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DIRECTED ORTHO METALATION REACTIONS.
SYNTHESIS OF THE NATURALLY-OCCURRING BENZ[a]ANTHRAQUINONES
X-14881 C AND OCHROMYCINONE

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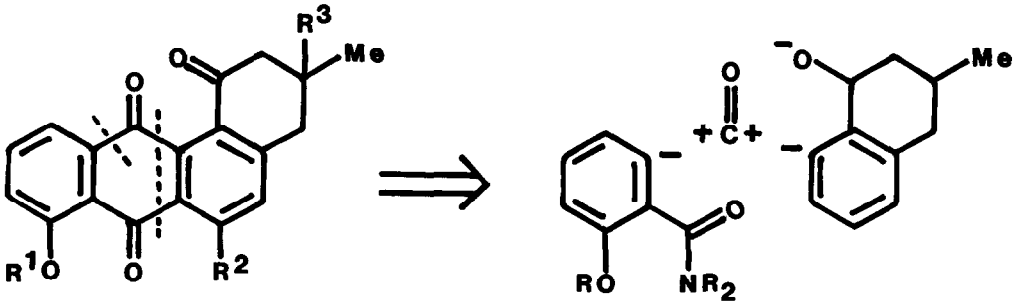
Abstract: The synthesis of the benz[a]anthraquinone natural products X-14881 C **(1c)** and ochromycinone **(1a)** via an aromatic directed metalation strategy **(Scheme 1)** is described.

Among the profuse heterogeneous classes of naturally-occurring quinones, the benz[a]anthraquinones comprise a compact, functionally uniform group of substances elaborated by several strains of Streptomyces[1] which show varied antibacterial,[1b,1d] enzyme inhibitory,[1c] and antitumor[1d] activity. In spite of the "angular" skeletal relationship of this class to the antitumor anthracyclines,[2] synthetic efforts have been confined to a classical preparation of tetrangulol (ring A aromatized **1a**) [3] and an innovative synthesis of the unnatural 3-deoxyrabelomycin **(1b)** via an anionic 1-tetralol chromium tricarbonyl complex.[4] We wish to disclose the first total synthesis of one of the most recent and one of the earliest isolated natural benz[a]anthraquinones, X-14881 C **(1c)** [1e] and ochromycinone **(1a)** [5] respectively, by a regiospecific convergent route based on the aromatic directed metalation strategy.[6]



