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SEQUENTIAL DIRECTED ORTHO METALATION REACTIONS. A SYNTHESIS OF ANTHRAMYCIN.

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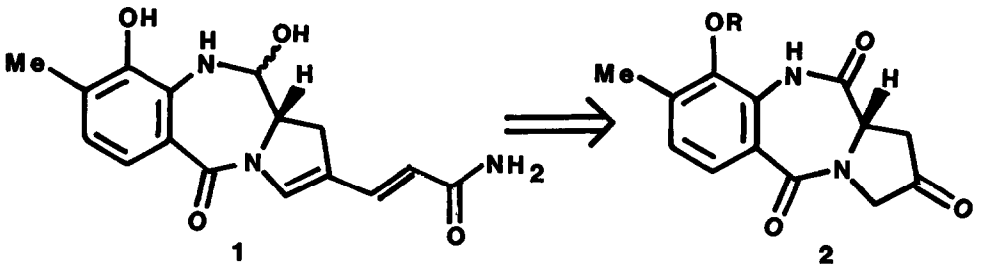
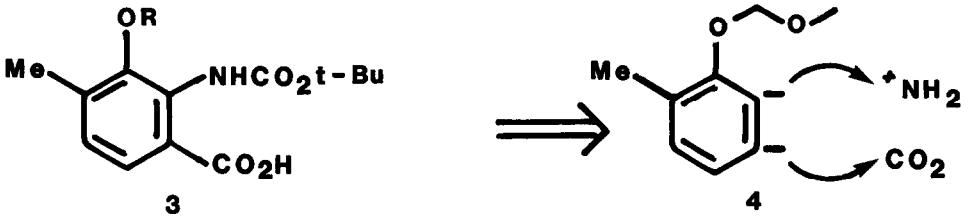
Abstract: The pyrrolo[1,4]benzodiazepine **2** (R = Me), a key intermediate in the synthesis of anthramycin (**1**), has been prepared via a new approach involving two sequential directed ortho metalation reactions (**4**) and a previously unreported isatoic anhydride construction (**8** → **9**).

The pyrrolo[1,4]benzodiazepine antibiotics, isolated from Actinomycetes and structurally exemplified by the prototype anthramycin (**1**), have enjoyed a sustained synthetic interest[1] owing to the continuing discovery of new members[2] and to their unique biosynthetic origin[3] and mechanism of antitumor action.[3,4] The two reported syntheses[1e,5] of **1** invoke the elaboration of a polysubstituted benzene derivative by classical aromatic chemistry. We report on the synthesis of ketone **2** (R = Me), a late key intermediate in one of the previous routes[1e] to anthramycin, by a new approach which



