Total Synthesis of (±)-Fredericamycin A. Use of Radical Spirocyclization

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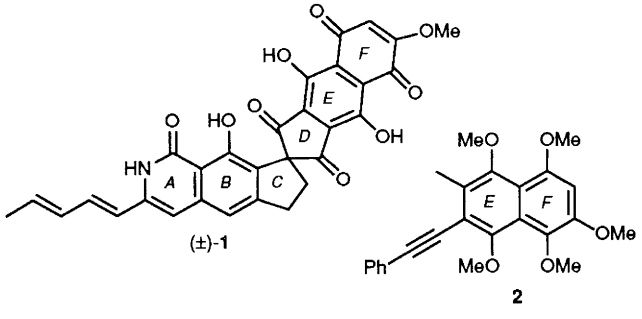
(±)-Fredericamycin A **1** is synthesized using 5-*exo*-digonal radical closure of selenide **15** (Scheme 2), and an unusual procedure for both selective demethylation of the advanced intermediate **22** and adjustment of the stereochemistry in the pentadienyl side chain.

We report the synthesis of crystalline (±)-fredericamycin A (**1**). The natural material, which is an optically active metabolite of *Streptomyces griseus*,[1] has powerful antitumour properties,[2] and many studies have been directed at its synthesis.[3,4] Our approach involves making the spirocyclic framework by 5-*exo*-digonal radical closure[6] (**16**→**17**, Scheme 2), the required radical being generated from a precursor (**14**, Scheme 2) that is assembled from two components—bromonaphthalene **2** and aldehyde **12** (Scheme 1). Fredericamycin A has one methoxy substituent (see **1**), and in any attempted synthesis much would depend on the choice of protecting groups for the other oxygens. We decided to make extensive use of *O*-methyl ethers in the first instance, as such experiments (see Scheme 2) would largely expose the nature of the synthetic problems to be overcome; we would then repeat the work with better protecting groups if selective demethylation,[7] or total deprotection, followed by monomethylation,[8] should prove impossible.[7,9]

The pentamethoxy bromide **2** was prepared along lines already reported,[5] but with some technical improvements, while the other component **12**, was made from **3**[10] as summarized in Scheme 1.

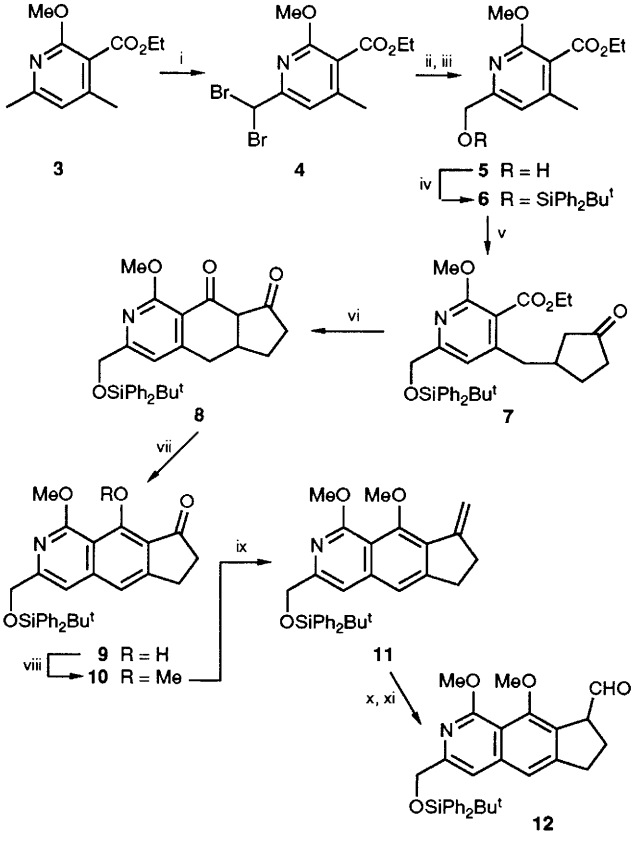
Condensation of **12** with the carbanion derived from bromide **2** (by halogen–metal exchange with BuLi) gave (THF, −78 °C, 45 min) alcohol **13** (68%) as a single isomer (Scheme 2). Oxidation (Ph_3BiCO_3)[11] took the route as far as ketone **14**, and phenylselenenylation yielded the radical precursor **15**. From this point, the α-keto radical[12] **16** was best generated at room temperature with Ph_3SnH in the presence of Et_3B and air.[13] The radical underwent 5-*exo*-digonal closure and we isolated (≥50%)[7] the spirocyclic compound **17** as a single isomer† whose stereochemistry was not established.

