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AN EXAMPLE OF OVERRIDING CYANATION DURING REACTION OF A PRIMARY ALCOHOL WITH *o*-NITROPHENYL SELENOCYANATE‡

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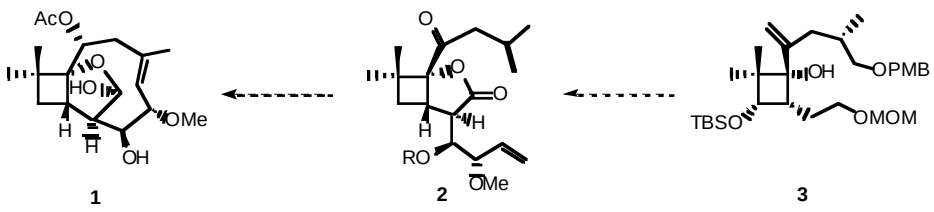
Abstract – The first example of a nitrile as the end product of a Mitsunobu substitution involving *o*-nitrophenyl selenocyanate and tributylphosphine is reported. Neighboring group participation operates and leads favorably to competitive formation of a 2-cyanotetrahydrofuran.

We recently described a useful variant of the zirconocene-promoted vinylfuranoside ring contraction[1] wherein an asymmetric route to highly-functionalized cyclobutanes was realized.[2] The objective of this study was to explore the possibility of extending this unique chemistry to the synthesis of pestalotiopsin A (**1**).[3,4] We envisioned that the successful early construction of intermediate (**3**)[5] might provide a workable pathway via **2** ultimately to this bioactive target (Scheme 1).

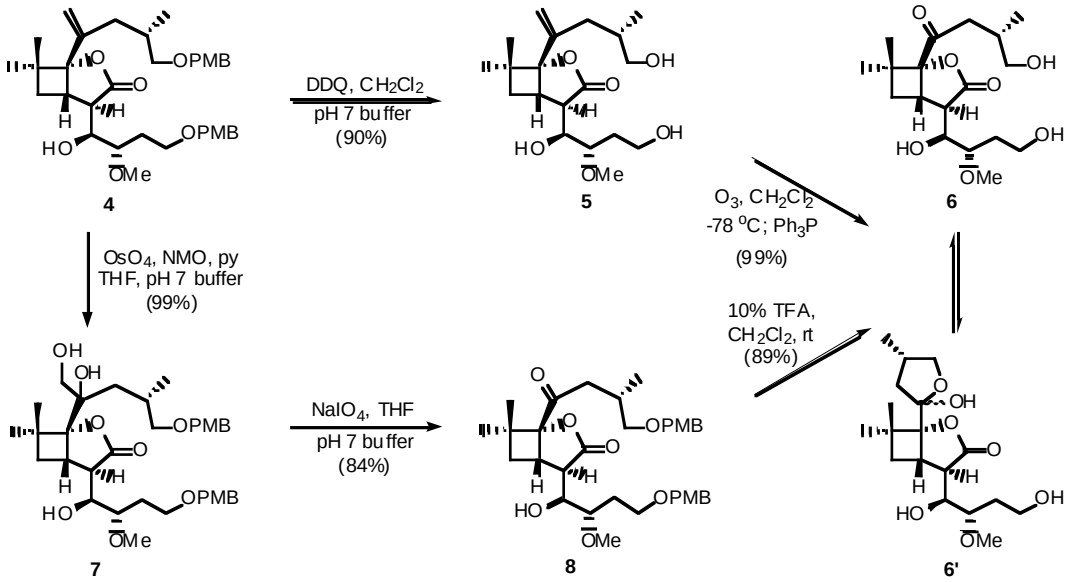
Scheme 1



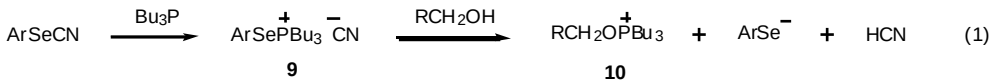
‡ This paper is dedicated to Professor Yoshito Kishi, a friend and colleague responsible for many elegant accomplishments in synthetic organic chemistry.

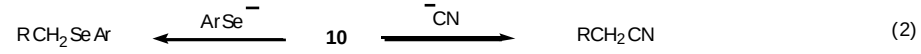
In order to test the feasibility of this concept, **3** was transformed over several steps into hydroxy lactone (**4**).[6] The unreactivity of the hydroxyl functionality in **4** was soon recognized. This inertness, which is attributed to the heightened level of steric congestion in the proximate vicinity, caused us not to be concerned with a protection strategy en route to **6** (Scheme 2).

