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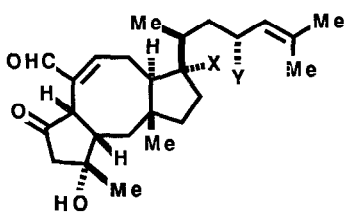
SYNTHETIC STUDIES ON OPHIOBOLINS

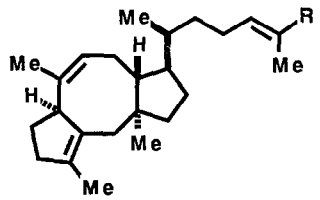
Michael Rowley and Yoshito Kishi*
Department of Chemistry, Harvard University,
12 Oxford St., Cambridge, Massachusetts 02138, USA

Summary: The tricyclic ketone **14**, an ophiobolin analogue lacking only the C-ring side chain, was synthesized in optically active form; the key step was the intramolecular $NiCl_2/CrCl_2$ mediated coupling of **10** to yield **11**.

Ophiobolins (e.g. **1a-c**)[1] and ceroplastols (e.g. **2a-b**),[2] tricyclic sesterterpenes isolated from fungi and insects respectively, have received much synthetic attention, due to their biological activity[3] and interesting molecular architecture. A number of approaches to these molecules has appeared in the literature,[4] but only one total synthesis has been recorded to date; Kato and Takeshita[5] recently reported a synthesis of albolic acid and ceroplastol II, in which the two five membered rings were joined by $CrCl_2$ mediated coupling of an allylic chloride with an aldehyde and the eight membered ring was formed by the McMurry coupling of a dialdehyde. In this communication we would like to outline our approach to the synthesis of the 5-8-5 ring system contained in these natural products and the development of the functionality and stereochemistry present in ophiobolins A-C.

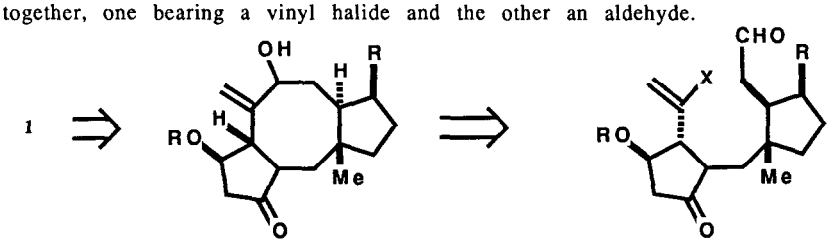


1a X=Y=O Ophiobolin A
b X=OH, Y=H Ophiobolin B
c X=Y=H Ophiobolin C

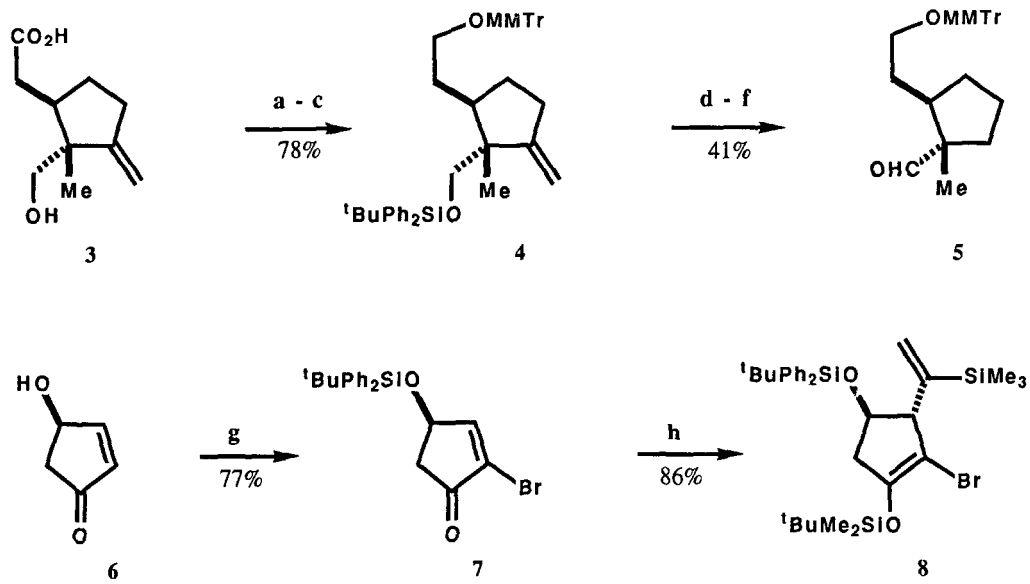


2a $R=CH_2OH$ Ceroplastol II
b $R=CO_2H$ Albolic acid

We envisaged that the eight membered ring could be formed directly by the intramolecular coupling of a vinyl halide with an aldehyde mediated by $NiCl_2/CrCl_2$.[5] Although this coupling has been used in an intermolecular sense on a number of occasions, we believe that this is the first time it has been used intramolecularly. To test this coupling, we needed a system with two five membered rings joined together, one bearing a vinyl halide and the other an aldehyde.