Vicinal hydroxylation, **17**→**18**, could be achieved (97%) with an excess of OsO_4 in pyridine, and diol cleavage, **18**→**19**, was then effected with $Pb(OAc)_4$. At this stage we were ready to construct the pentadienyl side chain and, to prepare for that, the spiro diketone was desilylated and oxidized, **19**→**20**→**21**. Wittig reaction, preferably with (*E*)-(but-2-enyl)methyldiphenylphosphonium iodide[14] and $(Me_3Si)_2NK$, gave **22** as a mixture of geometrical isomers, whose proportions could be altered by exposure to laboratory lighting or to iodine (and, possibly, also to acid), although the changes are not synthetically useful.



† We did not examine the reaction mixture for products derived (see ref. 7) from intramolecular hydrogen abstraction by the intermediate vinyl radical.

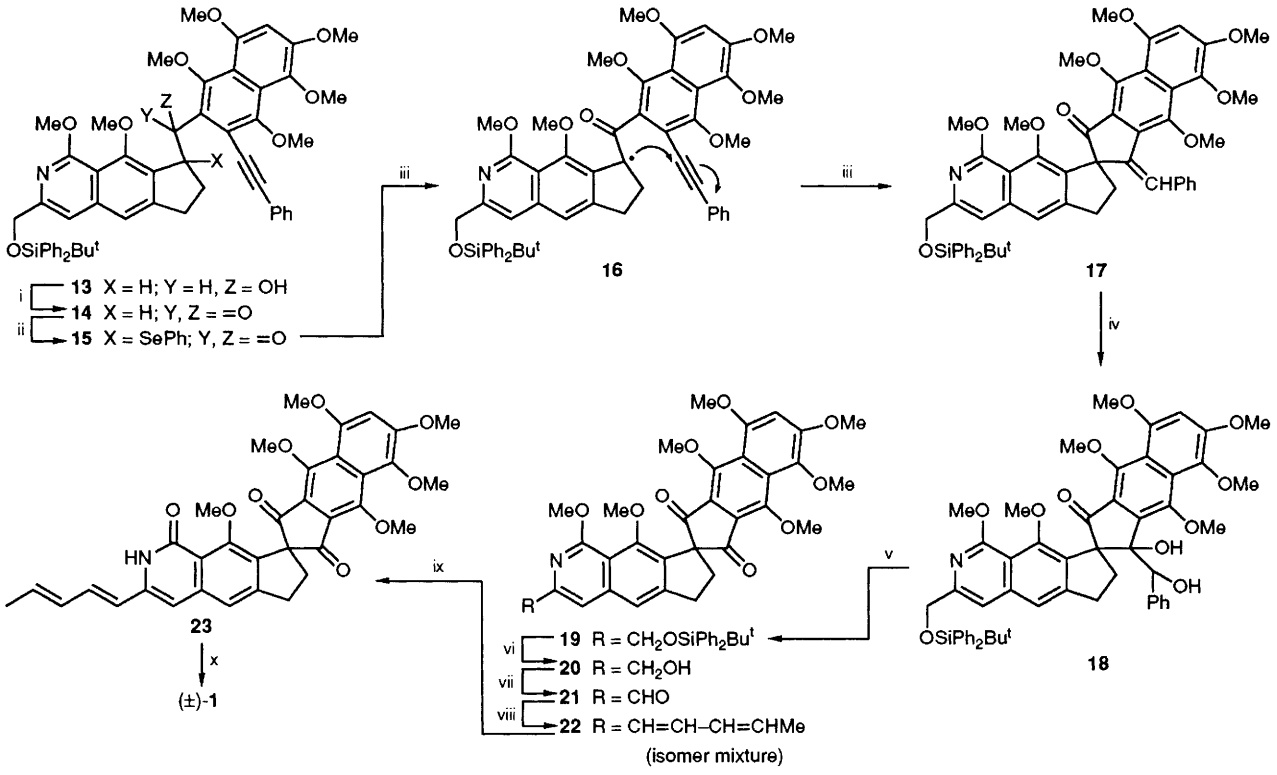
Adjustment of the diene geometry in **22** and removal of six of the seven *O*-methyl groups were closely linked problems that were handled as follows: Reaction of alkene mixture **22** with an excess of Me_3SiCl and NaI[15] served to deprotect ring *A* (and only ring *A*), and to isomerize‡ the diene system, giving **23** (61% from **22**) with the desired *E*,*E* geometry. Compound **23** is isomerized in light, but this tendency is not shared, at least to such a significant degree, by fredericamycin A itself. Lastly, treatment of **23** with an excess of BBr_3,§[7] followed by mild hydrolysis[16] in the presence of air (and in the



