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BENZAMIDE DIRECTED ORTHO METALATION

A ROUTE TO THE A/B RING SYNTHON OF DAUNOMYCINONE†

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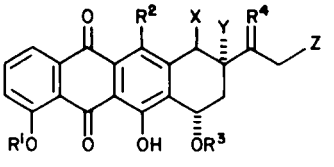
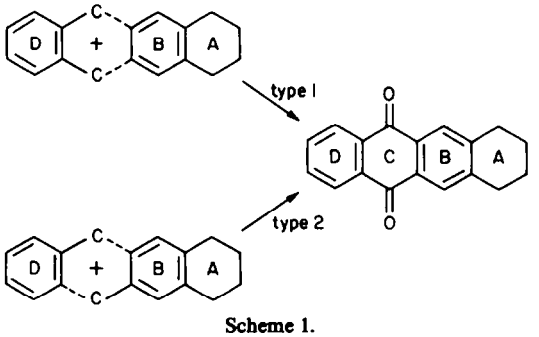
Abstract—The A/B ring synthon **13**, previously converted into daunomycinone (**6**) by Keay and Rodrigo,[6] has been prepared in seven steps and 38% overall yield using benzamide directed ortho metalation strategy. Significant steps are: the incorporation of a four-carbon Grignard unit (**10**) into **9**, dibal reduction of **11**, and intramolecular aldol condensation of the resulting product **12** to give the dihydronaphthalene **13**.

The anthracyclinone antibiotics,[1] exemplified by the key functionalized types **1** → **5**, constitute a class of natural products which is currently making a significant impact in the fields of cancer chemotherapy and, *ipso facto*, in organic synthesis. Since the seminal work in 1963 describing the isolation of daunomycin (**1**) from *Streptomyces* species,[2] the structures of over forty members of this class of compounds have been elucidated. The isolation work continues to be actively pursued stimulated by the highly promising broad spectrum antitumor activity coupled with the with the aim of providing test compounds with improved antitumor activity and selectivity and reduced toxicity.[3] As part of a synthetic approach to the anthracyclinones[4] involving comprehensive use of the aromatic directed ortho metalation reaction,[5] we have developed and report herein a short route for the construction of the A/B ring synthon **13** of daunomycinone (**6**). Since compound **13** has been recently synthesized by a totally different route and converted into daunomycinone,[6] our work constitutes a formal total synthesis of this natural product.



	R^1	R^2	R^3	R^4	X	Y	Z	
1	Me	OH	L-α-daunosamine	O	H	OH	H	Daunomycin
2	Me	OH	L-α-daunosamine	O	H	OH	OH	Adriamycin
3	H	OH	L-α-daunosamine	O	H	OH	H	Carminomycin
4	Me	OH	L-α-daunosamine	O	H	OH	OH	Doxorubicin
5	H	H	L-α-N,N-dimethyl-daunosamine	H_2	CO_2Me	OH	H	Aklavin
6	Me	OH	H	O	H	OH	H	Daunomycinone
7	H	H	H	H_2	CO_2Me	OH	H	Aklavinone



Scheme 1.

unprecedented therapeutic value.[1e] In the last decade, intense effort has been devoted to develop synthetic routes to the aglycone, daunomycinone (**6**) and, more recently, alkavinone (**7**), as well as a variety of analogues

According to the excellent synthetic analysis and classification provided by Kelly,[3d] the A/B ring synthons has been used in two modifications of a D + BA → DCBA approach in the construction of anthracyclinones (Scheme 1) in which the impendent formation of ring C occurs by coupling a bare B/A ring with a D ring containing two ortho related, functionalized carbon substituents (type 1)[7e-i] or a

