Total Synthesis of 4-Demethoxyfeudomycinone C[1]

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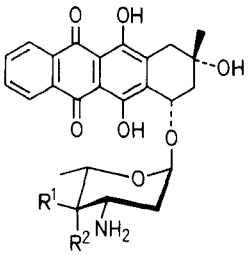
A synthesis of 4-demethoxyfeudomycinone C is described from the anthraquinone approach utilizing the carbon framework of (3*R*, 5*S*)-3-hydroxy-5-hydroxymethyl-3-methyl-2-oxotetrahydrofuran. The latter is easily derived from α-D-isosaccharinic acid.

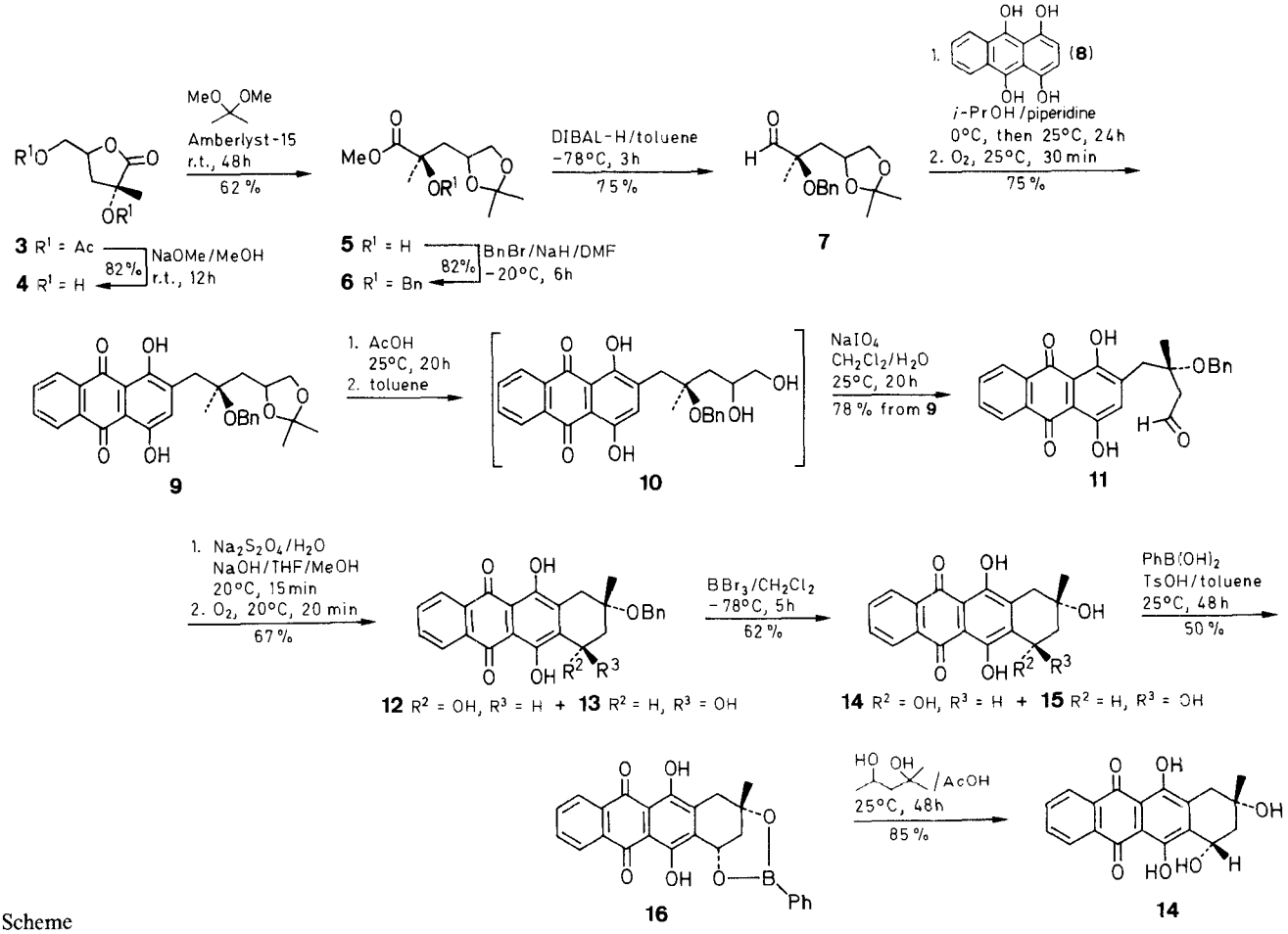
4-Demethoxyfeudomycinone C (**14**) is the aglycon moiety of a novel class of anthracycline derivatives[2,3] such as **1** and **2**. These 9-methylanthracyclines are highly efficient versus P 388 and L 1210 leukemia, present cell differentiating ability and preliminary *in vitro* investigations indicate that they may have useful activity as antitumor drugs against some Doxorubicin-resistant cell lines.



