Synthesis of Spiro-compounds Related to Fredericamycin A

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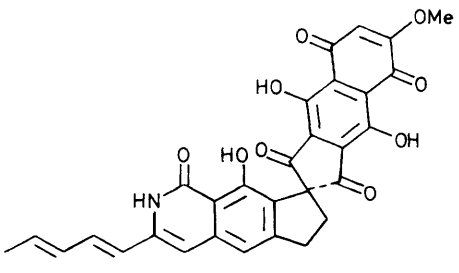
Spiro-compounds [e.g., (**8**), (**13**)] that resemble the four central rings of the antitumour agent fredericamycin A have been synthesized by methods that are based on (i) intramolecular acylation and high-pressure Diels–Alder chemistry [(**5**) → (**8**)] or (ii) radical spiro-cyclization [*e.g.*, (**11**) → (**13**)].

The natural product fredericamycin A[1] has the unusual spiro-structure (**1**) and possesses biological properties[1] that may prove important. In particular, it shows appreciable antitumour activity,[1a,c] although the relationship between its structure and mode of action is unknown. The compound is attracting attention as a synthetic target[2] because its structure is complicated and a total synthesis is likely to afford an opportunity for evaluating the anticancer properties of analogues that lack one or more features of the natural material. We report two methods (Schemes 1 and 2) for constructing the central spiro ring system.

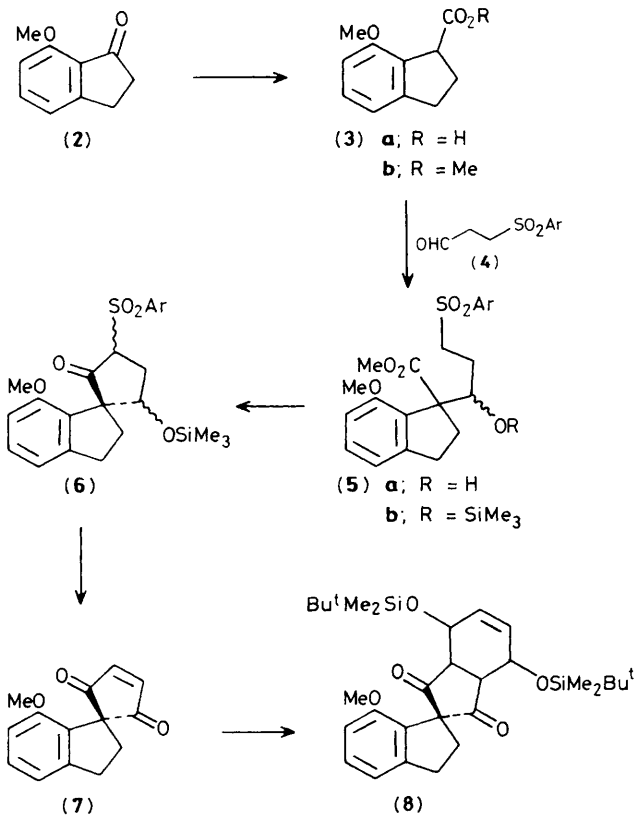
The first approach (Scheme 1) begins with acid (**3a**), easily accessible from 7-methoxyindan-1-one (**2**)[3] by Wittig reaction[4] with (methoxymethylene)triphenylphosphorane, acid hydrolysis (toluene-*p*-sulphonic acid, 1:3 aqueous dioxane, reflux, 14 h), and oxidation[5] (chromic acid, acetone, 0 °C) [>C=O → >C=CH(OMe) → >CHCHO → >CHCO$_2$H; 71% overall]. Methylation (diazomethane) gave the ester (**3b**) (99%), which was deprotonated [lithium di-isopropylamide (LDA) (1.5 equiv.), tetrahydrofuran (THF), −78 °C, 1 h] and treated with 3-(*p*-tolylsulphonyl)propanal (**4**)[6] (1.76 equiv., −78 °C, 30 min; room temp., 15 min). The resulting diastereoisomeric alcohols (**5a**) (78%) were protected by silylation to give (**5b**) [1:1 hexamethyldisilazane–chlorotrimethylsilane, dimethyl sulphoxide (DMSO), room temp., 3 h; 93%] and deprotonated by addition to LDA (2.5 equiv., THF, −78 °C, 1 h; 0 °C, 1 h). The spiro-compound (**6**) was then isolated in 85% yield as a mixture of isomers.[7] Oxidation in acetone at 0 °C with Jones' reagent[5] followed by chromatography (some elimination of toluene-*p*-sulphinic acid occurs) over silica gel (2:1 hexane–ethyl acetate) gave the spiro-enedione (**7**)† directly (88%; m.p. 103.5—105 °C). This substance is not a very reactive dienophile, probably for steric reasons,[8] but, when exposed to the action of (*E*,*E*)-1,4-bis[(t-butyldimethylsilyl)oxy]buta-1,3-diene[9] under high pressure (*ca.* 20 kbar, room temp., 55 h), it was converted into the diastereoisomeric (^{1}H n.m.r.) adducts (**8**) (48%), which are functionalized in a manner that should permit further elaboration into the quinone system of fredericamycin A.

