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Enantioselective Synthesis of Nagilactone F Via Vinylsilane-Terminated Cationic Cyclization

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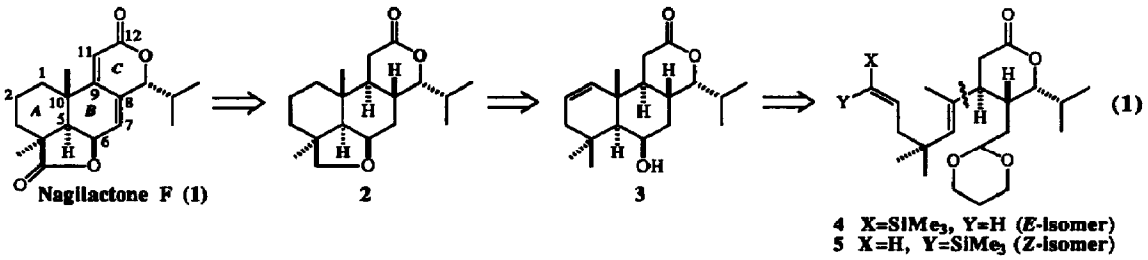
Abstract: An enantioselective total synthesis of nagilactone F is described. Functionalized tricyclic intermediate 3 was prepared using a high-yielding acetal-initiated/vinylsilane-terminated polyene cyclization of 5. Intramolecular alkoxy radical-mediated remote functionalization established the D-ring of the nagilactone system.

Isolated from the seeds and root bark of *Podocarpus nagi*, the nagilactones constitute a structurally and biologically important class of nearly fifty nor- and bisnorditerpenoid dilactones.[1] Members of this family exhibit a broad spectrum of biological activity as antitumor agents against human sarcoma,[2] allelochemicals for plant growth regulation with toxicity for insect larvae and termites,[3] and mammalian herbivore antifeedants.[4] Nagilactone F (**1**) is one of the simplest congeners, with others exhibiting higher oxidation patterns in the A-ring.[5] We have previously reported a stereoselective vinylsilane-mediated polyene cyclization entry[6] to precursors of the nagilactone family[7] and herein describe an enantioselective total synthesis of nagilactone F.

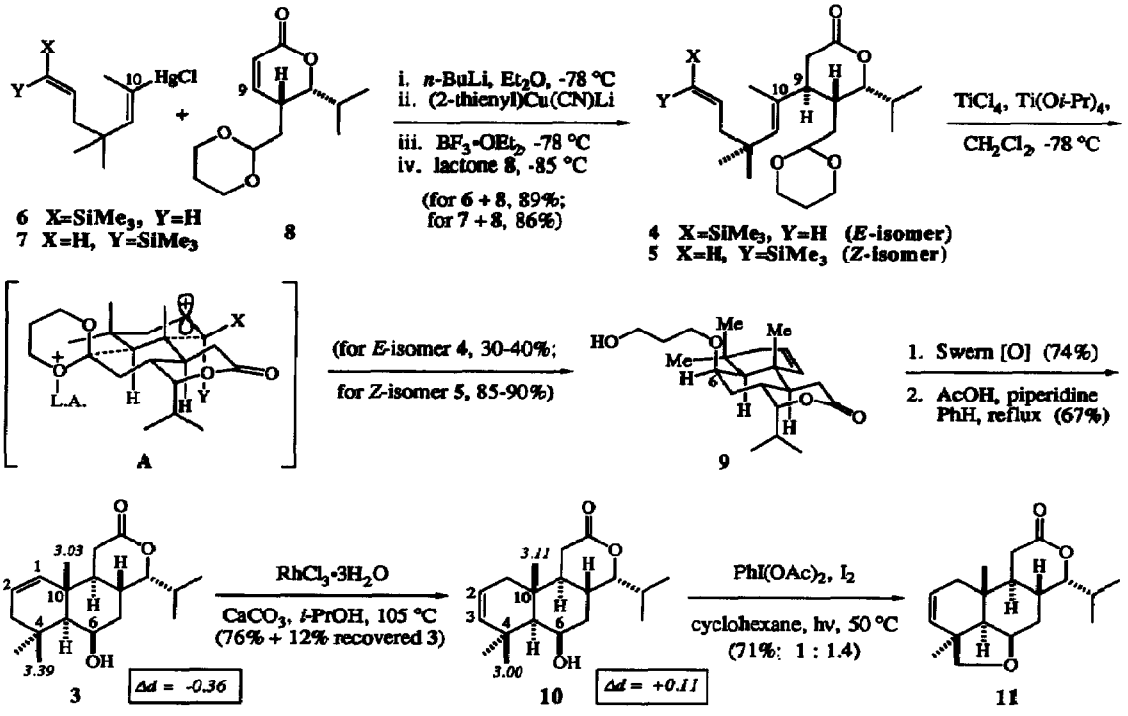
As delineated antithetically in eq 1, the D-ring in tetracyclic furan **2** was anticipated to arise from a remote oxidative functionalization tactic employed late in the synthetic route using alcohol **3** or a structurally analogous



substrate. Cationic polyene cyclization about the appropriate pentanolide template (**4** or **5**) would establish the functionalized tricyclic intermediate **3** in enantiomerically pure form.