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

Broadhurst and co-workers reported the first total synthesis of 4-demethoxyfeudomycinone C starting from the fully functionalized bicyclic precursor and using an intramolecular Diels–Alder reaction as the key step in constructing the tetracyclic framework of **14**.[4] In an alternative approach, Krohn et al.[5] have achieved a synthesis of **14** from leucoquinizarin and (*S*)-(−)-hydroxysuccinic acid featuring an aldol strategy.

We now report the enantioselective total synthesis of 4-demethoxyfeudocyminone C based on aldol methodology (Scheme). 3-Acetoxy-5-acetoxymethyl-3-methyl-2-oxotetrahydrofuran (**3**), easily prepared[6] from isosaccharinic acid, was used as starting material. Transesterification of **3** with sodium methoxide in methanol afforded the diol lactone **4** which in turn was reacted with 2,2-dimethoxypropane in methanol in the presence of Amberlyst 15[7] to give **5**. Benzylation of **5** with benzyl bromide in dimethylformamide (82% yield) followed by reduction of **6** with diisobutylaluminum hydride at −78 °C in toluene (75%) led to the desired aldehyde **7**. The Lewis process[8] was utilized for the coupling of the chiral aldehyde **7** with leucoquinizarin (2,3-dihydro-9,10-dihydroxy-1,4-anthracenedione, **8**) to afford the adduct **9** in good yield (75%).



Scheme

Removal of the isopropylidene blocking group in aqueous acetic acid followed by oxidative cleavage of the diol **10** with periodate led to the aldehyde **11** in 78% overall yield. The subsequent step which involved an intramolecular Marschalk reaction[9] afforded a mixture of the diastereoisomers **12** and **13** (67%). The ratio of these diastereoisomers was estimated by the ^{1}H-NMR spectral analysis to be 6:4; however, the configuration of each diastereoisomer was not determined.

Deprotection of the benzyl group of the mixture of **12** and **13** was accomplished in 62% yield with boron tribromide in dichloromethane. Reaction of the resultant mixture of the *cis*-, **14**, and *trans*-diol **15** with phenylboronic acid[10] in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene gave the boronate **16** (50%). The *trans*-diol **15** already described by Krohn[5] was not epimerized under these conditions. The boronate **16** was cleaved with 2-methyl-2,4-pentanediol to give **14** (85%) whose spectral data were identical with those previously reported.[4] The preparation of 9-methyl-4-demethoxyanthracyclines different from **1** and **2** is in progress.

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the results obtained were within ± 0.4% of the theoretical values. IR spectra were determined on a Perkin-Elmer Model 1710 spectrophotometer and ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (270 MHz) using TMS as an internal standard. Mass spectra were recorded on a Nermag R 10.10C (DCI/NH_3) spectrometer. Optical rotations were measured at 20°C with a Perkin-Elmer Model 241 polarimeter. Flash chromatography[11] was performed on Merck silica gel 60 (Art. 9385). In all cases the solvent system used for the chromatographic separations was chosen such that, on TLC, an R_f of 0.25–0.30 was observed for the compound to be isolated.