In the second route (Scheme 2), which is not dependent on special (high pressure) apparatus, the acid (**3a**) was deprotonated (LDA, 2.4 equiv., THF, −78 °C, 1 h; +50 °C, 1 h) and

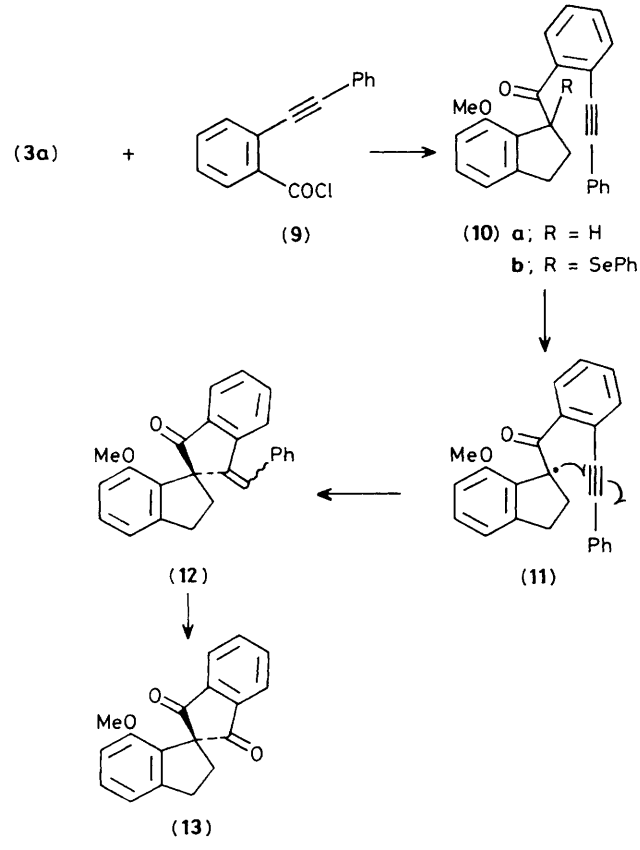


(**1**)

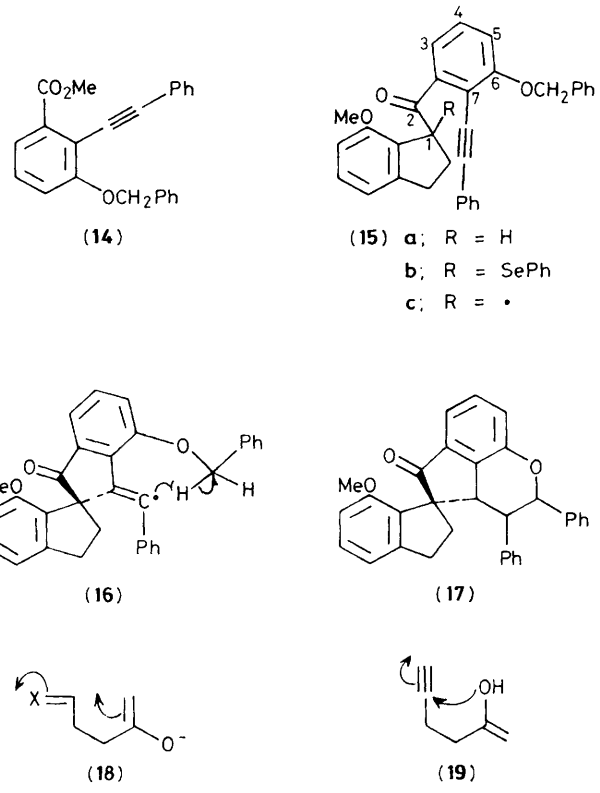
† Satisfactory elemental analyses were obtained. (**7**): Fourier transform i.r. (cast from CCl_4) 2858.0, 1700.5, 1260.0, and 1077.0 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 7.33 (s, 2H), 7.22 (t, *J* 7.75 Hz, 1H), 6.91 (dd, *J* 1.0 and 7.5 Hz, 1H), 6.61 (d, *J* 8.0 Hz, 1H), 3.62 (s, 3H), 3.19 (t, *J* 7.5 Hz, 2H), and 2.34 (t, *J* 7.75 Hz, 2H); ^{13}C n.m.r. ($CDCl_3$, 100.614 MHz) δ 206.0, 155.2, 148.3, 148.0, 130.4, 127.7, 117.5, 108.6, 61.3, 55.3, 34.2, and 32.2; *m/z* 228.0790 (calc. 228.0787). (**13**): Fourier transform i.r. (cast from CCl_4) 1740.0, 1705.4, and 1592.1 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 8.03 (m, 2H), 7.88 (m, 2H), 7.23 (t, *J* 8.0 Hz, 1H), 6.94 (dd, *J* 7.5 and 0.75 Hz, 1H), 6.57 (d, *J* 8.0 Hz, 1H), 3.42 (s, 3H), 3.28 (t, *J* 7.25 Hz, 2H), and 2.46 (t, *J* 7.25 Hz, 2H); ^{13}C n.m.r. ($CDCl_3$, 100.614 MHz) δ 202.8, 155.1, 148.4, 141.8, 135.4, 130.3, 129.3, 123.2, 117.5, 108.6, 64.8. 55.2, 35.0, and 32.6; *m/z* 278.0945 (calc. 278.0943).



