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SILICON IN BENZAMIDE DIRECTED ORTHO METALATION REACTIONS
SYNTHESIS OF PERI-METHYL SUBSTITUTED PAHs AND NATURAL ANTHRAQUINONES

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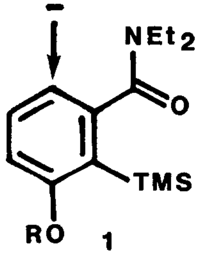
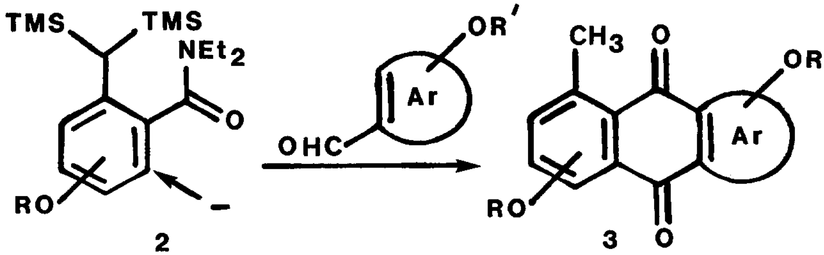
Summary: The α,α-bis(trimethylsilyl)-o-toluamides 4 and 9, systems protected from benzylic deprotonation, are available starting materials for the short syntheses of peri-methyl substituted benz[a]anthraquinones 6a and 6b and desoxyerythrolaccin trimethyl ether 12 respectively.

The recent demonstration[1] of alternate benzamide directed metalation[2] reactivity by silicon protection (1 and 2) expands the utility of this methodology for the syntheses of polysubstituted aromatics. In this Letter, we delineate a potential general strategy 2 → 3 for the construction of peri-methyl substituted polycyclic aromatic hydrocarbon (PAHs) carcinogens[3] and naturally occurring anthraquinones.[4] We illustrate this approach by short and efficient syntheses of benz[a]anthraquinones 6a and 6b and desoxyerythrolaccin trimethyl ether 12. In the accompanying Letter[5], we describe how the above strategy with compounds of the type 1, coupled with F⁻- or Br⁺-induced desilylations achieve similar synthetic advantages.



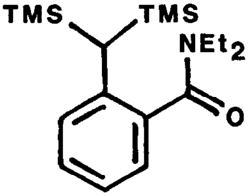
1



2

3

Metalation (*s*-BuLi/TMEDA/THF/-78°C/1h) of the bis-trimethylsilyl *o*-toluamide 4[1] followed by sequential treatment with 2-naphthaldehyde, cesium fluoride (DMF-H_2O/reflux/9h) and TsOH(PhMe/reflux/9h) without purification of intermediates gave the phthalide 5a[6] in 52% yield. Hydrogenolysis ($CuSO_4$ activated Zn/10% NaOH/reflux/24h)[7] followed by Friedel-Crafts cyclization (TFAA/HOAc/RT/9h)[8] and oxidation ($Na_2Cr_2O_7$/HOAc/RT/9h) afforded 11-methyl-7,12-benz[a]anthraquinone 6a in 31% overall yield from 4. By an identical sequence of reactions, but substituting 1-naphthaldehyde for 2-naphthaldehyde, the synthesis of the intermediate phthalide 5b (58%) and thence 8-methyl-7,12-benz[a]anthraquinone 6b was effected in 43% overall yield from 4. The conversion of 6a into the highly carcinogenic 7,11,12-trimethylbenz[a]anthracene has been previously achieved.[9] Analogous methods for the conversion of 6a and 6b into the corresponding PAHs are well documented.[10]



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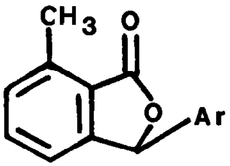
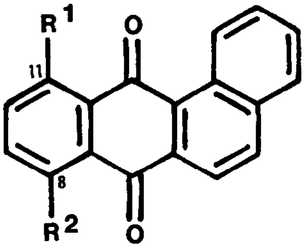