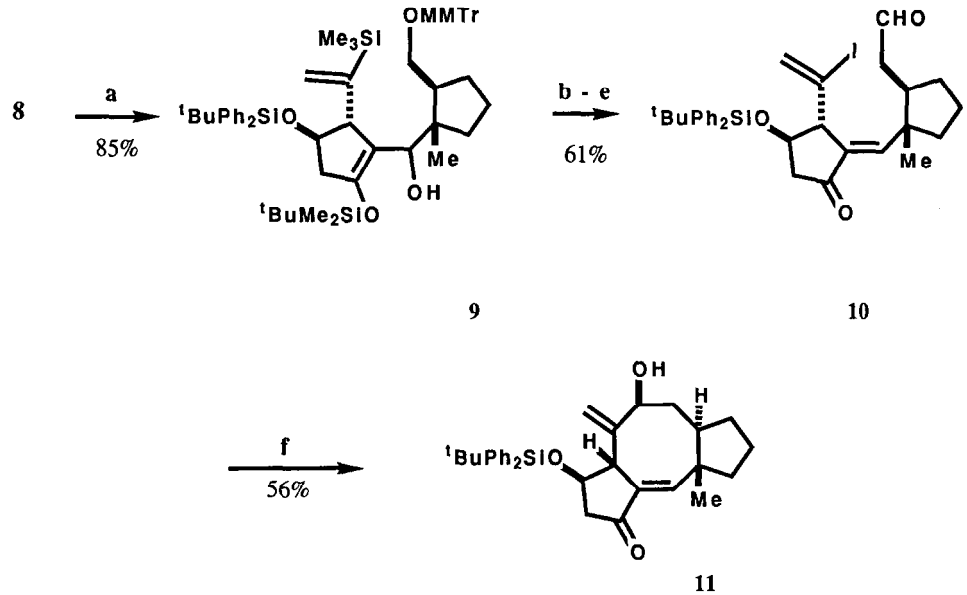
Our synthesis starts with the hydroxy acid **3**,[7] derived in 4 steps from 3-*endo*-bromocamphor, and (*R*)-4-hydroxycylopentenone (**6**),[8] available in 91% e.e. from D-(-)-tartaric acid. Protection of the hydroxyl group in **3** as a *t*-butyldiphenylsilyl ether (with concomitant esterification of the acid), followed by reduction and treatment with *p*-anisyldiphenylmethyl chloride (MMTrCl) and base, gave the differentially protected diol **4**. The 'extra' methylene was removed by a three step procedure; ozonolysis with reductive work-up gave a mixture of secondary alcohols which were treated with thiocarbonyldiimidazole, then reduced with tributyltin hydride under free radical conditions. Removal of the silicon protecting group and oxidation gave the aldehyde **5**.



Reagents: **a**. *t*-BuPh2SiCl/AgNO3/pyridine **b**. LiAlH4 **c**. MMTrCl/Et(*i*-Pr)2N **d**. i. O3 ii. NaBH4 iii. Thiocarbonyldiimidazole iv. Bu3SnH/AIBN **e**. TBAF **f**. Swern oxidation **g**. i. *t*-BuPh2SiCl/AgNO3/pyridine ii. Br2 iii. Et3N **h**. i. [Me3SiC(CH2)CuC≡CPr]Li ii. *t*-BuMe2SiOTf

Protection of the hydroxyl group in **6**, followed by bromination-dehydrobromination, gave the vinyl bromide **7**. Our original plan was to protect this ketone as an acetal; however, under no conditions could we do this satisfactorily. Instead, we performed a Michael addition using a cuprate derived from α-trimethylsilylvinyllithium and trapped the enolate as its silyl enol ether **8**. The stereoselectivity of this addition is approximately 20:1, as judged by ^{1}H NMR. The relative stereochemistry was proved by an NOE experiment on a later compound.