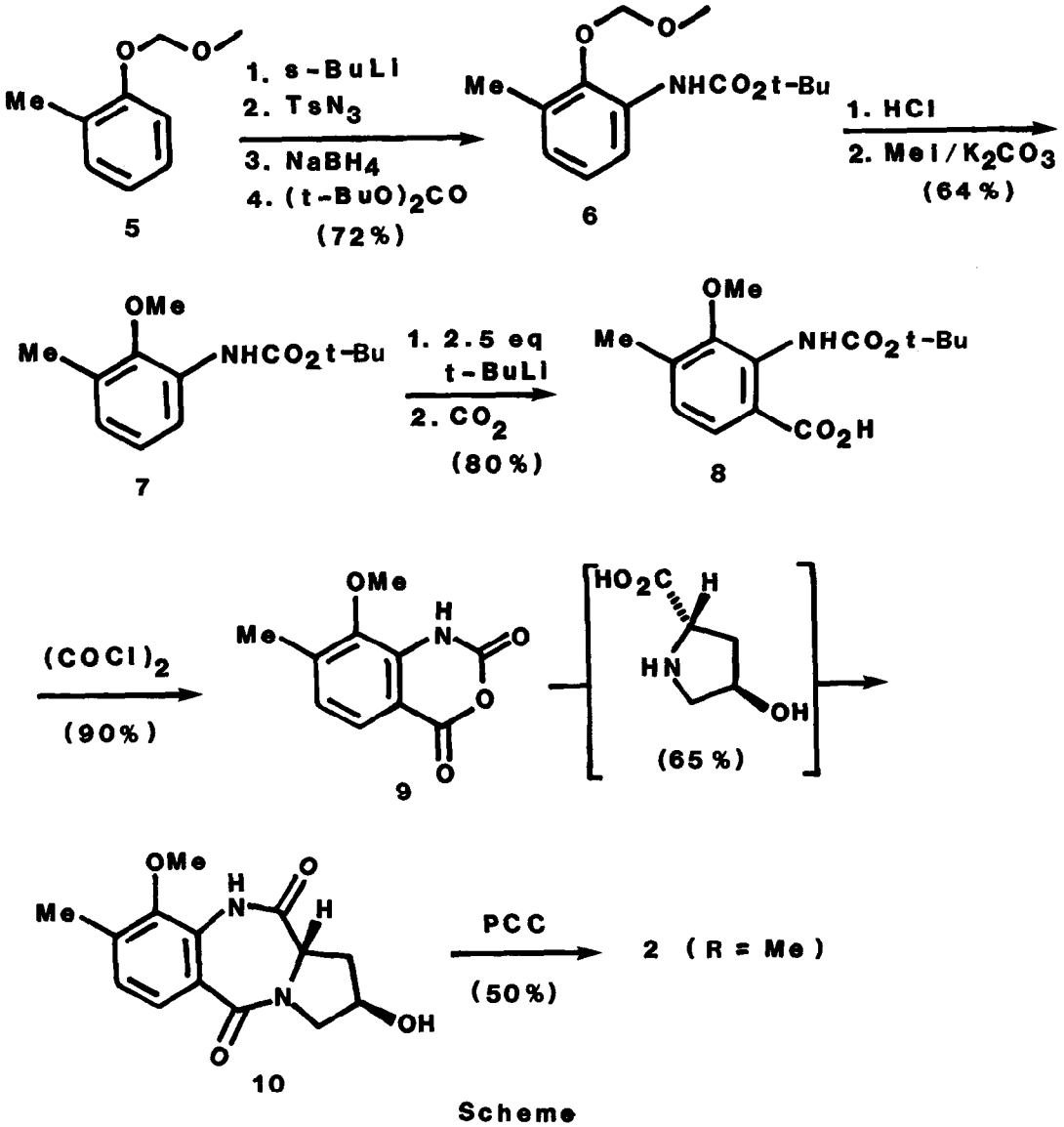
1 **2**

features a) the construction of the contiguously tetrasubstituted benzenoid fragment **3** by sequential directed ortho metalation strategy **(4)**, b) new methodology for the direct conversion of **3** into an isatoic anhydride derivative, and c) coupling[6] of the latter with trans-4-hydroxy-L-proline to arrive at the anthramycin ring skeleton.



The requisite substituted benzene unit **8** **(Scheme)** was assembled starting with o-methyl methoxymethoxybenzene **(5)**. Regiospecific ortho deprotonation of **5** with t-BuLi[7] followed by $^{+}NH_2$ synthon incorporation using the $TsN_3/NaBH_4$ tactic[8] and N-t-butylcarboxylation led to the carbamate **6** in high overall yield. Although **6** appears poised for the second ortho metalation reaction, its treatment with t-BuLi[9] followed by carboxylation gave low yields of desired product due to partial demethoxymethylation under the strongly basic conditions.[10] Therefore, the methoxymethyl was first exchanged for a methyl group without disturbing the $NHCO_2tBu$ functionality (1. 3N HCl/THF(1:1); 2. MeI/K_2CO_3/Acetone). The resulting product **(7)**, when subjected to t-BuLi metalation[9] and carboxylation, smoothly furnished the anthranilic acid derivative **8**. Brief exposure (3 min) of **8** to oxalyl chloride in refluxing benzene afforded the isatoic anhydride **9** in excellent yield. This constitutes a new and potentially general method for the synthesis of substituted isatoic anhydrides[11] based on the NCO_2t-Bu directed ortho metalation group.[9,12]

In an improvement of the literature procedures,[6] **9** was treated with trans-4-hydroxy-L-proline in DMSO to smoothly give the anthramycin **10**. PCC oxidation[13] of **10** provided in unoptomized yield the ketone **2** (R = Me) which was shown to be identical with authentic material by comparison of spectral properties.[14] Since compound **2** (R = Me) has been converted into **2** ($R = CH_2Ph$)[1e] which served as a key intermediate in the original Leimgruber synthesis of anthramycin,[5] the sequence depicted in the **Scheme** constitutes a formal synthesis of this natural product.


Me
O
O
5
1. s-BuLi
2. TsN3
3. NaBH4
4. (t-BuO)2CO
(72%)
NHCO2t-Bu
6
1. HCl
2. MeI/K2CO3
(64%)
OMe
7
1. 2.5 eq
t-BuLi
2. CO2
(80%)
CO2H
8
(COCl)2
(90%)
9
HO2C
H
HN
OH
(65%)
10
PCC
(50%)
2 (R = Me)

Scheme

Aside from presenting the total synthesis of anthramycin [11%) overall yield to **2** (R = Me)] which should also be readily adaptable to the preparation of other members of this class of natural products[1a-c,1f,1g] and analogues,[1b] this work submits a new efficient method for the assemblage of synthon **3** which potentially has broader utility.[15] In addition, by way of the conversion **8** → **9**, it offers a further example[16] of how the directed ortho metalation protocol may be connected to other operations of synthetic value.[17,18]

References and Footnotes

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12. For a related result, see Scherrer, R.A. U.S. Pat. 3, 238, 201; Chem. Abstr. **1966**, 64, 17614c.
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14. **2** (R = Me) showed superimposable IR and ^1H NMR spectra with those provided by Prof. Y. Ban (ref. 1e). Since this compound is a viscous oil, direct comparison of **10** (mp 179-180°C) with an authentic sample (mp 179-180°C) also kindly provided by Prof. Ban was carried out and showed undepressed mixture mp and identical HPLC, IR, and ^1H NMR data.
15. E.g. as benzyne precursors for anthracyclinones: Warrener, R.N.; Russell, R.A.; Marcuccio, S.M. Austr. J. Chem. **1980**, 33, 2777; for actinomycins: Brockmann, H.; Muxfeldt, H. Angew Chem. **1956**, 68, 69; for N-heteroannelation: Walsh, D.A. Synthesis, **1980**, 677; Caluwe, P. Tetrahedron **1980**, 36, 2359.
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17. All new compounds show analytical and spectral (IR, ^1H NMR, MS) data fully consistent with the assigned structures. Reported yields correspond to isolated and purified materials.

18. We are indebted to NSERC Canada for financial support. JNR thanks NSERC for a Graduate Scholarship. We are grateful to Professor Y. Ban for a sample of compound **10** and spectral data of compound **2** (R = Me).

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