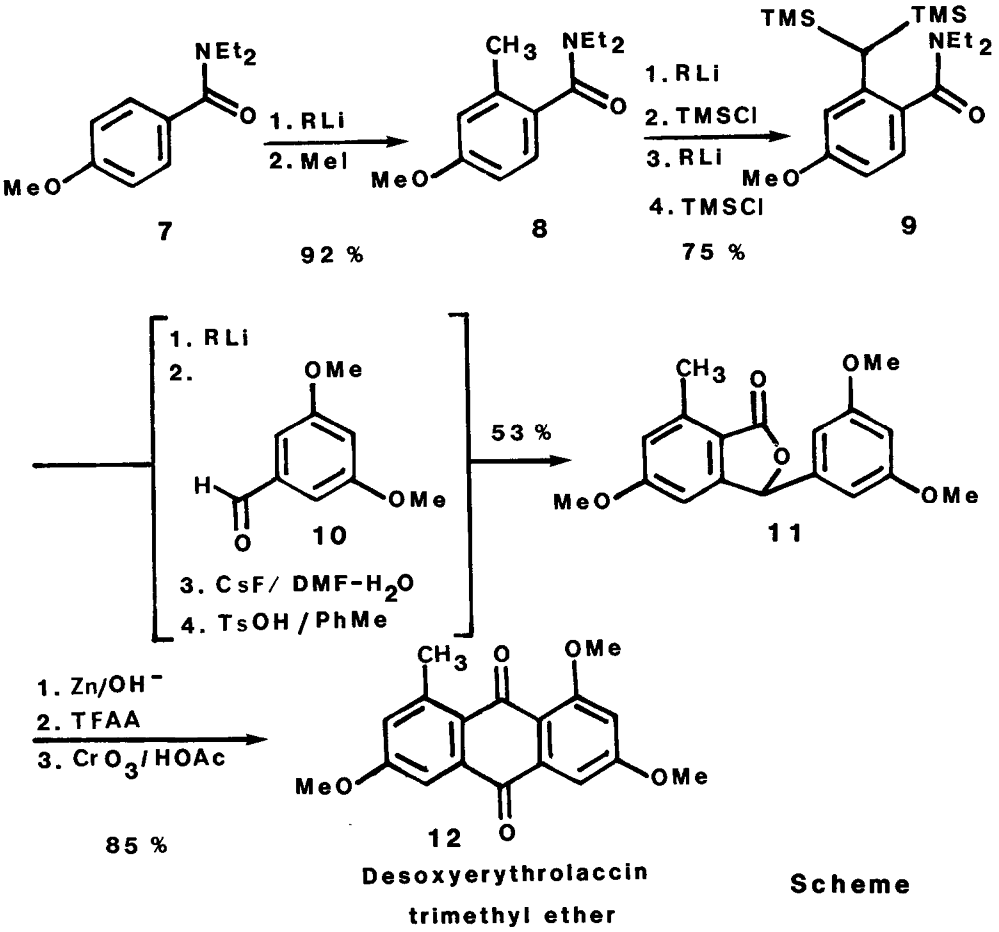
5a Ar = 2-naphthyl
5b Ar = 1-naphthyl



6a R^1 = Me, R^2 = H
6b R^1 = H, R^2 = Me

The synthesis of desoxyerythrolaccin trimethyl ether 12 (Scheme) commences with the introduction of a bistrimethyl methine moiety, 7 → 8 → 9, via the standard methodology.[1] Using similar conditions to those described for the preparation of 5a and 5b, compound 9 was converted into the phthalide 11 using 10 as the aldehyde component.[11] To complete the synthesis, 11 was subjected to hydrogenolysis and cyclization as for 5a and 5b with a variation in the oxidation (CrO_3/HOAc/RT/9h) to afford 12 shown to be identical with authentic material.[12] This constitutes a formal total synthesis of desoxyerythrolaccin since 12 has previously been converted into the natural product.[13]

The high overall yields [6a (31%); 6b (43%); 12 (61%)], and the brevity of these routes should encourage the general use of silicon protection in the context of directed ortho metalation chemistry for the regiospecific preparation of methyl substituted anthraquinones of unnatural and natural origins.[14]



Scheme

References and Footnotes

1. Mills, R.J.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1565.
2. Review: Beak, P.; Snieckus, V. *Accts. Chem. Research* **1982**, *15*, 306.
3. Dipple, A. in Searle, C.E.,ed., "Chemical Carcinogens", ACS Monograph 173, American Chemical Society: Washington, D.C., **1976**; Cooke, M.; Dennis, A.J.; Fisher, G.L., eds. "Polynuclear Aromatic Hydrocarbons: Physical and Biological Chemistry", Battelle Press: Columbus, Ohio, **1982**, pp. 1, 39, 157, 183, 193, 743.
4. Thomson, R.H. "Naturally Occurring Anthraquinones", 2nd ed., Academic Press: New York, **1971**.
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6. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with their assigned structure. Salient spectral features are: **5a**: mp 104°C (Et_2O); ^1H NMR

($CDCl_3$, 400 MHz) δ 2.78 (s, 3H), 6.49 (s, 1H); IR ($CHCl_3$) ν_{max} 1750 cm^{-1}: **5b**: mp 155-156°C (CH_2Cl_2-hexane); ^1H NMR ($CDCl_3$) δ 2.77 (s,3H), 7.20 (s, 1H); IR ($CHCl_3$) ν_{max} 1745 cm^{-1}. **6a**: mp 185-186°C (CH_2Cl_2-Hexane); ^1H NMR ($CDCl_3$) δ2.86 (s, 3H). **6b**: mp 169-171°C ($CHCl_3$); ^1H NMR ($CDCl_3$) δ2.86 (s, 3H). **11**: mp 116-117°C (CH_2Cl_2-Et_2O); ^1H NMR ($CDCl_3$) δ2.68 (s, 3H), 6.14 (s, 1H); IR ($CHCl_3$) ν_{max} 1740 cm^{-1}.

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8. deSilva, S.O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.
9. Newman, M.S.; *J. Org. Chem.* in press. We express our gratitude to Professor Newman for providing a preprint of this paper and a comparison sample of **6a**, with careful notes on handling such compounds.
10. Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.*, **1980**, *102*, 1457.
11. The synthesis of **11** was abbreviated by incorporating an *in situ* preparation of **9** from **8** into an overall 6-step, 3-pot sequence.
12. Mp 205-206°C ($CHCl_3$), mixture mp with a synthetic sample (mp 203-204°C) graciously provided by Professor P. Brassard showed no depression: Brassard, P.; Roberge, G.; *J. Chem. Soc. Perkin Trans I* **1978**, 1041.
13. Brassard, P.; Roberge, G. unpublished results (see Roberge, G. Ph.D. thesis, Université Laval, Quebec, 1980).
14. We thank NSERC of Canada and the Ontario Ministry of the Environment (Air Resources Branch) for financial support.

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