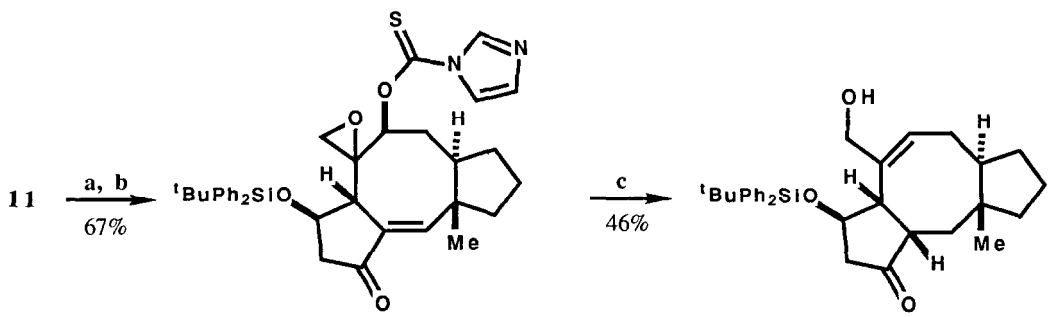
Coupling of fragments **5** and **8** proceeded smoothly; treatment of the vinyl bromide **8** with two equivalents of *t*-butyllithium, followed by the aldehyde **5**, gave the vinylogous hemiacetal **9**. This could be hydrolyzed with hydrofluoric acid to the *E*-enone, iododesilated[9] by treatment with iodine monochloride then acidic tetrabutylammonium fluoride (TBAF), deprotected, and oxidized to the aldehyde **10**.



Reagents: **a**. *t*-BuLi, then addition of **5** **b**. HF **c**. i. ICl ii. TBAF/HF **d**. MeOH/*p*-TsOH
e. Swern oxidation **f**. $NiCl_2$(1%)-$CrCl_2$/DMS(1%)-DMSO

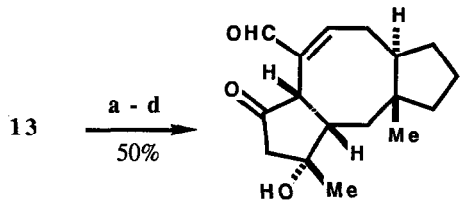
Treatment of this vinyl iodide-aldehyde with an excess of chromium(II) chloride containing 1% nickel(II) chloride in a mixture of DMSO and dimethylsulfide (DMS) gave the cyclized product **11** as a single diastereoisomer in 56% yield.[10]

In order to set up the functionality present in ophiobolin C, we now had to transpose the allylic alcohol and reduce the enone double bond. The allylic transposition was performed by the method of Barton and Motherwell.[11] Epoxidation of the allylic alcohol and treatment with thiocarbonyldiimidazole gave the imidazolide **12**. Brief treatment of **12** with tributyltin hydride under free radical conditions gave the desired transposed alcohol, but longer reaction times also resulted in reduction of the enone double bond,[12] giving the ketone **13** with the desired *cis* ring fused stereochemistry. This stereochemistry, and that of the chiral center introduced in the Michael addition, was proved by an NOE experiment; irradiation of the angular methyl group gave NOE's to both A-B ring juncture protons, proving the relative stereochemistry at both centers.



Reagents: **a**. *t*-BuOOH/$VO(acac)_2$ **b**. Thiocarbonyldiimidazole **c**. Bu_3SnH/AIBN

Finally, we added methyl magnesium bromide to the ketone, having protected the primary alcohol as its *t*-butyldimethylsilyl ether.[13] This gave us a single tertiary alcohol whose stereochemistry was proved to be that of the desired compound by an NOE experiment on the final product. Deprotection of both alcohols and oxidation gave the tricyclic ketone **14**, which contains all the functionality present on the ring system of ophiobolins A-C, lacking simply the C-ring side chain.[14] Studies towards the total synthesis of ophiobolin C continue in this laboratory.



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Reagents: **a**. *t*-BuMe$_2$SiCl/imidazole **b**. MeMgBr **c**. TBAF **d**. Swern oxidation

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References and Notes

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10. The relative stereochemistry of the new chiral center, whilst not important for the synthesis, was determined by an NOE experiment on a compound not described herein.
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13. If this protection is not performed, a good deal of elimination of the β-silyloxy ketone occurs, presumably as the alkoxide formed can deprotonate the ketone.
14. The spectra (^{1}H and ^{13}C NMR, IR, UV) of **14** are strikingly similar to those of natural ophiobolin C.

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