Tetrahedron Letters, Vol.32, No.36, pp 4655-4658, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Synthesis of (+)-Fragolide and (-)-Pereniporin B Via Vinylsilane Terminated Cationic Cyclization

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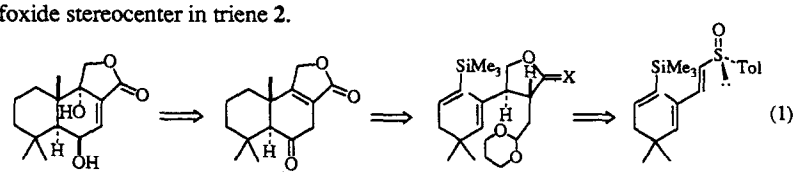
Key Words: vinylsilane-mediated cationic bicyclization; drimane sesquiterpene synthesis, [3,3] and [2,3] sigmatropic rearrangements; sulfur-to-carbon stereogenicity transfer

Abstract: *Enantioselective syntheses of (+)-fragolide and (-)-pereniporin B are detailed. Marino's lactone annulation method was employed to establish relative and absolute stereochemistry at carbon in the bicyclization substrate. Regio- and stereoselective oxidations of tricyclic drimane precursors are described.*

Pereniporin B (**1**)[2] and fragolide (**10**)[3] are representatives of the drimane sesquiterpenes, which possess an oxidized bicyclofarnesol skeleton.[4] Antifungal,[2e] insect antifeedant,[5] plant growth inhibitory,[2a] and cytotoxic properties have been observed for various compounds of this type.[6] Pereniporin B has specifically been found to be cytotoxic toward Friend leukemia cells, F5-5, at a concentration of 3.91 μg/mL.[2a,b] As a further demonstration of the effectiveness of acetal initiated/vinylsilane terminated cationic cyclizations,[7] we report herein enantioselective syntheses of (+)-fragolide and (-)-pereniporin B. As illustrated in eq 1, fragolide is a synthetic precursor to pereniporin B in this work, and the relative and absolute stereochemistry in each arises from the sulfoxide stereocenter in triene **2**.

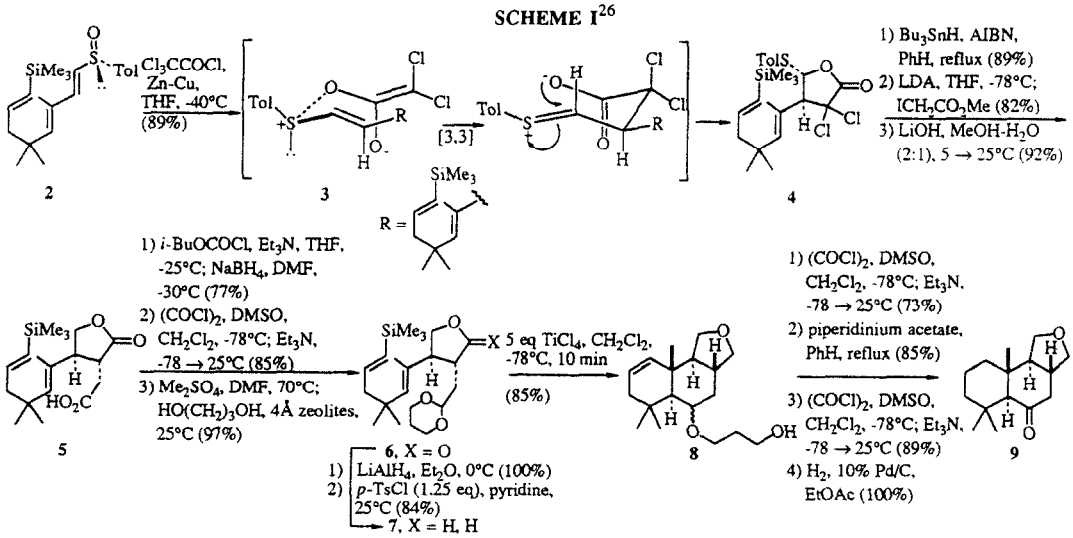


(-)-Pereniporin B (1) **(+)-Fragolide (10)** **2**

As shown in Scheme I, transfer of stereogenicity from sulfur in **2**[8] to carbon in **4** was accomplished by Marino's method.[9] Treatment of vinylsulfoxide **2** with dichloroketene, generated *in situ*, proceeded to give **4** in 89% yield via the presumed intermediates shown. Equatorial deployment of the large aryl substituent on sulfur in **3**, [3,3] sigmatropic rearrangement via a chair-like transition state, and rapid intramolecular trapping of the thionium ion by the carboxylate establishes the β- and γ-carbon stereocenters in lactone **4** at the expense of asymmetry at sulfur.[9] Radical dechlorination and desulfurization of lactone **4** was accomplished in high yield with Bu_3SnH/AIBN.[10] The optical purity of the product so obtained was found to be 94% ee by ^{19}F NMR analysis of derived Mosher's esters.[11]

Lactone enolate alkylation with methyl iodoacetate proceeded stereoselectively to give, after ester hydrolysis, the *trans*-disubstituted lactonic acid **5** as a solid. Adjustment of oxidation state via reduction of the derived mixed anhydride[12] and Swern oxidation[13] was followed by acetalization. Standard acid-catalyzed

SCHEME I[26]



