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TOTAL SYNTHESIS OF PSEUDOGUAIANOLIDES V

STEREOCONTROLLED APPROACHES TO THE FASTIGILINS:

(±)-2,3-DIHYDROFASTIGILIN C

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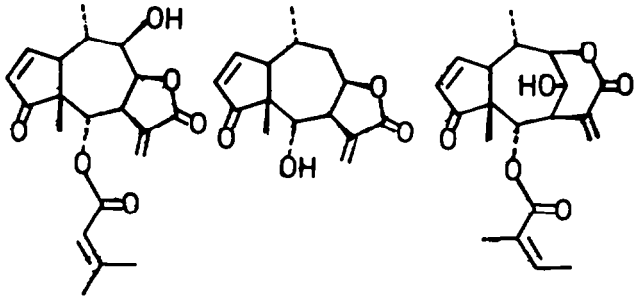
Abstract: A synthetic route to highly-oxygenated pseudoguaianolide intermediates has been developed. The functional groups on the seven-membered rings were introduced stereoselectively at all seven chiral centers. In addition, regioselective esterification at C-6 hydroxyl groups, in the presence of a C-9 hydroxyl site, was achieved.

Fastigilin C(1) and cogeners, isolated from cytotoxic extracts of Baileya multiradiata[1] and Gallardia fastigiata[2] are among the most bioactive and structurally-complex known pseudoguaianolides.[3] Although a variety of creative synthetic approaches to the pseudoguaianolides have been developed,[4] no total syntheses of 1 or related compounds, in which each carbon of the seven-membered ring is chiral, have been reported. Grieco[5] and Schlessinger[6] succeeded in preparing helenalin (2), which lacks the free C-9 hydroxyl group found in 1. Such a group is on occasion involved in a δ-lactone ring, as in linearifolin B[7] (3), although most poly-hydroxylated



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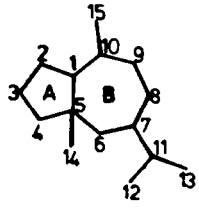
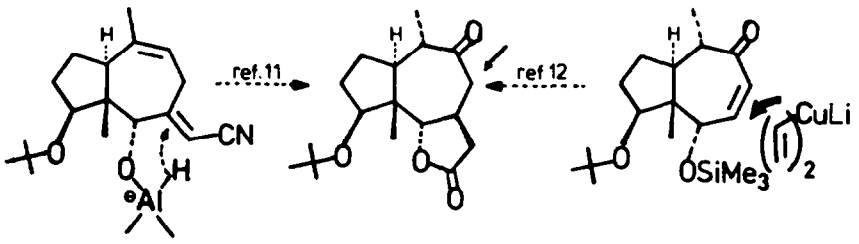


sesquiterpene lactones exist with α-methylene-γ-lactone rings.[3] It appears that synthetic approaches to 1 will be challenged by the possible existence of three different lactone rings fused onto ring B and the need to intermolecularly acylate only at C-6. In addition to the plethora of sensitive and diverse functional groups, stereochemistry is also a matter requiring constant attention as the synthesis unfolds.

Seven-membered rings have substantial conformational flexibility with low barriers to ring inversion; both chair and boat conformers are often encountered. Indeed, among the pseudoguaianolides whose structures have been elucidated by X-ray crystallography, helenalin (2) and radiatin[8] possess chair conformations of the seven-membered ring and in autumnolide that ring prefers a boat conformation.[9] One may anticipate that stereoselectivity will be as much a concern in approaching 1 as chemoselectivity. Indeed it will be seen that ring B in certain synthetic intermediates will have chair conformations while in others boat forms will dominate (vide infra).

In the course of working toward the goal of synthesizing 1 for the past several years,[10] we reported two complementary synthetic approaches to keto-ester 4 (Scheme I). These routes utilized an existing chiral C-6 hydroxyl center to establish the relative configuration of the C-7 acetic acid side chain in 4. In the first case, this was initiated by intramolecular α-side hydride

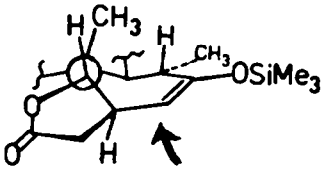
Scheme I



5 4 6

transfer, via a C-6 alkoxyhydride intermediate, to a neighboring α,β-unsaturated nitrile[11] (cf. 5). Alternatively, if an α-oriented C-6 hydroxyl group was protected by a bulky group, as in 6, intermolecular conjugate addition of lithium divinylcuprate was directed to the less hindered β-face of the cycloheptenone moiety.[12] As before, further elaboration[11,12] led expeditiously to 4.