Scheme 1 *Reagents and conditions*: i, 2 NBS, CCl_4, *hν*, heat; ii, aq $AgNO_3$, EtOH, 70 °C, 0.5 h; iii, $NaBH_4$, EtOH, room temp. (60% from **3**); iv, Bu^tPh_2SiCl, DMAP, CH_2Cl_2, room temp., 12 h (76%); v, (a) LDA, THF; (b) 2-cyclopentenone, −78 °C, 0.5 h (85%); vi, EtOH, NaH, 0 °C, 3 h; vii, DDQ, PhH, room temp., 1.5 h; viii, MeOH, Ph_3P, EtOOC–N=N–CO_2Et, THF, −78 °C to room temp., 12 h (64% from **7** without isolation of intermediates); ix, $Ph_3P{=}CH_2$, dioxane, room temp., 0.5 h (94%); x, $BH_3{\cdot}SMe_2$, THF, 0 °C, 0.5 h; 30% H_2O_2, NaOH, room temp., 1 h (92%); xi, Swern oxidation, CH_2Cl_2, −78 °C to room temp., 0.5 h (86%); NBS = *N*-bromosuccinimide, LDA = lithium diisopropylamide, THF = tetrahydrofuran, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

‡ Iodine is liberated in the reaction, which is done without protection from light. The stage at which isomerization occurs was not established.

§ Treatment of **22** with BBr_3 did not appear to remove the methyl groups on rings *A* and *B*.



Scheme 2 *Reagents and conditions:* i, Ph_3BiCO_3, PhMe, 80 °C, 48 h (80%); ii, LDA, THF, −78 °C; BuLi; PhSeCl, −78 °C, *ca.* 1 min (70%); iii, Ph_3SnH, Et_3B, air, 4:1 PhH–hexane, *ca.* 10 min (≥50%); iv, OsO_4, pyridine, room temp., 3.5 h (97%); v, $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0 °C, 0.5 h (86%); vi, Bu_4NF, THF, room temp., 2 h (80%); vii, MnO_2, Et_2O, room temp., 1 h (77%), viii, $(Me_3Si)_2NK$, (*E*)-(but-2-enyl)methyldiphenylphosphonium iodide, THF, −78 °C, 10 min (88%); ix, Me_3SiCl, NaI, 1:1 CH_2Cl_2–MeCN, room temp., 1 h (61%); x, BBr_3, CH_2Cl_2, −78 °C, 1 h; 3:1 THF–H_2O, room temp., 72 h (64% overall)

light), gave (±)-fredericamycin A as dark-red crystals¶ (64%, after chromatography and crystallization from 1:1:trace $CHCl_3$–MeOH–AcOH), indistinguishable [^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100.64 MHz, $CDCl_3$), FABMS, TLC (silica, 87:3:3 $CHCl_3$–MeOH–AcOH; RP-18 silica, 70:30:1 MeOH–H_2O–AcOH] from a sample of the natural product.

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¶ The crystals darken but do not melt <360 °C.