Scheme 1. Ar = 4-MeC_6H_4.



Scheme 2



condensed with the acid chloride (**9**)‡ (1.4 equiv., THF, −78 °C, 20 min; 0 °C, 20 min) to afford directly (55%) the ketone (**10a**) that results from decarboxylation of the intermediate β-keto-acid. Phenylselenenylation (LDA, 1.6 equiv., −78 °C, 1 h; phenylselenenyl chloride, 1.7 equiv., −78 °C, 1 h; 0 °C, 15 min) served to generate the (phenylseleno)ketone (**10b**) (76%). Treatment under standard conditions[12] with triphenyltin hydride and a trace of azoisobutyronitrile in refluxing benzene generated radical (**11**) and this species underwent 5-*exo*-digonal cyclization [see (**11**), arrows] to give the *Z*- and *E*-spiro-ketones (**12**) (85%). Ozonolysis ($CHCl_3$, −60 °C; dimethyl sulphide, room temp., 36 h) produced the desired known β-diketone (**13**)[2f] (84%) (m.p. 160—163 °C).†

Radical spiro-cyclization is a general process applicable to compounds more highly substituted than (**10a,b**). For example, double deprotonation of (**3a**) [n-butyl-lithium (2.1 equiv.), THF, 0 °C, 1 h; hexamethylphosphoric triamide (HMPA) (2.1 equiv.), 0 °C, 30 min] and condensation with the ester (**14**)§ (0 °C, 30 min; +50 °C, 2 h) gave (**15a**) (51%), which exists to some extent as an enol. Conversion (81%) into (**15b**) and treatment in the usual way[12] with triphenyltin hydride generated the radical (**15c**), which cyclized: (**15c**) → (**16**). However, the intermediate radical (**16**) rearranged by 1,6-hydrogen transfer [see (**16**), arrows] to yield, after subsequent ring closure, (**17**) as a mixture of two (^1H n.m.r.) isomers (62%).

This intramolecular hydrogen transfer is a very easy process and, even when the stannane reduction of (**15b**) was carried out by adding all the triphenyltin hydride (1.4 equiv.) in one

‡ Prepared by Jones' oxidation (76%) of 2-phenylethynylbenzaldehyde (ref. 10) and treatment with oxalyl chloride (63%). 2-Bromodiphenylacetylene was made by the method of ref. 11.

§ 3-Benzyloxy-2-iodobenzoic acid (ref. 13) was esterified (diazomethane) and coupled (90%) with copper(I) phenylacetylide (*cf.* ref. 11).

portion, as opposed to addition over *ca.* 10 h,[12] (**17**) was again formed (95%).

The synthesis of fredericamycin A by radical cyclization requires that the methodology should be applicable to sterically congested structures. The present experiments [(**10**) → (**13**), (**15**) → (**17**)] establish that this condition is satisfied and that a judicious choice of substituent must be made for C-6 [see (**15**)].¶

Closure of α-keto-*radicals* of type (**11**) needs a further comment; it is clear that this cyclization [see (**11**)] does not encounter the kinetic barrier that inhibits 5-(enol *endo*)-*exo*-trigonal cyclizations of *carbanions* [see (**18**)].[14] Under ionic conditions, simple keto-acetylenes often cyclize through oxygen [*cf.* (**19**)].[15] We have not established, however, if the ease of *carbo*cyclization of (**11**) is a special characteristic of the phenyl-conjugated system or is a general property of flexible and/or non-conjugated α-keto-δ-acetylenic radicals.[16]

We thank the Alberta Heritage Foundation for Medical Research for a Postgraduate Studentship (to S. M. B.), Mr. D. Lucyk, Mr. P. Cumming, and Ms. F. Sartorelli for experimental assistance, and Drs. J. Sedgeworth and B. R. Dent for helpful discussions.

Received, 26th February 1986; Com. 263

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¶ Relocation of the benzyloxy group to C-3 [see (**15**)] is a potential alternative to changing the nature of the protecting group.