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ENANTIOSELECTIVE SYNTHESIS OF THE NAGILACTONE RING SYSTEM VIA VINYLSILANE-MEDIATED POLYENE CYCLIZATION.

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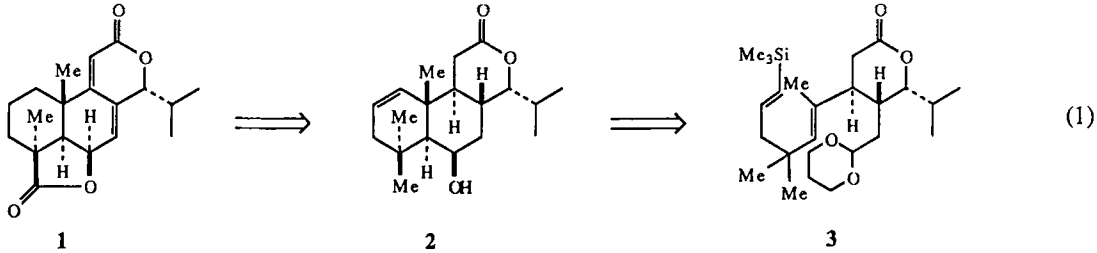
Abstract: The functionalized tricyclic nagilactone precursor **19** was synthesized by a route featuring a vinylsilane terminated/1,3-dioxane acetal initiated bicyclization. Relative and absolute stereochemical control were achieved via the optically active pentenolide template **14**.

Nagilactone F (1) is representative of a class of more than forty nor- and bisnorditerpenoid dilactones isolated from the seeds and root bark of *Podocarpus nagi*.[2] Members of this class show biological activity as antitumor agents,[3] plant growth regulators,[4] and insect toxins.[5] We report herein a new approach[6] to this class of natural products. Specifically, an acetal initiated/vinylsilane terminated polyene cyclization[7] about a pentanolide template (eq 1) serves



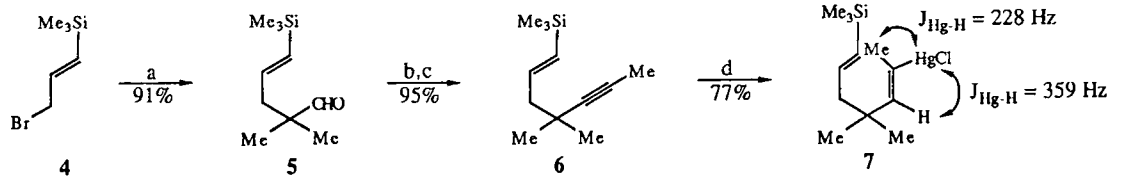
(1)

1 **2** **3**

to establish a functionalized tricyclic intermediate in optically active form. The overall strategy is illustrated in the antithetic sequence **1** → **2** → **3**. Conjugate addition of an achiral dienic A-ring progenitor to an optically active pentenolide was to provide a convergent route to the cyclization substrate **3**.

Scheme I[8] details the preparation of the A-ring synthon with inclusion of an *E*-vinylsilane moiety. The allylic bromide **4** was prepared from (*E*)-3-trimethylsilyl-2-propen-1-ol[9] by use of the Corey-Kim procedure[10] (NBS, Me_2S, CH_2Cl_2, 0°C, 1.75h, 77%). Alkylation of the dicyclohexyl

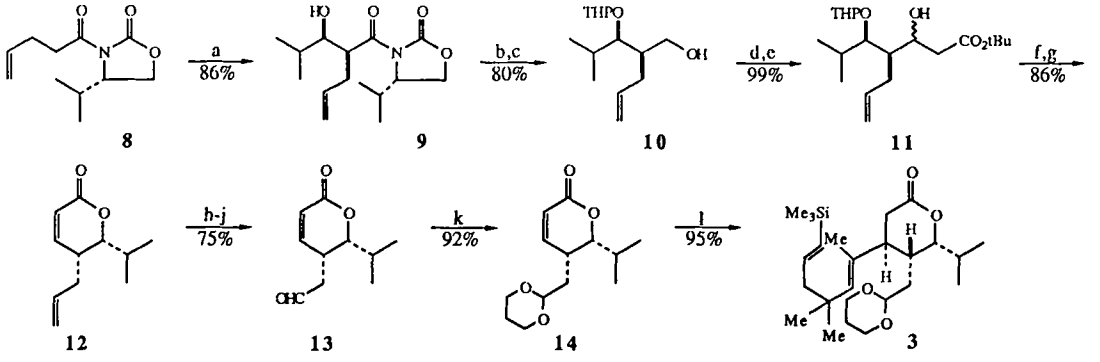
SCHEME I[8]



4 **5** **6** **7**

(a) $(cyclohexyl)_2NCH{=}C(CH_3)_2$, CH_3CN, 25°C → reflux, 5h. (b) CBr_4, Ph_3P, CH_2Cl_2, 0 → 25°C. (c) 2.5 equiv. *n*-BuLi, THF, -78 → 25 → -78°C, 2.5h; 2.3 equiv. CH_3I, -78 → 25°C, 36h. (d) catecholborane, 105°C for 6h, then 25°C overnight; NaOAc, $Hg(OAc)_2$, THF, -78 → 0°C; aq. NaCl.