The availability of 4 provided a versatile intermediate with five chiral centers correctly juxtaposed on the seven-membered ring. Moreover, the presence of the diequatorially, trans-fused γ-lactone ring in 4 ($J_{6,7}$=11.3 Hz) imposes considerable rigidity, thus raising expectations that C-8,9 enolates and related nucleophilic double bonds derivable from 4 (e.g. 7) would react



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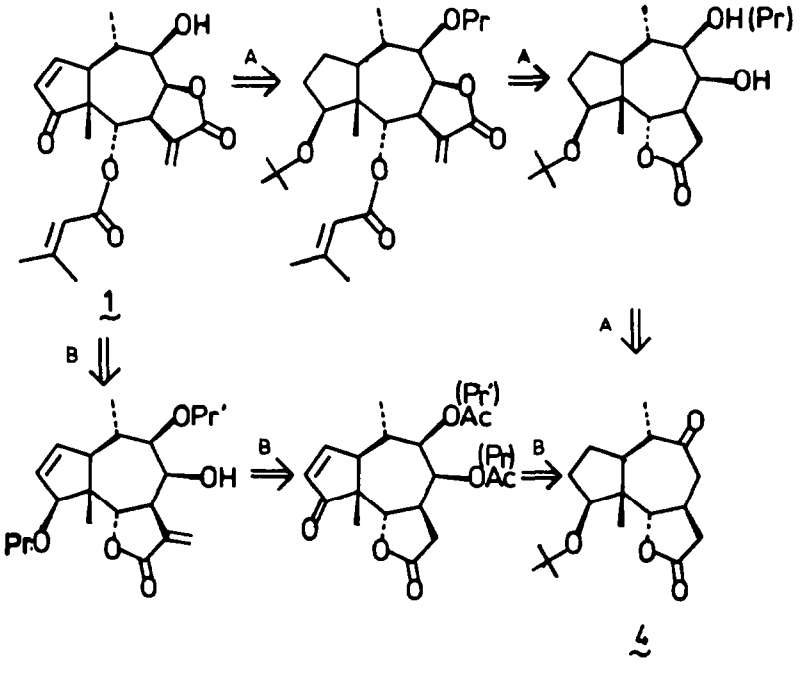
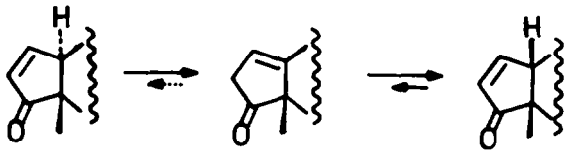
diastereoselectively from the α-face (arrow) when called upon. Such considerations led to two retrosynthetic strategies for proceeding toward 1.

Scheme II



Pr = appropriate protecting groups.