(3*R*,5*S*)-3-Hydroxy-5-hydroxymethyl-3-methyl-2-oxotetrahydrofuran (4):

A solution of **3** (3.8 g, 16.52 mmol) in MeOH (60 mL) is stirred for 12 h at r.t. in the presence of a methanolic solution of NaOMe (2 M, 0.4 mL). After neutralization by addition of Amberlite IRC-50C, the solution is filtered through Celite and the filtrate is evaporated. The crude residue is purified by silica gel flash chromatography (elution with hexane/acetone, 3:1) to afford **4**; yield: 1.97 g (82%); mp 107–108°C; $[\alpha]_D^{25}$ + 49° (*c* = 1.1, MeOH).

$C_6H_9O_4$	calc.	C 49.31	H 6.89
(145.1)	found	49.53	6.90

IR (KBr): ν = 3434, 3284, 3006, 2980, 2963, 2951, 2878, 2806, 1762 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.56 (s, 3H, CH_3), 1.85 (br s, 1H, OH), 2.15 (dd, 1H, *J* = 13, 9.1 Hz, 3-H), 2.28 (br s, 1H, OH), 2.33 (dd, 1H, *J* = 13, 6.4 Hz, 3-H), 3.65 (m, 1H, 5-H), 4.00 (m, 1H, 5-H), 4.76 (m, 1H, 4-H).

MS (DCI/NH_3): *m/z* = 164 (M^+ + 18).

Methyl (2*R*,4*S*)-2-Hydroxy-4,5-(isopropylidenedioxy)-2-methylpentanoate (5):

A solution of **4** (9.8 g, 67.12 mmol) in a mixture of MeOH (45 mL) and 2,2-dimethoxypropane (100 mL) is stirred for 48 h at r.t. in the presence of ion-exchange resin Amberlyst 15 (approximately 5 g). The resin is removed by filtration, and the solvent evaporated under reduced pressure. The crude mixture is purified by silica gel flash chromatography (elution with EtOAc/hexane, 1:4, then 1:1) to give **5**; yield: 9.12 g (62%); mp 43°C; $[\alpha]_D^{25}$ − 19° (*c* = 1.1, MeOH).

$C_{10}H_{18}O_5$	calc.	C 55.03	H 8.31
(218.2)	found	55.19	7.99

IR (KBr): ν = 3516, 2991, 2939, 2881, 1724, 1683 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.28, 1.33 (2s, 6H, $C(CH_3)_2$), 1.44 (s, 3H, CH_3), 1.82 (dd, 1H, *J* = 14, 4 Hz, 3-H), 2.15 (dd, 1H, *J* = 14, 8 Hz, 3-H), 3.56 (dd, 1H, *J* = 9, 8 Hz, 5-H), 3.75 (s, 3H, OCH_3), 4.04 (dd, 1H, *J* = 9, 7 Hz, 5-H), 4.23 (m, 1H, 4-H).

MS (DCI/NH_3): *m/z* = 236 (M^+ + 18), 217 (M^+ + 1).

Methyl (2*R*,4*S*)-2-Benzyloxy-4,5-(isopropylidenedioxy)-2-methylpentanoate (6):

A solution of **5** (2 g, 9.17 mmol) in anhydr. DMF (40 mL) is stirred with NaH (60%, 550 mg, 12.5 mmol) at − 20°C for 2 h. BnBr (1.4 mL, 11.7 mmol) is added and the mixture is stirred for 4 h at − 20°C, and then treated slowly with a sat. aq NH_4Cl. The product is extracted with Et_2O, and the organic layer is dried and concentrated. The residue is purified by silica gel flash chromatography (elution with EtOAc/hexane, 1:9, then 1:4) to afford **6** as a colorless liquid; yield: 2.3 g (82%); $[\alpha]_D^{25}$ − 2° (*c* = 1.1, $CHCl_3$).