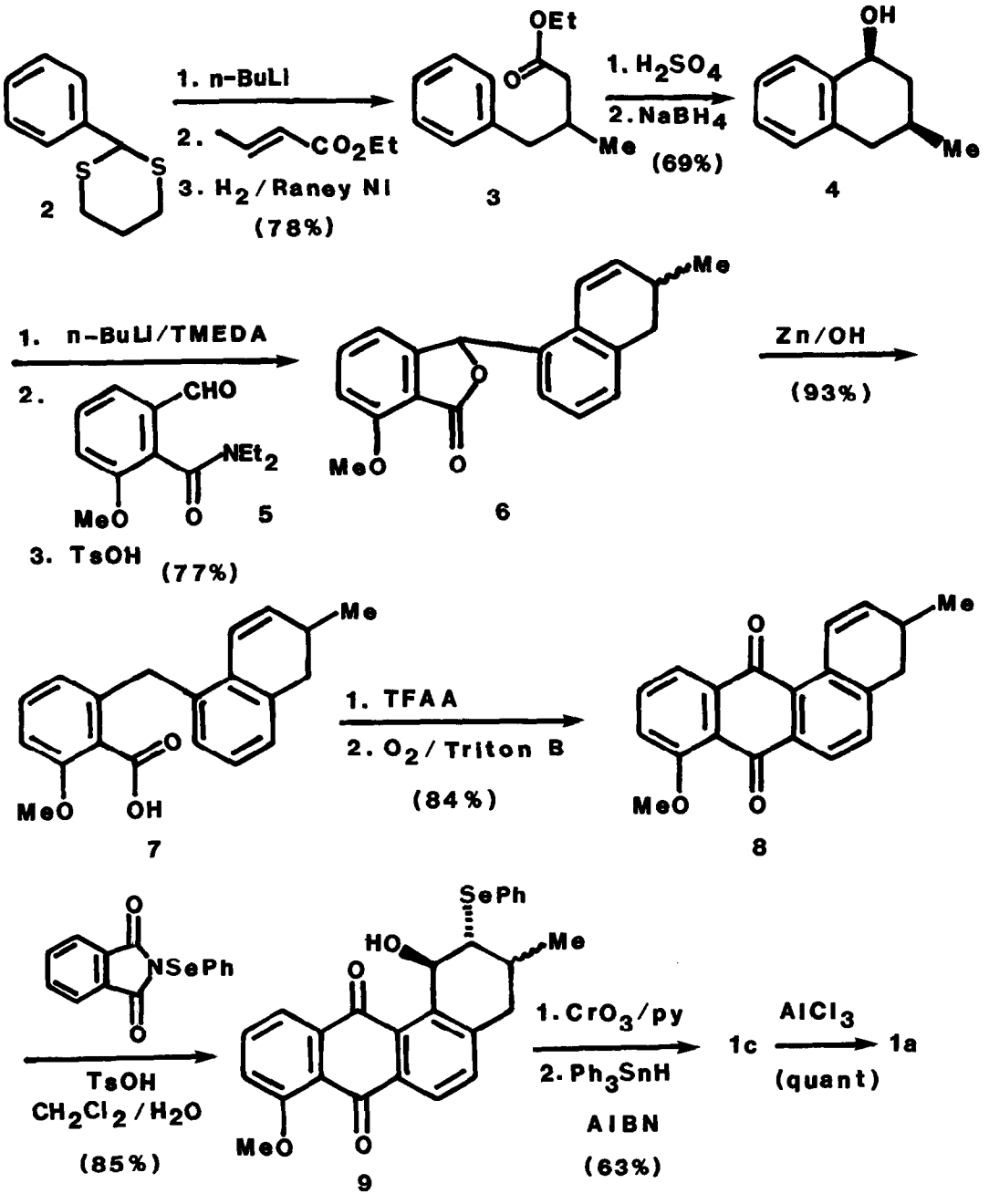
1 **Scheme 1**

a: $R^1 = R^2 = R^3 = H$; **b:** $R^1 = R^3 = H$, $R^2 = OH$; **c:** $R^1 = Me$, $R^2 = R^3 = H$

The bond dissections depicted in **Scheme 1** take advantage of maximum convergence, efficiency, and the retrosynthetic foundation of our directed ortho metalation protocol for anthraquinone synthesis.[7] The preparation of the requisite 3-methyl-1-tetralol (**4**, **Scheme 2**) was initiated by the Michael addition of ethyl crotonate to the lithiated species of the dithiane **2** followed by hydrogenolysis to give the ester **3**. Sequential Friedel-Crafts cyclization and hydride reduction afforded predominantly the cis isomer, **4**.[8,9] The pure cis-isomer was metalated (2 equiv. n-BuLi/TMEDA/Et_2O/reflux) and the resulting dilithiated species was coupled at -40°C[10] with the amide aldehyde **5** derived in 75% yield from the reaction of lithiated N,N-diethyl-o-anisamide with DMF.[11] The intermediate amide alcohol was not isolated but subjected to reaction with TsOH (≈ 0.5 equiv) in refluxing toluene to give in good yield the phthalide olefin **6** as a diastereomeric mixture.[12,13]