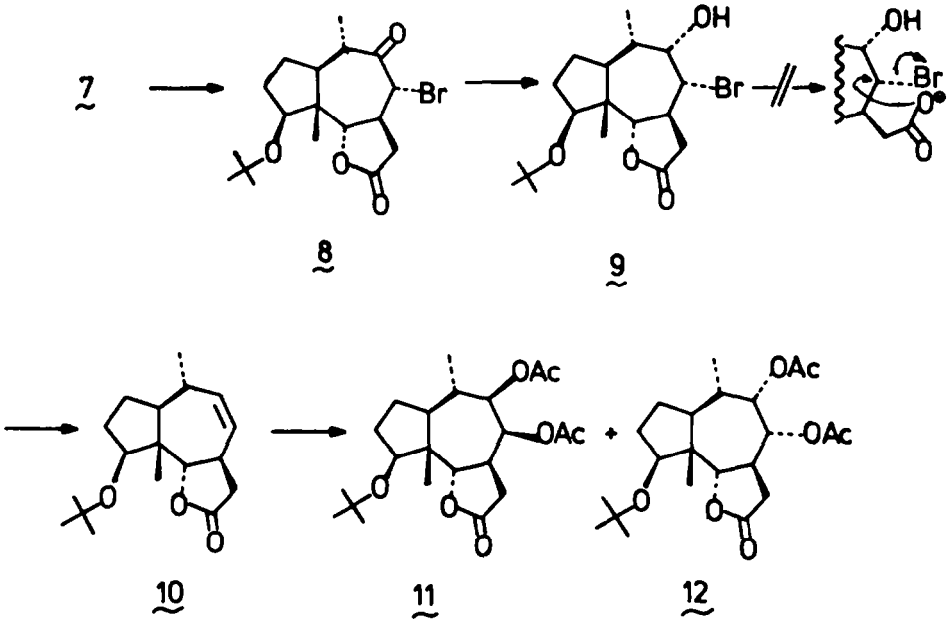
Strategy A would begin with introduction of the β-oriented C-8 and C-9 hydroxyl groups, followed by transposition of the C-6,7 trans-lactone to the C-7,8 cis-fused isomer, based on the relative stabilities found for such lactones in the helenalin series.[5] However, the possible intervention of 7,9 δ-lactones[7] posed an additional problem that did not exist in the synthesis of 2. A priori, α-methylenation could be carried out before or after the lactone transposition. Finally, the sensitive trans-fused cyclopentenone moiety in 1 would be unveiled at the latest possible moment, as we had done in previous pseudoguaianolide syntheses,[10a,b] in order to avoid acid- or base-induced deconjugation and/or γ-epimerization.[13] If the cyclopentenone ring were to



be elaborated from 4 at an early stage (strategy B), extra steps would be necessary to protect it, e.g. as a cyclopentenol,[5,6] and ultimately to deprotect and oxidize. In both routes, up to four secondary carbinol centers should be differentiable at all times, by means of appropriate protecting groups and/or sufficiently different reactivities during oxidation, esterification and deesterification inter alia.

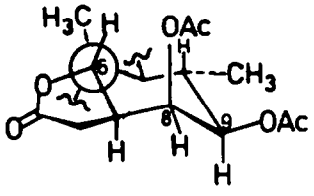
Scheme III depicts the transformations[12b,14] that resulted in completion of stereoselective ring B functionalization, commencing with 4. Lithium hexamethyldisilazide was used to generate the C-8 kinetic enolate, which then was silylated (→7) followed by N-bromosuccinimide reaction to give the α-bromoketone 8 ($\nu_{C=O}$ 1785, 1705 cm^{-1}). This was followed by stereoselective sodium borohydride reduction to bromohydrin 9 ($J_{7,8}$ = 10.8 Hz, $J_{8,9}$=2.7 Hz). Since the C-9 hydroxyl configuration was opposite that required for our purposes, base-induced lactone transposition via intramolecular S_N2 displacement of bromide at C-8 was not pursued. Instead 9 was subjected to

Scheme III



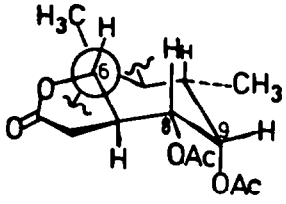
zinc-induced elimination (>90% yields). The unsaturated conformationally-fixed lactone 10 was hydroxylated by the "wet" Prevost method[15] and the crude hydroxy-acetates immediately acetylated (→11 and 12) to facilitate purification. From inspection of models, we had anticipated that

iodonium ion formation would occur in 10 preferentially from the α-face of the flattered cycloheptene; this would culminate in preponderant β,β-diol formation. Fractional crystallization of chromatographed diacetates (90% yield) afforded pure 11 and 12 in a satisfying ratio of 5:1, respectively. ^{1}H NMR analysis (see below) clearly revealed that the major diastereomer 11 had the correct relative configuration at all B ring stereocenters for conversion ultimately to 1.