SCHEME II[8]



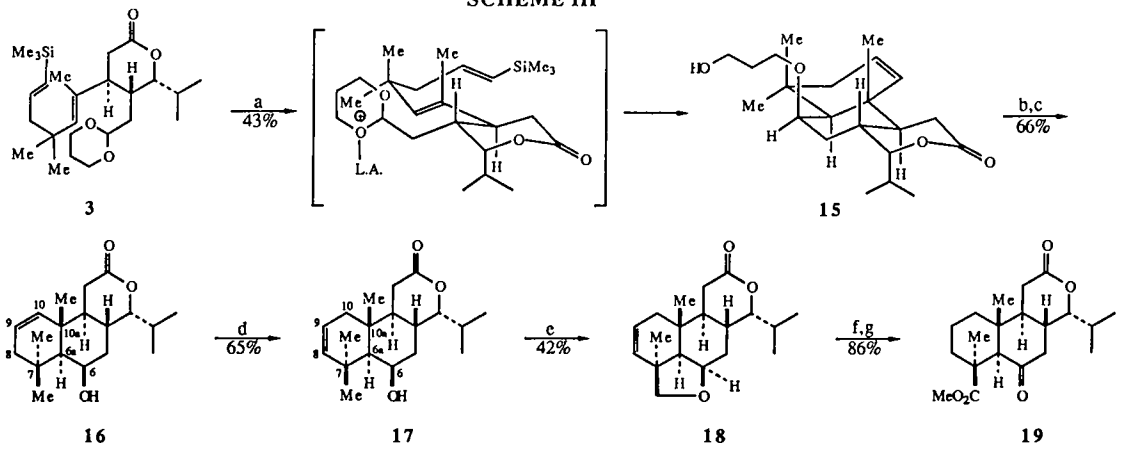
(a) 1.2 equiv *n*-Bu_2BOTf, CH_2Cl_2, -78°C; *i*-Pr_2NEt, -78→0°C, 1h; isobutyraldehyde, -78→0°C, 3.5h. (b) dihydropyran, PPTS, CH_2Cl_2, 0→25°C, 16h. (c) $LiAlH_4$, Et_2O, 0°C. (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, -78→25°C, 3h. (e) $H_2C{=}C(OLi)Ot$-Bu (2.1 equiv.), -78°C, 1h. (f) *p*-TsOH, MeOH, 25°C, 4h. (g) *p*-TsOH, PhH, reflux, 11h. (h) *m*-CPBA, CH_2Cl_2, 0→25°C, 50h. (i) 3.5% aq $HClO_4$, THF, 0→25°C, 4.5h. (j) $NaIO_4$, aq THF, 0°C, 25 min. (k) $HO(CH_2)_3OH$, PPTS, PhH, reflux, 3h. (l) **7** (Scheme I), *n*-BuLi, Et_2O, -78°C; Li(2-thienyl)CuCN, -78→0→-78°C; $BF_3{\cdot}Et_2O$; **14**, Et_2O, -85°C, 30 min.

enamine of isobutyraldehyde[11] with allylic bromide **4** in acetonitrile gave (91%, 12.3g) the aldehyde **5**. Conversion to the disubstituted acetylene **6** was accomplished in high yield by the Corey-Fuchs protocol.[12] Hydroboration and transmetallation[13] gave regio- and stereoselective access to the vinylmercurial **7**, with the indicated diagnostic ^{199}Hg-^{1}H coupling constants.[14]