$C_{17}H_{24}O_5$	calc.	C 66.21	H 7.84
(308.4)	found	65.88	7.89

IR ($CDCl_3$): ν = 3091, 3067, 3033, 2989, 2953, 2877, 1740 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.37, 1.42 (2s, 6H, $C(CH_3)_2$), 1.59 (s, 3H, CH_3), 2.02 (dd, 1H, *J* = 15, 6 Hz, 3-H), 2-30 (dd, 1H, *J* = 15, 5 Hz, 3-H), 3.57 (dd, 1H, *J* = 9, 7 Hz, 5-H), 3.79 (s, 3H, OCH_3), 4.12 (dd, 1H, *J* = 9, 6 Hz, 5-H), 4.26 (m, 1H, 4-H), 4.48 (d, 1H, *J* = 10 Hz, CH_2Ph), 4.64 (d, 1H, *J* = 10 Hz, CH_2Ph), 7.39 (m, 5 H_{arom}).

MS (DCI/NH_3): *m/z* = 326 (M^+ + 18), 308 (M^+ + 1).

(2*R*,4*S*)-2-Benzyloxy-4,5-(isopropylidenedioxy)-2-methylpentanal (7):

To a − 78°C solution of **6** (8.04 g, 26.10 mmol) in toluene (120 mL) is added DIBAL-H solution in toluene (1.5 M, 48 mL, 72 mmol). The mixture is stirred at − 78°C for 3 h, treated with abs. MeOH (16 mL) and poured into a mixture of sat. aq sodium potassium tartrate (300 mL) and Et_2O (200 mL). The organic phase is separated, washed with H_2O, and filtered. The filtrate is dried and concentrated. Flash chromatography of the residue on silica gel (elution with EtOAc/cyclohexane, 1:3) affords **7**; yield: 5.43 g (75%).

IR ($CDCl_3$): ν = 3068, 3034, 2989, 2940, 2875, 1736 cm^{-1}.

^{1}H-NMR (90 MHz, $CDCl_3$/TMS): δ = 1.30, 1.33 (2s, 6H, $C(CH_3)_2$, 1.36 (s, 3H, CH_3), 1.91 (s, 1H, 3-H), 2.00 (d, *J* = 1 Hz, 3-H), 3.46 (dd, 1H, *J* = 9, 7 Hz, 5-H), 4.00 (dd, 1H, *J* = 9,. 6 Hz, 5-H), 4.35 (m, 1H, 4-H), 4.56 (s, 2H, CH_2Ph), 7.31 (m, 5 H_{arom}), 9.73 (s, 1H, CHO).

MS (DCI/NH_3): *m/z* = 296 (M^+ + 18), 278 (M^+ + 1).

2-[(2*S*)-2-Benzyloxy-1,4-dihydroxy-4,5-(isopropylidenedioxy)-pentyl]-2-methyl-9,10-anthraquinone (9):

A solution of dry piperidine (61.4 mL, 0.62 mol) in *i*-PrOH (200 mL) is treated at 0°C under N_2 with glacial AcOH (18.3 mL, 0.32 mol). A solution of **7** (5.4 g, 19.42 mmol) in *i*-PrOH (120 mL) is added at this temperature, followed by leucoquinizarin **(8)** (15 g, 61.9 mmol). The resulting solution is stirred at 25°C for 24 h, oxidized by bubbling air through it over 30 min, and quenched with 1 N HCl. The product is extracted with CH_2Cl_2, washed with H_2O, and then evaporated under reduced pressure. The crude product is purified by silica gel flash chromatography (elution with acetone/toluene, 0.1:99.9) to afford **9** as a red syrup; yield: 7.3 g (75%); $[\alpha]_D^{25}$ − 155° (*c* = 0.01, $CHCl_3$).