11

	δ	J_{vic}
C-6	4.48	6,7 = 10Hz
C-8	5.40	7,8 < 1Hz
C-9	4.58	8,9 = 3.6
		9,10 = 10.2

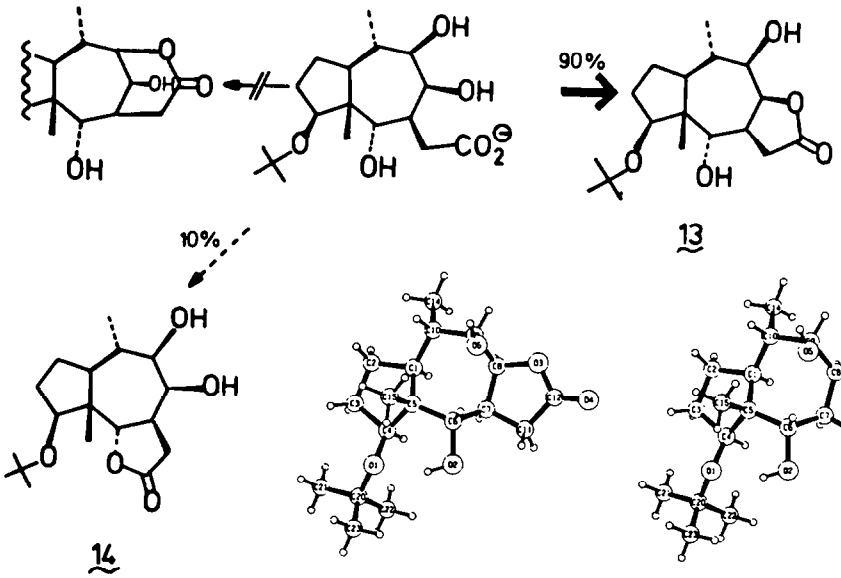


12

	δ	J_{vic}
C-6	4.01	6,7 = 10.5
C-8	4.81	7,8 = 10.5
C-9	5.12	8,9 = 3.2
		9,10 < 2

Further confirmation of structure 11 was postponed until lactone transposition (cf. Scheme II), whereupon the question of which of three possible unepimerized lactones would predominate at equilibrium could also be answered. Saponification of 11 with aqueous sodium hydroxide, followed by acidification and heating in refluxing benzene afforded 90% of dihydroxylactone 13 and 10% of the untransposed lactone 14 (definitely from the opened trihydroxy acid); no evidence for a δ-lactone (esterification at C-9) could be found by infrared spectral examination of the crude

Scheme IV



13

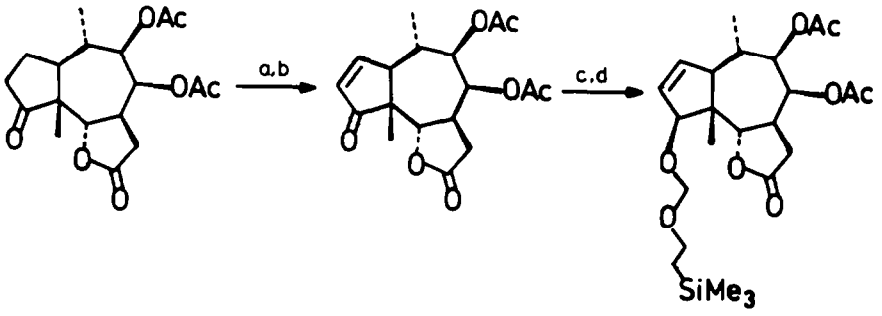
14

lactonization product.[16] The relative configuration of 13 was established by single crystal X-ray analysis,[17] which also showed that ring B is in a boat conformation,[18] unlike most pseudoguaianolides. Apparently, this arrangement of the central ring in 13 is stabilized in part by an intramolecular hydrogen bond between the C-6 hydroxyl group and C-4 oxygen atom ($O_1 \cdots O_2$ distance ca. 2.8 Å). A similar situation exists in autumnolide,[9] which also has a symmetrical boat conformation of the seven-membered ring.

