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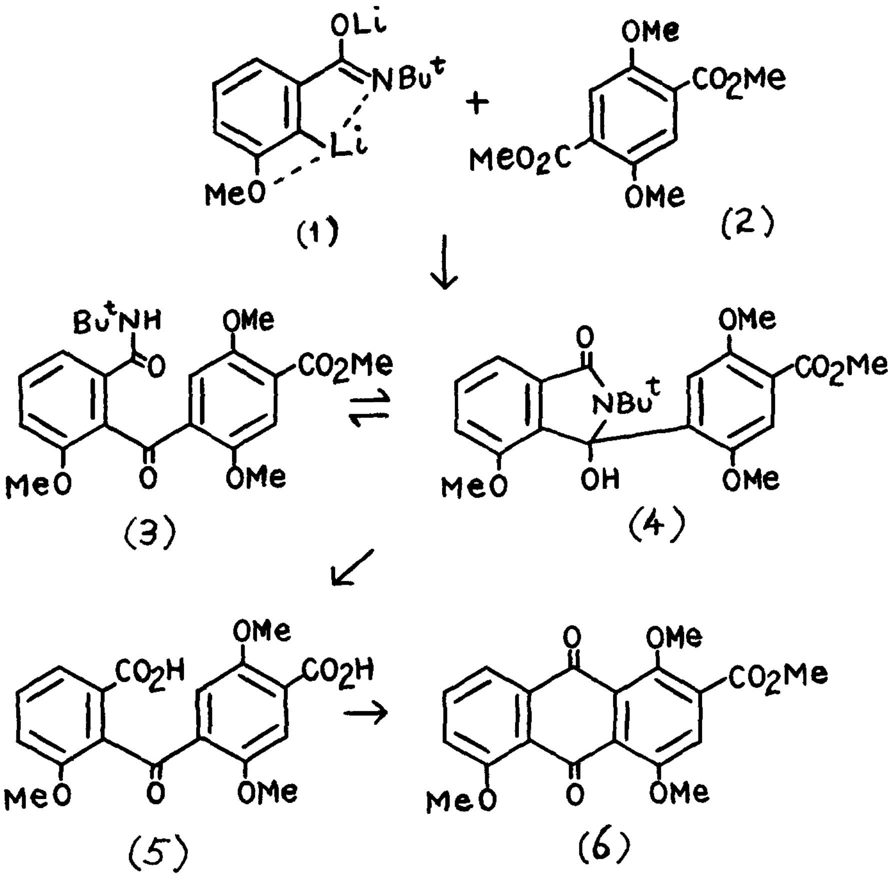
REGIOSELECTIVE SYNTHESIS OF AN ANTHRAQUINONE PRECURSOR OF THE ANTHRACYCLINONES

Ian Forbes, Richard A. Pratt and Ralph A. Raphael*
University Chemical Laboratory, Lensfield Road, Cambridge
CB2 1EW, U.K.

A recent report[1] on the above theme prompts us to record a related series of reactions leading regioselectively to the substituted anthraquinone (6) in which the carbomethoxyl is strategically positioned for unambiguous elaboration to the fourth ring of the aglycones of the anthracycline antibiotics.

Reaction of N-tert. butyl-3-methoxybenzamide in tetrahydrofuran with n-butyl lithium (2 equivs. at -78° for 20 mins. then at -10° for 30 mins; no TMEDA necessary) produced exclusively the dilithio-derivative (1)with regioselective deprotonation of the benzenoid ring between the two substituent groups. This derivative reacted readily with electrophiles such as aldehydes (to give the corresponding phthalides after acidic workup) and with nitriles and esters to give ketoamides. In particular (1) underwent reaction with excess of the dimethoxydiester (2) to give a mixture m.p. 183 - 190° of the ketoamide[2] (3) and its cyclic tautomer[2] (4). Hydrolysis of this mixture with hydrochloric acid (5N) gave the diacid (5).

Cyclisation[3] of the diacid (PPA at 100° for 2 hr. or conc. H_2SO_4 at 100° for 15 mins.) followed by two-stage methylation (diazomethane followed by dimethyl sulphate - potassium carbonate) gave the required anthraquinone ester[2] (6;20% from 3) m.p. 177 - 178°. Further elaboration of (6) is now in hand.



References and Notes

1. J.E. Baldwin and K.W. Bair, Tetrahedron Letters, 1978, 2559.
2. All spectroscopic properties and elemental analysis were consistent with the structure shown.
3. A Hayashi rearrangement is unlikely with the substitution pattern of (5); M.S. Newman, Accounts of Chem. Research, 1972, 5, 354
4. We thank the Science Research Council for support.

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