IR ($CDCl_3$): ν = 3069, 3033, 2988, 2937, 2872, 1623, 1589 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (s, 3H, CH_3), 1.42, 1.46 (2s, 6H, $C(CH_3)_2$), 1.87 (dd, 1H, *J* = 15, 6 Hz, 3-H), 2.11 (dd, 1H, *J* = 15, 7 Hz, 3-H), 3.14 (s, 2H, 1-H), 3.53 (dd, 1H, *J* = 9, 7 Hz, 5-H), 4.11 (dd, 1H, *J* = 9, 5 Hz, 5-H), 4.46 (m, 1H, 4-H), 4.51 (d, 1H, *J* = 11 Hz, CH_2Ph), 4.60 (d, 1H, *J* = 11 Hz, CH_2Ph), 7.37 (m, 5 H_{arom}), 7.44 (s, 1 H_{arom}), 7.80 (m, 2 H_{arom}), 8.27 (m, 2 H_{arom}), 12.78 (s, 1H), and 13.49 (s, 1H, OH phenol).

MS (DCI/NH_3): *m/z* = 503 (M^+ + 1).

(3*S*)-3-Benzyloxy-4-(1,4-dihydroxy-9,10-anthraquinon-2-yl)-3-methylbutanal (11):
A solution of **9** (7.3 g, 14.54 mmol) in AcOH (90%, 100 mL) is stirred at 25 °C for 20 h. Toluene (200 mL) is added under reduced pressure. The crude diol **10** (7.22 g) thus obtained is diluted in CH_2Cl_2 (250 mL) and H_2O (250 mL) at 25 °C, and treated with $NaIO_4$ (8 g, 37.4 mmol). After being stirred for 20 h, the organic phase is separated, washed with H_2O, dried, and concentrated. The residue is purified by silica gel flash chromatography (elution with EtOAc/cyclohexane, 1:6) to give **11**; yield: 4.9 g (78%); mp 92–93 °C, $[\alpha]_D^{25}$ + 12° (c = 0.04, $CHCl_3$).

$C_{26}H_{22}O_6$ (430.5) calc. C 72.54 H 5.15 found 72.39 5.01

IR (KBr): ν = 3063, 3027, 2978, 2838, 2740, 1869, 1793, 1772, 1719, 1628, 1591 cm^{-1}.

^{1}H-NMR (90 MHz, $CDCl_3$/TMS): δ = 1.45 (s, 3 H, CH_3), 2.63 (m, 2 H, 2-H), 3.13 (s, 2 H, 4-H), 4.58 (s, 2 H, CH_2Ph), 7.23 (s, 1 H_{arom}), 7.30 (m, 5 H_{arom}). 7.73 (m, 2 H_{arom}), 8.20 (m, 2 H_{arom}), 9.90 (m, 1 H, CHO), 12.76, 13.46 (2 s, 2 H, OH phenol).

MS (DCI/NH_3): m/z = 448 (M^+ + 18), 431 (M^+ + 1).

(7*S*,9*S*)-, and (7*R*,9*S*)-9-Benzyloxy-7,8,9,10-tetrahydro-6,7,11-trihydroxy-9-methyl-5,12-naphthacenedione (12) and (13):
To a stirred solution of **11** (2 g, 4.65 mmol) in a mixture of MeOH/THF (120 mL, 1:1) cooled to − 20 °C, is added under N_2, a solution of NaOH (400 mg, 10 mmol) and $Na_2S_2O_4$ (1.12 g, 6.43 mmol) in H_2O (20 mL). The mixture is stirred for 15 min at 20 °C, oxidized by bubbling air through it for 20 min, and quenched with 1 N HCl. The products are extracted with EtOAc, dried, and concentrated. Chromatography of the crude solid on silica gel (elution with toluene/acetone, 95:5) affords a mixture of **12** and **13**; yield: 1.34 g (67%).

IR (KBr): ν = 3548, 3469, 3033, 2936, 1624, 1588 cm^{-1}.

MS (DCI/NH_3): m/z = *431* (M^+ + 1).