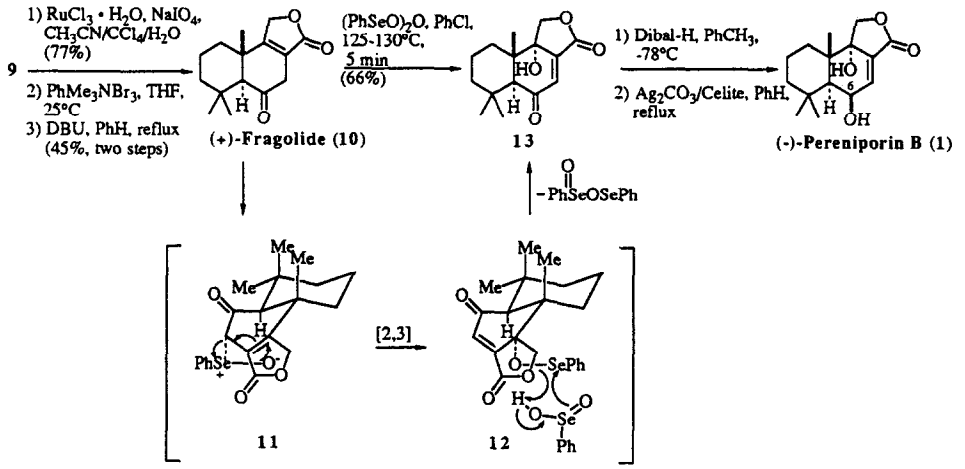
procedures failed to give acetal **6**, in that protiodesilylation occurred. The mild procedure developed by Kantlehner,[14] using DMF/dimethylsulfate, gave **6** in 97% yield as white flakes, mp 34-35°C.

We were surprised to find that lactone **6** failed to undergo the intended cationic cyclization upon treatment with various Lewis acids under a variety of conditions. Our successful prior experience[15] with a similar substrate having acetal and 1,5-diene units vicinal and trans on a δ-lactone was misleading. In contrast to those studies directed at nagilactones, the carbonyl in lactone **6** is well-situated for bidentate coordination to the Lewis acid, along with the acetal. If so, the acetal unit would be held out of position for electrophilic cyclization. Support for this conjecture rests with the fact that the easily derived tetrahydrofuran **7** is an excellent substrate for the bicyclization, providing in 85% yield a 6:1 mixture of axial and equatorial epimers **8**. Removal of the acetal remnant by Johnson's procedure,[16] Swern oxidation[13] of the resulting epimeric alcohols, and catalytic hydrogenation gave the tricyclic ketone **9**, mp 72-73°C.

Oxidation of **9** to give (+)-fragolide (**10**) and further conversion to (-)-pereniporin B (**1**) is shown in Scheme II. Ruthenium oxidants have shown the combined attributes of high oxidizing strength and great sensitivity toward steric factors.[17] Use of Sharpless' $RuCl_3/NaIO_4$ conditions[17a] reintroduced the lactone carbonyl with perfect regiocontrol. Formation of the α-bromoketone with phenyltrimethylammonium tribromide[18] and elimination with DBU in refluxing benzene was accompanied by olefin migration to yield (+)-fragolide (**10**), mp 165-166°C, $[\alpha]_D^{22}$ +125 (*c* 0.16, $CHCl_3$) [lit.[3] mp 165-166°C, $[\alpha]_D^{20}$ +149 (*c* 1% in $CHCl_3$)] which was spectroscopically identical to the natural product.

Conversion of (+)-fragolide to (-)-pereniporin B was accomplished in three steps. Treatment of **10** with benzeneseleninic anhydride[19] in refluxing chlorobenzene for five minutes resulted in the transient formation of the allylic selenoxide **11**, which underwent a [2,3] shift to afford the allylic alcohol **13** after decomposition of intermediate **12**, as shown. Treatment of **13** with dibal-H in toluene at -78°C effected ketone and lactone reduction. Treatment of the purified mixture of lactols with Fetizon's reagent[20] in refluxing benzene reestablished the lactone carbonyl, affording (-)-pereniporin B (**1**)[21] and its C(6) epimer in a 3:1 ratio. Attempts

SCHEME II[26]



to improve the chemo- and stereoselectivity of the ketone reduction by using $Zn(BH_4)_2$, $Me_4NHB(OAc)_3$,[22] 9-BBN,[23a] K-Selectride®,[23b] $LiEt_3BH$, dibal-H in THF,[24] and Luche reduction[25] failed.

In summary, enantioselective syntheses of (+)-fragolide (**10**) and (-)-pereniporin B (**1**) from the trienic sulfoxide **2** have been accomplished. Key steps include: (1) stereogenicity transfer from sulfur to carbon by the Marino lactone annulation (**2** → **4**); (2) acetal initiated/vinylsilane terminated bicyclization (**7** → **8**); and (3) oxidative allylic transposition with benzeneseleninic anhydride (**10** → **13**), involving a [2,3] sigmatropic selenoxide rearrangement.

Acknowledgment. We gratefully acknowledge the National Institutes of Health, the Alfred P. Sloan Foundation, and the National Science Foundation for generous financial support.

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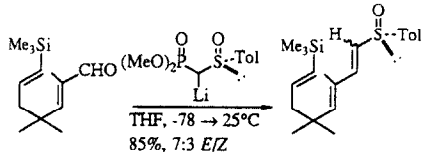

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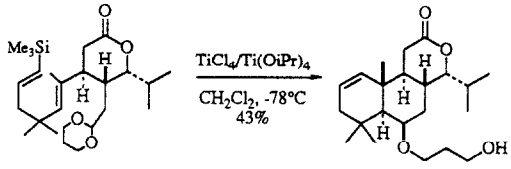

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26. All products in the Schemes have been fully characterized by standard spectroscopic and analytical methods. All yields are for chromatographically purified substances.

(Received in USA 23 April 1991)