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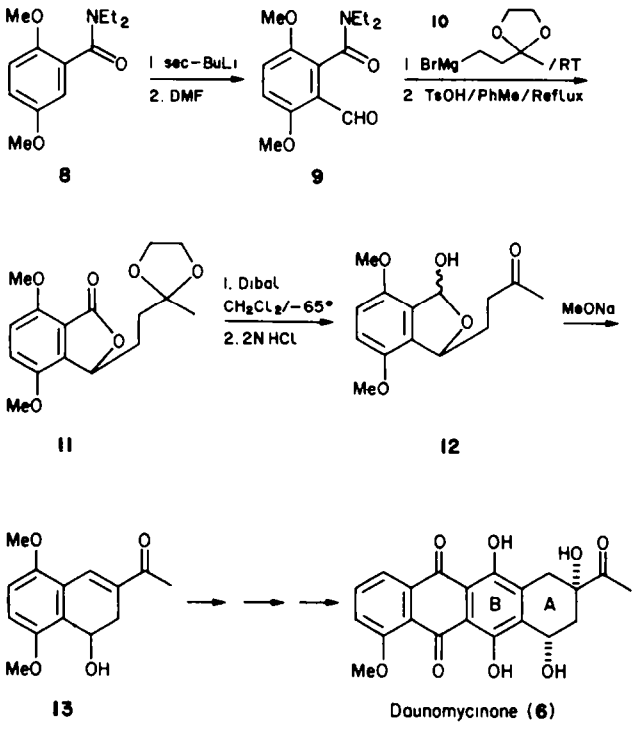
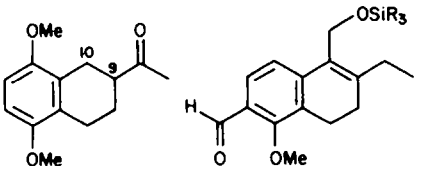


Scheme 2.

carbon-substituted B/A system with a one carbon-containing D fragment (type 2).[7m-q] Our synthetic route falls into the type 1 categorization.

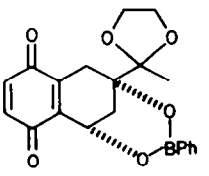
The 2,5-dimethoxybenzamide **8** (Scheme 2) was subjected to standard metalation conditions (s-BuLi/TMEDA/−78°/1 hr)[8] and quenched with an excess of DMF to afford the contiguously tetrasubstituted benzene derivative **9** in 80% yield. The four-carbon Grignard synthon **10**,[9] constituting the complete requirement for ring A assemblage, was condensed with **9** to give, after toluene sulfonic acid cyclization[8] of the intermediate amide alcohol, the phthalide **11** in 90% overall yield. Careful Dibal reduction followed by mineral acid hydrolysis provided the intermediate keto hemiacetal **12**. Compound **12** was immediately subjected to sodium methoxide catalyzed intramolecular aldol condensation to afford the unsaturated ketone **13** in 70% yield. Compound **13** was shown to be identical by direct comparison of physical and spectral properties (Experimental) with an authentic sample prepared by Keay and Rodrigo[6] at our institution.

Thus starting with benzamide **8**, our synthesis provides the A/B ring synthon **13** regiospecifically in seven steps and 38% overall yield. By way of comparison, the route developed by Keay and Rodrigo from 2,5-dimethoxy benzyl alcohol affords **13** in five steps and 18% overall yield.[6] Four other comparisons of recent A/B ring construction are relevant: compounds **14**, **16**, and **15** lacking C-7 and C-13 oxygen substituents have been prepared by Wong and coworkers[7a] (eight steps, 36% overall yield), by Kende and Rizzi[7p] (five steps, 29% overall yield[10a]), and by Russell and coworkers[7d] (five steps, 27% overall yield) respectively while compound **17**, with complete oxygen functionalization, was assembled by Hassall and coworkers[7m] (ten steps, 23% overall yield[10b]). Our route of **13** (Scheme 2) compares favorably with these syntheses of related A/B units. In addition, it represents one of the few constructions[6,7m] of the A/B ring synthon which embodies a 7-hydroxy, a functionality usually introduced inefficiently at a terminal stage of the synthesis.[3] In view of the conversion of **13** into daunomycinone (**6**), our route constitutes a formal total synthesis of this anthracyclinone. The utility of this chemistry in a comprehensive aromatic metalation approach to daunomycinone is in progress.[4]