Scheme 2



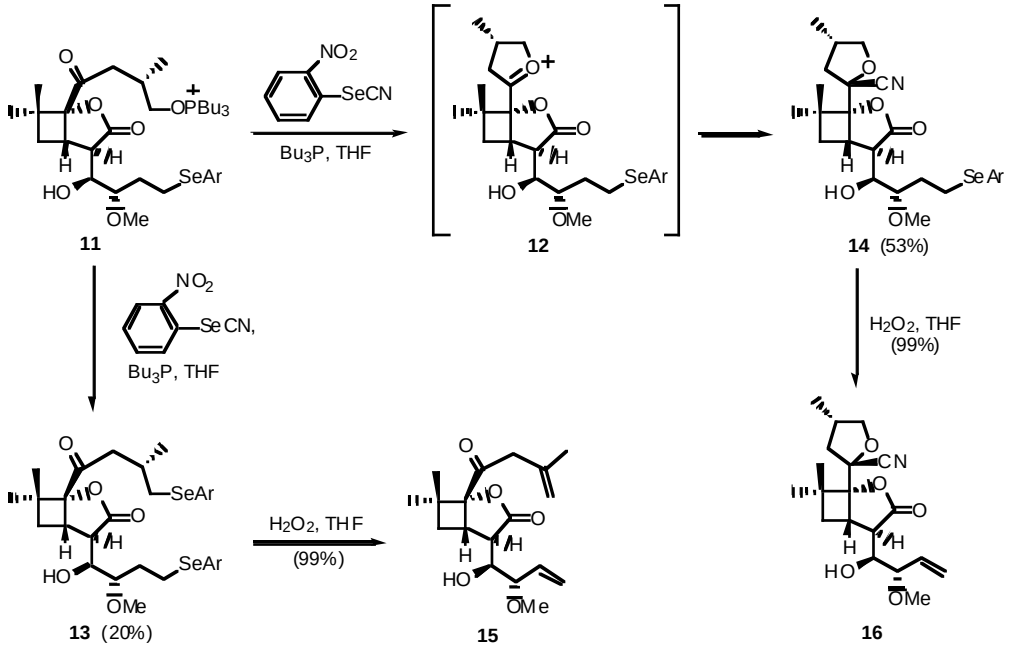
The shorter of two pathways from **4** to this triol entailed removal of the pair of PMB groups to provide **5** and subsequent ozonolytic cleavage of its double bond. Alternatively, application of the Johnson-Lemieux protocol resulted in arrival at keto lactone (**8**) in advance of the dual deprotection step.[7] The availability of **6**, whose complex ^{1}H NMR spectrum indicated the existence of an equilibrium with **6'**, was projected to allow serial application of the Mitsunobu aryl selenylation with *o*-nitrophenyl selenocyanate (5.0 equiv) and tributylphosphine (5.0 equiv), and subsequent Grieco olefination upon exposure to hydrogen peroxide.[8] The first of these steps relies on the transient intervention of intermediates generalized by **9** and **10** (Eq. 1). In light of the high nucleophilicity of selenium anions in S_N2 reactions of primary oxaphosphonium salts such as **10**, alkyl aryl selenides have been isolated uniquely from these reactions in high yield (Eq. 2).[9] In the specific case of **11**, however, activation of the "upper" CH_2OH group in this manner is met with competitive neighboring group participation, giving rise to oxonium ion (**12**). Subsequent nucleophilic attack by the sterically less demanding cyanide ion leads to **14** as the major end product.[10,11]





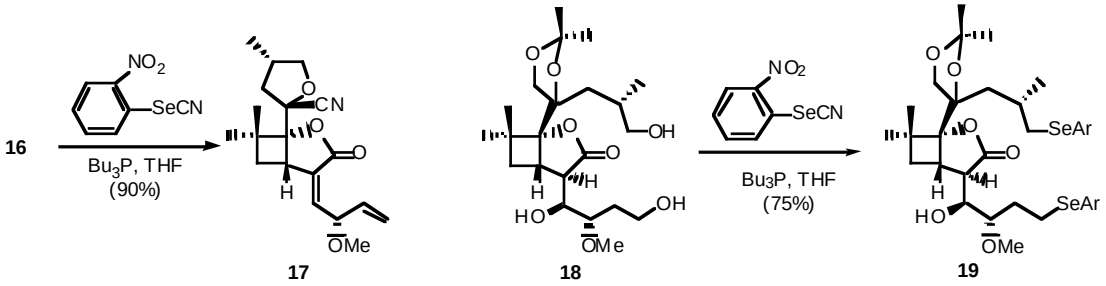
The *R*-configurational assignment accorded the newly introduced anomeric center in **14** and its congeners is based on the anticipated lower enthalpy arising from the endo-anomeric effect, in addition to dipole moment and steric considerations.[12]

Scheme 3



Selenoxide eliminations applied to **13** and **14** led to **15** and **16**, respectively. Once the terminal double bond had been introduced as in **16,** the remaining hydroxyl group participates readily in a spontaneous elimination reaction to deliver **17** (Scheme 4). Also, the unprecedented diversion associated with the formation of nitrile (**14**) can be redirected simply by making alternate recourse to acetonide (**18**). Its efficient conversion to **19** provides added support for the likely intervention of oxonium ion (**12**). This mechanistic pathway may serve as the basis of a cyclizative synthetic approach to 2-cyanotetrahydrofurans.[13]

Scheme 4



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9. For recent examples, consult: (a) T. Yoshimitsu, S. Sasaki, Y. Arano, and H. Nagaoka, *J. Org. Chem.*, 2004, **69**, 9262. (b) M. Uyanik, H. Ishibashi, K. Ishihara, and H. Yamamoto, *Org. Lett.*, 2005, **7**, 1601.
10. The Mitsunobu aryl selenylation of **6** likely proceeds via the hydroxy ketone form because the significant steric shielding present in **6'** is expected to preclude activation by tributylphosphine.
11. A referee has offered an alternative mechanism for consideration. In this view, CN anion attacks stereoselectively the keto carbonyl in the oxophosphonium intermediate (**11**), which follows an internal attack of the resulting oxy anion on the terminal methylene bearing the oxophosphonium group leading to **14**. However, in our opinion, intramolecular neighboring group participation should be kinetically advantaged leading to **12** as a more probable intermediate. If the intermolecular process were to dominate, the CN anion would be forced to attack the less hindered terminal methylene bearing the oxophosphonium group preferably, rather than the unactivated carbonyl group.
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