Incorporation of either an *E*- or *Z*-vinylsilane moiety into the cyclization precursor (**4** or **5**, respectively) was accomplished (Scheme I)[8] via conjugate addition of the mixed higher order cuprate derived from achiral A-ring synthon **6**[6a] or **7**[9] to optically active pentenolide **8**.[6a] Lactone **8** is available in multigram quantities by a sequence related to that described by Nakata and Oishi,[10] wherein control of absolute and relative stereochemistry eminates from the asymmetric aldol methodology of Evans.[11] Transmetallation of either vinylmercurial derivative (**6** or **7**) with *n*-BuLi in Et_2O at -78 °C was followed by reaction with lithium

Scheme I



2-thienylcyanocuprate.[12] Addition of BF_3•OEt_2 and then **8** at -85 °C led to the the coupled product δ-lactones **4** and **5** (**6** + **8**→**4**, 89%; **7** + **8**→**5**, 86%).

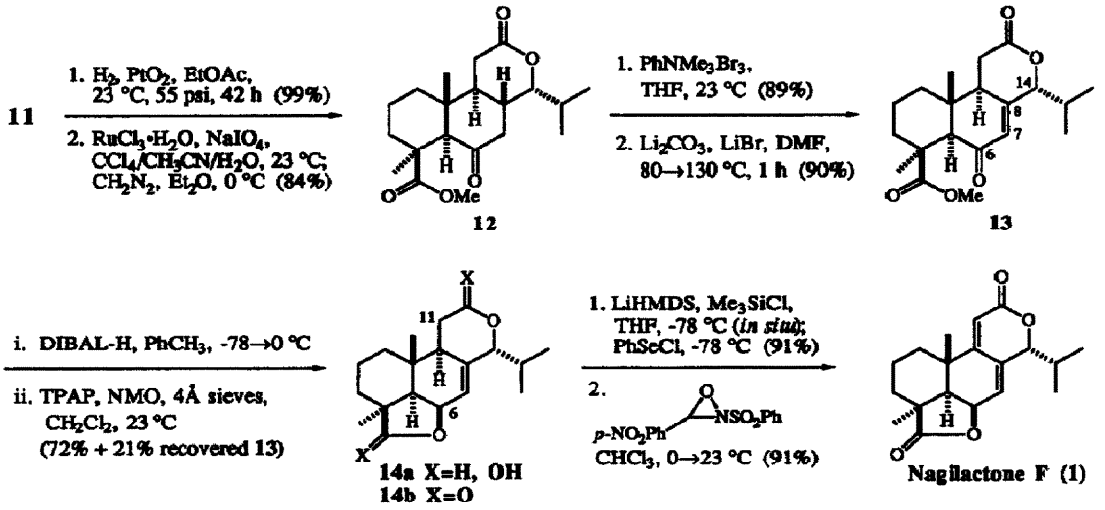
Initiation of the serial cationic bicyclization of either isomeric vinylsilane **4** or **5** by treatment with a mixture (5:1) of $TiCl_4$ and $Ti(O\textit{i}\text{-}Pr)_4$ in CH_2Cl_2 at -78 °C for 10 minutes afforded the *trans-anti-trans* tricyclic product **9** whose structure was confirmed by x-ray crystallographic analysis. Transfer of stereogenicity to the three nascent sp^3-stereocenters during these conversions is consistent with the respective chair-chair bicyclic intermediates (**A**), which also provide a rationale for the geometric constraints of the reaction and the striking superiority of *Z*-vinylsilane cyclization substrate **5**. Only inductive stabilization of the developing β-silyl cation is possible with *E*-isomer **4** (X=$SiMe_3$, Y=H), whereas the *Z*-vinylsilane geometry present in **5** (X=H, Y=$SiMe_3$) fulfills the stereoelectronic requirement for a full manifestation of the β-silicon effect due to hyperconjugative and inductive stabilization.[13] Cleavage of the acetal remnant in **9** followed the Johnson precedent,[14] with Swern oxidation of the hydroxypropyl ether side chain and subsequent β-elimination (piperidinium acetate) providing the crystalline secondary alcohol **3**.