14 **16**

15 9, 10-double bond



17

EXPERIMENTAL

General methods. Elemental analyses were performed by the analytical laboratories of the University of Waterloo and the Galbraith Laboratories, Knoxville, Tenn. M.ps were determined on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were measured on a Beckman IR-10 instrument in $CHCl_3$ unless otherwise specified. NMR spectra

were obtained using a Bruker WP-80 spectrometer in $CDCl_3$ with TMS as an internal standard unless otherwise specified. Spectra listed are tabulated in the order chemical shift (δ ppm); multiplicity; coupling constant (J in Hz); number of protons; assignment. Mass spectra were determined on a VG 7070F instrument at 70 eV unless otherwise specified. TLC was performed using Merck precoated silica gel sheets 60F-254. Merck silica gel of the size 70–230 mesh was used for column chromatography. Preparative HPLC was carried out on a Waters PREP-500 using a silica gel normal phase column. THF was dried by distillation under a nitrogen atmosphere from sodium/benzophenone ketyl radical. CH_2Cl_2 was distilled from anhydrous $CaCl_2$ and then from anhydrous P_2O_5. Tetramethylethylenediamine (TMEDA) and dimethylformamide were both dried and distilled from CaH_2 and were stored in amber screw cap bottles over 4 Å molecular sieves in a dessicator. The cyclohexane soln of s-BuLi (Aldrich Chem. Co.) was stored in a serum-capped bottle under nitrogen in a container over anydrous calcium chloride. This base was regularly titrated according to a literature procedure.[11]

N,N - *Diethyl* 2 - *formyl* - 3,6 - *dimethoxybenzamide* (**9**). To a stirred soln of s-BuLi (18.2 ml, 23.2 mmol) and TMEDA (3.5 ml, 23.2 mmol) in anhyd THF (400 ml) at −78° under N_2 was added by syringe injection a soln of 2,5-dimethoxy N,N-diethylbenzamide[8] (5.0 g, 21 mmol) in THF (25 ml). After 1 hr, the yellow soln was treated with excess of DMF (25 ml) and the mixture was allowed to warm to room temp over 18 hr. Treatment with sat NH_4Cl aq followed by evaporation to dryness *in vacuo* afforded a residue which was dissolved in Et_2O. The organic soln was washed with brine, dried (Na_2SO_4) and evaporated to dryness to give, after recrystallization (Et_2O), 4.45 g (80%) of compound **9**, m.p. 97–98°; IR ($CHCl_3$) ν_{max} 1685, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.1), 1.31 (t, 3H, J = 7.1), 2.94–3.72 (m, 4H), 3.79 (s, 3H), 3.89 (s, 3H), 6.95, 7.14 (AB q, 2H, J = 9.1), 10.43 (s, 1H, CHO); MS *m/e* (rel intensity) 265 (M^+, 2), 236 (100). (Found: C, 63.20; H, 7.19; N, 5.16. Calc for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.21; N, 5.27).

3 - (2,2 - *Ethylenedioxybutyl*) - 4,7 - *dimethoxyphthalide* (**11**). A literature method was adapted.[9a] A mixture of 1-bromobutan-3-one ethylene ketal[9b] (0.95 g, 12.5 mmol) and Mg (0.72 g, 30 mmol) in anhyd THF (20 ml) was treated with a few drops of 1,2-dibromoethane at room temp and the mixture was stirred for 2 hr in which time it turned gray. The soln of the thus formed Grignard reagent **10** was treated with a soln of **9** (2.8 g, 10 mmol) in THF (30 ml). The resulting red mixture was stirred for 18 hr, treated with sat NH_4Cl aq (30 ml), and then THF was removed *in vacuo*. The residue was extracted using CH_2Cl_2 (6 × 25 ml). The combined CH_2Cl_2 layer was washed with brine (50 ml), dried over anhyd Na_2SO_4 and evaporated to dryness to yield the intermediate amide alcohol (3.75 g) which without purification was dissolved in toluene (30 ml) and the resulting soln was treated with *p*-toluenesulfonic acid (20 mg) and refluxed with stirring for 24 hr. The mixture was cooled and washed successively with sat $NaHCO_3$ aq and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness to furnish, after recrystallization (CH_2Cl_2-hexane), 2.75 g (90%) of **11**, m.p. 118–120°; IR ($CHCl_3$) ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.57–2.6 (m, 4H), 3.85 (s, 3H), 3.92 (s, 3H), 3.93 (s, 4H), 5.3–5.6 (m, 1H, C-3 H), 6.85, 7.06 (AB q, 2H, J = 8.7); MS *m/e* (rel intensity) 308 (M^+, 8) 206 (86), 87 (100). (Found: C, 62.60; H, 6.44. Calc for $C_{16}H_{20}O_6$: C, 62.32; H, 6.53).

