Protecting Group Improvement by Isotopic Substitution: Application to the Synthesis of the Quinone System of Fredericamycin A

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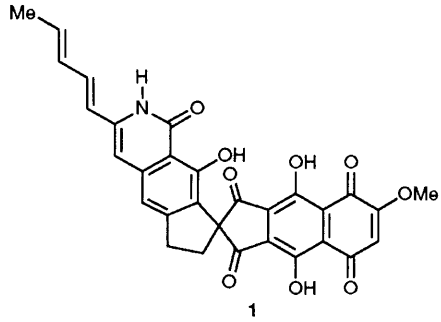
Use of a trideuteriomethoxy group for phenol protection, instead of the classical methoxy group, serves to suppress an unwanted intramolecular hydrogen transfer during a radical cyclization experiment, and leads to a spiro compound of a type that can be converted into the spiro diketone–quinone system of the antitumour agent, fredericamycin A.

During synthetic work[1] related to the antitumour agent, fredericamycin A **1**, the selenide **2** (Scheme 1, R = Me) was treated with triphenyltin hydride in the hope of generating the model compounds **5** (R = Me). Although these were indeed formed [*via* the sequence **2** → **3** → **4** → **5** (R = Me)], the yield was only 48%, the major by-products (41%) being the isomers **7**. This material arises because the intermediate vinyl radical **4** (R = Me) abstracts hydrogen from the adjacent methoxy group, RO (R = Me), to form a new radical **6**, which then undergoes 6-*endo* trigonal cyclization to **7**. The intermediate **6** does not abstract hydrogen directly from the stannane (to any appreciable extent) to give **5**, since treatment of **2** (R = Me) with triphenyltin deuteride gave a deuteriated analogue of **5** (31% yield), in which the deuterium was located only [^{1}H NMR (400 MHz)] on the vinyl carbon (PhCD= instead of PhCH=).†

† In this experiment the major product (42% yield) is that formed by intramolecular hydrogen transfer (*cf.* **7**).

We have found that deuterium isotope effects can be used to suppress the undesired pathway **4** → **6**, and the selenide **2** (R = CD_3) gives the required spirocycles **5** (R = CD_3) in ≥70% yield when treated under our standard conditions[1] with triphenyltin hydride. The ratio of **5** (R = CD_3) to the



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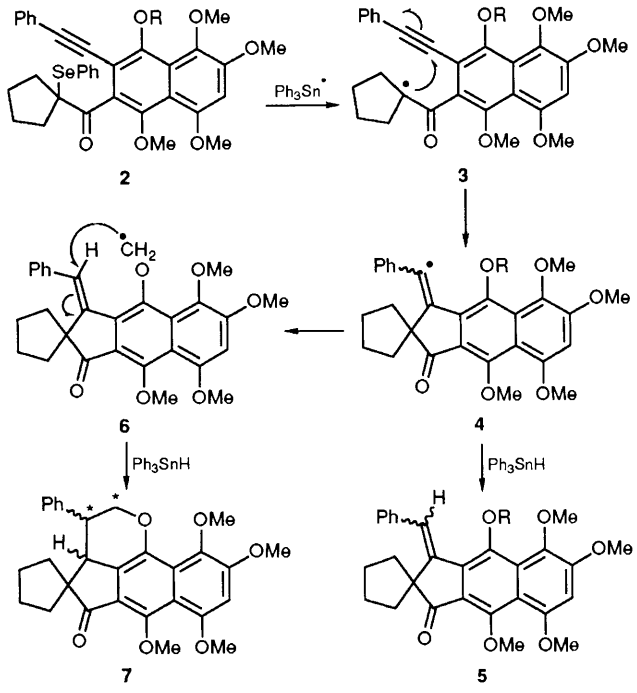
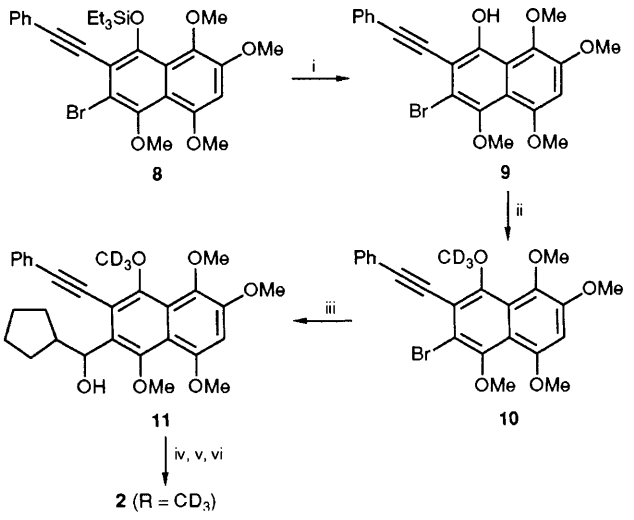