The preparation[15] of the pentenolide **14** in optically pure form and coupling with a vinylcopper derivative of **7** to give the cyclization substrate **3** is detailed in Scheme II.[8] Control of relative and absolute stereochemistry is dependent upon the application of the asymmetric aldol methodology of Evans.[16] Aldol condensation of the boron enolate derived from the acyl oxazolidone **8** with isobutyraldehyde gave, in 86% yield the single diastereomer **9**. Protection as the tetrahydropyranyl ether and reduction gave the primary alcohol **10** in 80% yield. Swern oxidation[17] and reaction with the lithium enolate of *t*-butyl acetate gave in nearly quantitative yield the diastereomeric mixture **11**. Acid catalyzed hydrolysis of the THP ether, cyclization, and dehydration gave the α,β-unsaturated δ-lactone **12** in 86% yield, with *cis* isopropyl and allyl substituents (J_{vic} = 3.10 Hz). Selective scission of the isolated alkene was accomplished by a three step sequence of epoxidation, hydrolysis and cleavage of the vicinal glycol with $NaIO_4$ in aq THF. The aldehyde **13** thus produced in 75% yield was converted to the crystalline acetal **14** (mp 71.5-72°C) in 92% yield by treatment with propylene glycol and pyridinium *p*-toluenesulfonate[18] in refluxing benzene. Coupling of the vinylmercurial **7** with the pentenolide **14** was accomplished in high yield via the mixed higher order cuprate. Transmetallation of **7** with *n*-BuLi in Et_2O at -78°C was followed by the addition of 2-thienyl(cyano)copper lithium.[19] Addition of $BF_3{\cdot}Et_2O$ and then pentenolide **14** at -85°C led to the coupled product **3** (95%, mp 61-62°C).[20] Although the stereochemistry of addition could not be ascertained by ^{1}H NMR analysis, subsequent crystallographic data (*vide infra*) confirmed the relationship among the three substituents on the lactone to be as shown. This sequence leading to the polyene cyclization substrate **3** required twelve synthetic steps and proceeded in an overall yield of 38%.

Treatment of the acetal **3** (Scheme III)[8] with a mixture of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 for 10 minutes at -78°C gave in 43% yield the crystalline *trans-anti-trans* tricyclic product **15** (mp

SCHEME III[8]



(a) $TiCl_4$ (5 equiv), Ti(O-*i*-Pr)$_4$ (1 equiv), CH_2Cl_2, -78°C, 10 min. (b) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 35 min; Et_3N, -78→25°C. (c) piperidine, HOAc, PhH, 25°C → reflux, 3h. (d) $RhCl_3 \cdot 3H_2O$, $CaCO_3$, *i*-PrOH, 95-100°C, 4.5h. (e) $Pb(OAc)_4$, I_2, PhH, $CaCO_3$, reflux, 45 min. (f) H_2 (50 psi), 10% Pd/C, EtOAc. (g) RuO_2, $NaIO_4$, CCl_4, CH_3CN, H_2O, 25°C; CH_2N_2, Et_2O.

94-95°C) as the sole characterizable material. Note that the hydroxypropyl ether side chain is axially oriented.[21] Transfer of stereogenicity to the three developing sp^3-stereocenters during the conversion of **3** to **15** is consistent with the bracketed intermediate shown. Formation of the B-ring requires the *trans*-diequatorial orientation of the involved vicinal sustituents on the δ-lactone. Lewis acid complexation to the least encumbered oxygen of the acetal in the reactive conformation results in the axial orientation of the residual acetal C-O bond in **15**. The structure of cyclization product **15** was confirmed by single crystal X-ray diffraction analysis.[22] Cleavage of the remnants of the trimethylenedioxy acetal was accomplished as described by Johnson[23] by Swern oxidation[17] and β-elimination (piperidinium acetate), producing the crystalline secondary alcohol **16** (mp 138-139.5°C) in 66% overall yield.

Comparison of **16** with the nagilactone F (**1**) structure reveals the need to raise the β-oriented (axial) C7 methyl group to the carboxylic acid oxidation level. It was our intention to accomplish this via an intramolecular remote functionalization involving the C6 alkoxy radical as in the Barton reaction[24] or a related process. This we have discussed in detail elsewhere[25] and will thus present only the essential results here. In **16** there are two β-oriented methyl groups (at C7 and C10a) bearing 1,3-diaxial relationships with the C6 hydroxyl. Application of the Heusler protocol[26] for generating the alkoxy radical (via the hypoiodite) to substrate **16** gave in 89% yield only the undesired tetrahydropyran involving the angular (C10a) methyl group. Computational molecular modeling studies[25] suggested that the $\Delta^{8,9}$-isomer **17** would be a better substrate than **16** in that a net ΔΔd of 0.47 Å[27] in the ground state C6-O to C10a and C7 methyl carbons predicted that the latter would be preferentially functionalized in **17**. Olefin isomerization with $RhCl_3 \cdot 3H_2O$[28] converted **16** to **17** (mp 134-135°C) in 65% yield. Execution of the hypoiodite reaction under thermal conditions gave a 1.1:1 ratio of angular and extra-annular tetrahydrofurans, the latter of which (**18**, mp 123-125°C) was isolated in 42% yield. Catalytic hydrogenation of the $\Delta^{8,9}$-unsaturation, RuO_2 oxidation[29] and esterification gave the tricyclic keto ester **19** in 86% overall yield in the absolute configuration shown.

This convergent and enantioselective sequence provides access to a highly functionalized precursor to the nagilactones and related diterpenoids, further illustrating the applicability of vinylsilane-mediated cyclizations in organic synthesis.

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