3 - (2 - *Butanoyl*) - 4,7 - *dimethoxyphthalal* (**12**). The procedure of Keay and Rodrigo[6] was adopted. A stirred soln of **11** (1.0 g, 3.2 mmol) in anhydrous CH_2Cl_2 (50 ml) at −65° (MeOH-dry ice bath) was treated with Dibal (1.52 M in toluene, 4.8 ml, 7.3 mmol) over 10 min. The mixture was stirred for an additional 70 min, quenched with MeOH (2 ml), and allowed to warm to room temp over 14 hr. The mixture was shaken with aqueous saturated brine soln for 15 min and the organic layer was separated, dried (K_2CO_3), and evaporated to dryness to give a solid. Recrystallization (CH_2Cl_2-hexane) afforded 805 mg (81%) of 3-(2-*butanoyl*)-4,7-*dimethoxyphthalal ethylene ketal*, m.p. 109–110°; IR ($CHCl_3$), ν_{max} 3600 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.6–2.3 (m, 4H), 3.3 (d, 1H, J = 6.8, C-1 H) 3.78 (s, 3H, OMe), 3.82 (s, 4H, ketal 2 × CH_2), 3.90 (s, 3H) 5.1–5.3 (m, 1H, C-3 H), 6.45 (d, 1H, J = 6.9, OH), 6.75 (s, 2H); MS *m/e* (rel intensity) 310 (M^+, 2), 292 (38). (Found: C, 61.70; H, 6.99. Calc for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15).

A soln of the above ketal (100 mg, 0.32 mmol) in a mixture of dimethoxyethane-H_2O (5 ml, 4:1) was treated with 2M HCl (10 drops) and the mixture was stirred under N_2 for 24 hr. The mixture was poured into water (100 ml) and extracted with CH_2Cl_2 (5 × 15 ml). The combined CH_2Cl_2 extracts were dried (K_2CO_3) and evaporated to dryness *in vacuo* to give a colorless solid which, upon recrystallization (CH_2Cl_2/hexane) afforded 78.4 mg (92%) of **12**, m.p. 123°–124°; IR ($CHCl_3$) ν_{max} 3397, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.82–2.72 (m, 4H), 2.10 (s, 3H), 3.64 (d, 1H, J = 6.7, OH), 3.78 (s, 3H), 3.83 (s, 3H), 5.18–5.30 (m, 1H, C-3 H), 6.46 (d, 1H, J = 6.7, C-1 H), 6.76 (s, 2H); MS *m/e* (rel intensity) 265 ($M^+ - 1$, 5) 250 (34), 248 (100), 231 (41). (Found: C, 63.31; H, 6.61. Calc for $C_{14}H_{18}O_5$: C; 63.15; H, 6.81).

1 - *Hydroxy* - 3 - *acetyl* - 3,4 - *dehydro* - 5,8 - *dimethoxynaphthalene* (**13**). A mixture of **12** (60 mg, 0.22 mmol) and NaOMe (10 mg) in dry MeOH (5 ml) was stirred at room temp under N_2 for 24 hr. The mixture was poured into water (100 ml) and the resulting aqueous soln was neutralized to pH 7 with gaseous CO_2. The mixture was diluted with water (100 ml) and extracted with CH_2Cl_2 (5 × 10 ml). The combined CH_2Cl_2 extracts were dried (K_2CO_3) and evaporated to dryness *in vacuo* to give a solid which was recrystallized (Et_2O—CH_2Cl_2) to afford 33.4 mg (70%) of **13**: m.p. 115–116°, lit.[6] m.p. 114–115°; IR ($CHCl_3$) ν_{max} 3592, 1656 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (br, 1H), 2.21–3.2 (m, 2H), 2.48 (s, 3H), 3.84 (s, 6H), 5.12–5.23 (br, 1H, C-1 H), 6.76–7.22 (m, 2H), 7.9 (d, 1H, J = 2.6, C-4 H).

Compound **13** was shown to be identical (m.p. IR, NMR) by direct comparison with a sample obtained from Dr. B. A. Keay and Professor R. Rodrigo.[6]

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