Zinc hydrogenolysis[14] of **6** in basic solution furnished the benzoic acid **7** which upon TFAA-mediated Friedel-Crafts cyclization in CH_2Cl_2 followed by base-catalyzed aerial oxidation in MeOH provided the dihydrobenz[a]anthraquinone **8**. Selenohydroxylation of **8** according to the procedure of Nicolaou[15] was a decisive step in the synthesis and led to the hydroxyselenide **9** in excellent yield. ^1H NMR data is in agreement with the assigned regiochemistry: δ 3.87, 1H, br t, C-2 H; δ 4.84, 1H, d, J = 4.3 Hz, D_2O-exchangeable; δ 5.34, dd, 1H, J = 4.3 and 2.4 Hz, C-1 H. Although of no consequence to the synthetic end result, the stereochemistry is tentatively assigned trans on the basis of the assumed trans addition.[16] In the concluding steps of the synthesis, **9** was oxidized (CrO_3/py) and deselenated (Ph_3SnH)[17] to yield X-14881 C (**1c**) whose identity with the natural product was established by comparison of its physical and spectral (IR, UV, ^1H NMR, MS) data with those reported in the literature.[1e,18] Demethylation using $AlCl_3$ in CH_2Cl_2 afforded ochromycinone (**1a**) whose identity with the natural quinone was similarly secured.[19]

Apart from demonstrating the first total syntheses of benz[a]anthraquinone natural products (17% overall yield) using ortho metalation, this work illustrates how high convergence and regioselectivity may be achieved by conceptualizing approaches based on two different directed ortho metalation inducers.[20,21]


1. n-BuLi
2. CO2Et
3. H2 / Raney Ni
(78%)
2
OEt
O
Me
3
1. H2SO4
2. NaBH4
(69%)
OH
Me
4
1. n-BuLi/TMEDA
2.
CHO
NEt2
MeO
O
5
3. TsOH
(77%)
Me
MeO
O
6
Zn/OH
(93%)
Me
MeO
OH
O
7
1. TFAA
2. O2 / Triton B
(84%)
Me
MeO
O
O
8
O
NSePh
O
TsOH
CH2Cl2 / H2O
(85%)
SePh
HO
Me
O
MeO
O
9
1. CrO3/py
2. Ph3SnH
AIBN
(63%)
1c
AlCl3
(quant)
1a

Scheme 2

References and Footnotes

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8. We thank E.G. Doadt for the initial development of this sequence.
9. The sodium borohydride reduction of 3-methyl-1-tetralone has been reported to give **4** and the corresponding trans-isomer in a ratio of 93:7, Mitsui, S.; Kasahara, A.; Hanaya, K. Bull. Chem. Soc. Japan **1968**, 41, 2526 and refs. cited therein.
10. These conditions were imperative to the success of the reaction. A number of other conditions previously reported for O,ortho dideprotonation of benzyl alcohol type systems gave much poorer results, cf. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. J. Org. Chem. **1983**, 48, 2349 and references cited therein; Meyer, N.; Seebach, D. Chem. Ber. **1980**, 113, 1304.
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12. Milder conditions (e.g. TsOH/PhH) gave mixtures of **6** and the corresponding 1-tetralol in which the latter predominated. This material was readily converted into the 1-ketone corresponding to **7** but further elaboration was prevented by the failure of the Friedel-Crafts reaction presumably due to the deactivating effect of the carbonyl group.
13. Interestingly, the trans-isomer corresponding to **4** is inefficiently metalated as evidenced by 24% deuterium incorporation.
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18. Mp 236-237°C, lit[1e] mp 235°C. We are indebted to Dr. H. Maehr, Hoffmann-La Roche, Nutley for providing the comparison spectral data.
19. Mp 168-169°C, lit[1a] mp 152-153°C identical IR, UV, ^{1}H NMR spectra; ochromycinone acetate: mp 175-176°C, lit (Bowie, J.H., personal communication) mp 170.5-171.5°C, mixture mp undepressed. We are unable to explain the mp discrepancies for ochromycinone. We are grateful to Prof. J.H. Bowie for providing a sample of ochromycinone acetate and spectral data of ochromycinone.
20. All new compounds show combustional analyses and spectral (IR, ^{1}H NMR, MS) data consistent with the assigned structures.
21. We are grateful to NSERC Canada for financial support and to E.G. Doadt for initial experimentation.

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