Examination of the lactonic D-ring of nagilactone F (**1**) reveals the need to raise the β-oriented (axial) C_4 methyl group in **3** to the carboxylic acid oxidation level. We had intended to achieve this via a regioselective intramolecular remote functionalization involving a C_6 alkoxy radical as in the Barton reaction[15] or a related process.[16] In **3**, the C_{10} methyl group, by virtue of its 1,3-diaxial relationship with the C_6 hydroxyl, is also in a suitable position for intramolecular hydrogen atom-transfer. Molecular mechanics evaluations[17] provided a

predictive correlation between proximity in the ground state and regioselectivity in the remote C-H activation reaction. For example, **3** and the corresponding dihydro derivative gave cleanly the undesired angular tetrahydrofuran derivatives (C_{10} angular methyl functionalization), reflecting the Δd values of -0.36 and -0.16 Å, respectively.[18] Rhodium-catalyzed olefin isomerization ($RhCl_3 \cdot 3H_2O$)[19] afforded the thermodynamic $\Delta^{2,3}$-alkene isomer **10** (Δd = +0.11 Å) in 76% yield along with 12% of recovered **3**. Execution of the hypoiodite reaction[16] using the photochemical conditions introduced by Suárez ($PhI(OAc)_2$, I_2)[20] gave the desired AB-ring bridging tetrahydrofuran **11** and its C_{10} angular methyl-derivatized counterpart in a ratio of 1:1.4 in 71% yield.

As outlined in Scheme II,[8] catalytic hydrogenation of the $\Delta^{2,3}$-unsaturation in **11** (99%) and RuO_4 oxidation of the resulting tetracyclic derivative **2** according to the Sharpless procedure[21] provided the tricyclic keto

Scheme II



ester **12** in 84% yield following ethereal diazomethane workup. Adaptation of a bromination ($PhNMe_3Br_3$; 89%)/dehydrobromination (Li_2CO_3, LiBr, DMF, Δ; 90%) sequence similar to that developed by Ando and co-workers[22] permitted elaboration to enone **13** without compromising the stereochemical integrity of the labile C_{14} center bearing a pseudoaxial isopropyl group. After several failed attempts to reduce only the C_6 ketone carbonyl in **13**, it was realized that this difficult selectivity was not necessary. Treatment of **13** with excess DIBAL-H in toluene at -78 °C accomplished reduction of C-ring lactone carbonyl, stereoselective 1,2-enone reduction at C_6, and reduction of the methyl ester to the corresponding aldehyde with concomitant closure to the bis(hemiacetal) **14a**. Subjection of this intermediate to tetrapropylammonium perruthenate (TPAP) and NMO[23] then reestablished both C- and D-ring lactone moieties giving **14b** in 71% yield along with 21% recovered **13**. The intermediate 5- and 6-membered hemiacetal structures derived from **13** thus prevented overreduction of the ester and lactone carbonyls, and prevented reoxidation at C_6. The requisite C_9-C_{11} unsaturation was next installed via a selenylation/oxidation protocol.[24] Accordingly, *in situ* generation of the silyl ketene acetal and exposure to PhSeCl at -78 °C delivered the C_{11} α-selenide as the sole diastereomer in 91% yield. Oxidation of the selenide with the Davis oxaziridine[25] triggered selenoxide elimination to provide nagilactone F (**1**),

mp 224.5-225.5 °C, $[\alpha]_D^{23}$ -121° (*c* 0.21, MeOH) [lit.[5,7b] mp 225-226 °C, $[\alpha]_D^{23}$ -131° (MeOH)] in its natural absolute configuration which was spectroscopically identical to the natural product.[5]

In summary, a convergent enantioselective synthesis of nagilactone F (**1**) has been realized. A high-yielding acetal-initiated/vinylsilane-terminated cationic polyene cyclization and an intramolecular remote oxidative functionalization are salient features in this route which produces the title compound in 14 steps and 5.3% overall yield from **7** and **8**.

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8. Yields cited in the Schemes are for chromatographically pure substances. All structural assignments are supported by high-field ^{1}H NMR, ^{13}C NMR, IR, and MS or combustion analyses.
9. Vinylmercurial **7** containing the *Z*-vinylsilane is readily available by hydroalumination/protonolysis of $Me_3SiC{\equiv}CCH_2C(CH_3)_2CH{=}CBr_2$ in a sequence analogous to that for the preparation of **6** (see ref. 6a).
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18. Measured (in Å) from the center of the oxygen to the center of the methyl group carbon; distance to "desired" extraannular C_4 methyl - distance to the "undesired" C_{10} angular methyl = Δd (see ref. 17).
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