(7*S*,9*S*)- and (7*R*,9*S*)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (14) and (15):
A mixture of **12** and **13** (2.8 g, 6.51 mmol) in dry CH_2Cl_2 (250 mL) is treated at − 78 °C under N_2 with a solution of BBr_3 in CH_2Cl_2 (1 M, 16 mL). The mixture is stirred for 5 h at − 78 °C, then treated with sat. aq $NaHCO_3$, and extracted with CH_2Cl_2, and the extract is washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The residue is purified by silica gel flash chromatography (elution with toluene/acetone, 80:20) and provides a mixture of **14** and **15**; yield: 1.38 g (62%).

IR (KBr): ν = 3418, 2931, 1625, 1587, 1436, 1376, 1244, 1121, 1057, 1016 cm^{-1}.

MS (DCI/NH_3): m/z = 340 (M^+).

[(1*S*,3*S*)-1,2,3,4-Tetrahydro-5,12-dihydroxy-3-methyl-6,11-dioxo-1,3-naphthacenediyl] Phenylboronate (16):
To a mixture of *cis*, **14**, and *trans* diol **15** (1.75 g, 5.14 mmol) in toluene (350 mL) at 25 °C under N_2, phenylboronic acid (815 mg, 6.68 mmol) and TsOH (80 mg, 0.46 mmol) are added. After 48 h, the mixture is treated with aq $NaHCO_3$, diluted with CH_2Cl_2, and washed with H_2O. The organic extract is concentrated, and the residue is chromatographed on silica gel (rapid elution with acetone/toluene, 20:80) giving the *cis*-phenylboronate **16**, yield: 1.1 g (50%); mp 258–260 °C, $[\alpha]_D^{25}$ + 193° (c = 0.04, $CHCl_3$).

IR (KBr): ν = 1625, 1589, 1440, 1413, 1390, 1374, 1325, 1297, 1241, 1207, 1160, 1123, 1088, 1023 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.71 (s, 3 H, CH_3), 2.09 (dd, 1 H, J = 14, 3 Hz, 8-H), 2.34 (bd, 1 H, J = 14 Hz, 8-H), 2.82 (d, 1 H, J = 20 Hz, 10-H), 3.40 (dd, 1 H, J = 20, 1 Hz, 10-H), 5.78 (m, 1 H, 7-H), 7.30 (m, 3 H_{arom}), 7.84 (m, 4 H_{arom}), 8.35 (m, 2 H_{arom}), 13.21, 13.48 (2 s, 2 H, OH phenol).

MS (DCI/NH_3): m/z = 444 (M^+ + 18), 427 (M^+ + 1).

(7*S*,9*S*)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (14):
A solution of the phenylboronate **16** (1.1 g, 2.58 mmol) in a mixture of CH_2Cl_2 (160 mL), 2-methyl-2,4-pentanediol (30 mL) and AcOH (5 mL) is stirred at 25 °C for 48 h. The solution is then washed with H_2O, dried, and evaporated. The residue is subjected to chromatographic purification in silica gel (elution with 20% acetone in toluene) to give the *cis*-diol **14**; yield: 0.75 g (85%); mp 210 °C; $[\alpha]_D^{25}$ + 133° (c = 0.001, dioxane); [Lit.[4] mp 214–215 °C; $[\alpha]_D^{20}$ + 152.5° (c = 0.1% in dioxane).

IR (KBr): ν = 3252, 2927, 1623, 1587, 1435, 1411, 1376, 1343, 1315, 1290, 1239, 1158, 1105, 1047, 1017 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.50 (s, 3 H, CH_3), 1.91 (dd, 1 H, J = 15, 5 Hz, 8-H), 2.37 (d, 1 H, J = 15 Hz, 8-H), 2.57 (d, 1 H, J = 19 Hz, 10-H), 3.23 (d, 1 H, J = 19 Hz, 10-H), 3.43 (br s, 1 H, OH exch. D_2O), 3.73 (br s, 1 H, OH exch. D_2O), 5.23 (m, 1 H, 7-H), 7.84 (m, 2 H_{arom}), 8.30 (m, 2 H_{arom}), 13.26, 13.55 (2 s, 2 H, OH phenol).

MS (DCI/NH_3): m/z = 431 (M^+ + 1).

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