Scheme 1



Scheme 2 *Reagents and conditions*: i, tetrabutylammonium fluoride, AcOH, tetrahydrofuran (THF), room temp., 30 min, 96%; ii, CD_3OTs, NaH, *N,N'*-dimethylformamide (DMF), room temp., 2.5 h, 82%; iii, Bu^nLi, THF, −78 °C, 5 min, then cyclopentanecarbaldehyde, −78 °C, 20 min, 87%; iv, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dioxane, 100 °C, overnight, 60%; v, $Me_3SiOSO_2CF_3$, Et_3N, CH_2Cl_2, 0 °C, 2 h, 88%; vi, PhSeCl, THF, −78 °C, 1 h, then room temp., 2 h, 91%

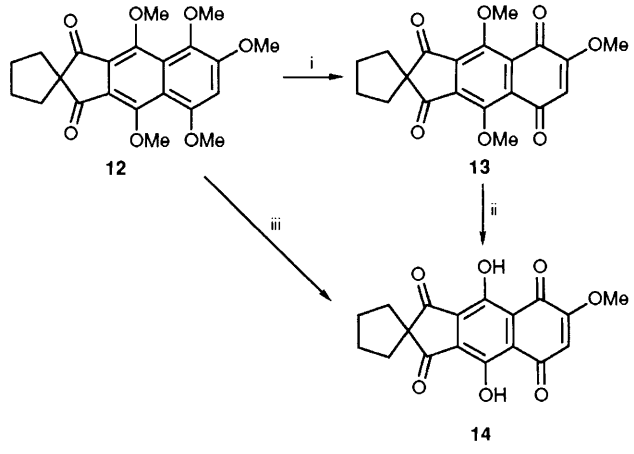
undesired product‡ is now 9.7:1 as opposed to 1.15:1 to 1.40:1§ in the absence of deuterium. As far as we are aware, isotopic modification of a protecting group (here *O*-methyl) has not been used before in synthetic radical chemistry, and the standard compendium[2] on protecting groups makes no mention of such a technique. Deuteriated protecting groups have, however, been used to simplify NMR spectra.[3]

The route we had used[1] to prepare compound **2** (R = Me) involved the silyl ether **8** (see Scheme 2) and, as shown in Scheme 2, this compound happened to be ideally constituted to try the isotopic replacement. The synthesis of **2** (R = CD_3) closely follows our earlier route[1] but requires trideuteriomethyl tosylate[4] in the final alkylation **9** → **10** instead of dimethyl sulfate.

Although intramolecular hydrogen transfer can be put to good use in the area of radical chemistry,[5] it can sometimes be a nuisance, and the present work illustrates a method for suppressing the transfer.

In the context of our planned synthetic studies, it now became worthwhile to examine methods for converting the spiroketones **5** (Scheme 1, R = CD_3 or Me) into quinone **14** (see Scheme 3).¶ This substance represents four contiguous rings of fredericamycin A.

Compounds **5** (R = Me) were degraded as before[1] into diketone **12**, and treatment of **12** with ceric ammonium nitrate served, as expected,[6,7] to oxidize (84%) ring A **12** → **13**.‖ Further treatment with an excess of boron tribromide at −78 °C resulted in selective deprotection (89%), the target



Scheme 3 *Reagents and conditions*: i, $Ce(NO_3)_3{\cdot}6H_2O$, MeCN, H_2O, room temp., 10 min, 84%; ii, BBr_3, CH_2Cl_2, −78 °C, 20 min, 89%; iii, BBr_3, CH_2Cl_2, −78 °C, 20 min; $CHCl_3$–HCl, room temp., air, 2 h, 75%

14[8]** being obtained as a red, crystalline substance, m.p. 247–249 °C. The same compound could be made directly (75%) from the pentamethoxy diketone **12** by treatment with boron tribromide (at −78 °C) and then with hydrochloric acid (at room temperature). The residual methoxy group in **14** is inert to boron tribromide at low temperature.[9] The ^1H and ^{13}C NMR spectra of **14**†† in deuteriochloroform show all the signals corresponding to the indicated structure but, in this preliminary work, we have not run the spectra under conditions where the results for fredericamycin A itself are sensitive to the solvent[10] and the presence or absence of oxygen.[11]

‡ This is a mixture of stereoisomers and corresponds to **7** with deuterium at the starred atoms.

§ The ratios varied from run to run: 1.51:1 [89% yield of **5** (R = Me) and **7**]; 1.31:1 (81%); 1.40:1 (85%).

¶ Scheme 3 shows the most efficient of the methods that we examined. We confirmed the location of the methoxy group by chemical means and also (see later) spectroscopically: reduction of quinone **13** ($Na_2S_2O_4$), acetylation, oxidation [$Ce(NO_3)_3{\cdot}6H_2O$], and hydrolysis of the acetate groups (LiOH) gave compound **14** in poor yield.

‖ The vinyl hydrogen of **13** had δ_H 6.10 ppm.

** The vinyl hydrogen of **14** had δ_H 6.30 ppm.

†† The tautomer shown is an arbitrary assignment. Irradiation of the ^1H NMR signal due to the vinyl hydrogen causes an enhancement of 14% in the intensity of the signal due to the methoxy group.

All new compounds were characterized by spectroscopic methods, including combustion analytical and/or high resolution mass spectra data.

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