), 287 (8840), 253 (32,390), 233 (23,170), 218 (19,615), 202 (18,690) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 2.21 (dd, $J=15$ and 5 Hz, 1H), 2.35 (br d, $J=16$ Hz, 1H), 2.43 (s, 3H), 2.82 (s, 6H), 2.90 (d, $J=18$ Hz, 1H), 3.23 (dd, $J=8$ and 4 Hz, 1H), 3.82 (br d, $J=5$ Hz, 1H), 4.60 (s, 1H), 5.35 (br t, $J=4$ Hz, 1H), 7.45 (s, 2H), 13.5 and 13.82 (s, each 1H). CIMS: m/z 396 (M^+), 360 (100%). HRMS for $C_{22}H_{20}O_7$: calcd 396.1208; found 396.1182.

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