With compounds 11 and 13 rigorously established and preparable, both retrosynthetic strategies illustrated in Scheme II could be tested experimentally. The five-membered ring in 11

was amenable to selective transformations, since acid-catalyzed removal of the C_4-t-butyl ether protecting group and Jones oxidation could be achieved without deacylating the hydroxyl functions at C-6,8 and 9 (cf. Scheme V compound 15). Accordingly, to assess the feasibility of sequence B, we converted[14] 15 in two steps to the cyclopentenone 16 (C-2 and C-3 vinyl protons at δ7.56 (dd, J=2,6) and 6.02 (dd, J=3,6), respectively) and immediately reduced the ketone to the cyclopentenol. Protection of the C-4 hydroxyl group with 2-(trimethylsilyl)ethoxymethyl chloride gave 17 (other protecting groups were also studied). Unfortunately many attempts to transpose the

Scheme V



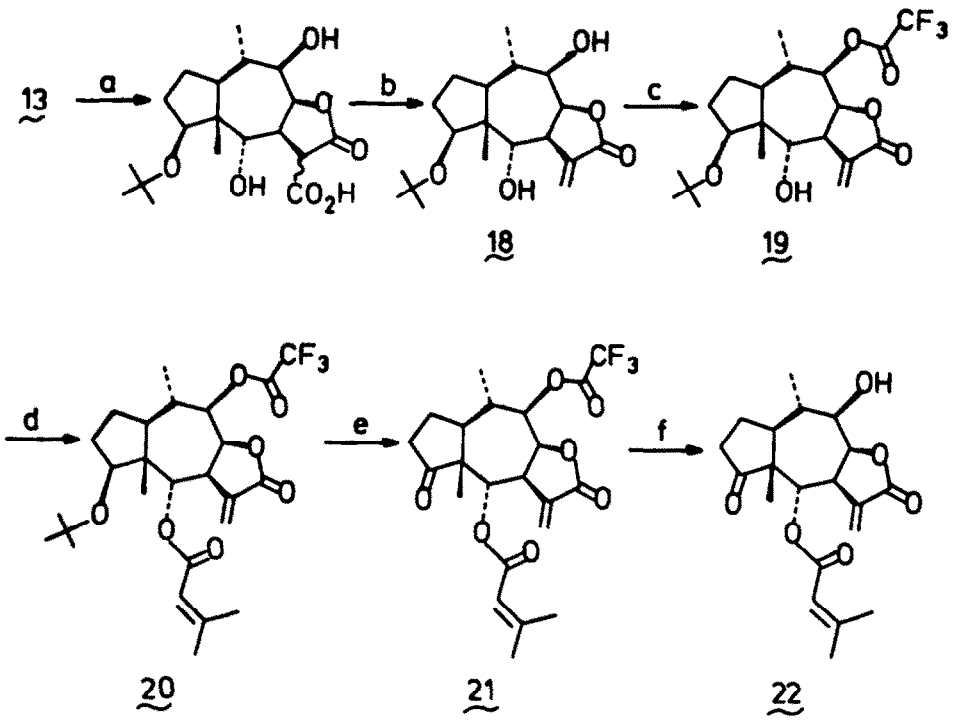
15 16 17

Reagents: C_6H_5SeCl/EtOAc-HCl; b) $NaIO_4$; c) $NaBH_4/CeCl_3$, MeOH; d) $Me_3SiCH_2CH_2OCH_2Cl$, Et_3N.

lactone ring in 17, (as was done with 11→13) were unsuccessful.[14] Consequently, subsequent efforts toward fastigilin C(1) et al. were focused on strategy A, with the lactone transposition "problem" already solved!

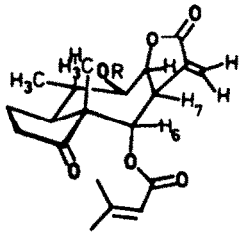
A variety of strategies for functional group elaboration in 13 were subjected to experimental scrutiny.[14] Scheme VI depicts the most direct series of transformations that enabled us to approach 1, while still avoiding unwanted oxidations at C-6 and C-9 and/or nucleophilic destruction of the electrophilic α-methylene-γ-lactone function. α-Methyleneation of dihydroxylactone 13, without hydroxyl protection, was carried out by initial enolate carboxylation and subsequent reaction of the α-carboxy-γ-lactone with Eschenmoser's salt. Selective manipulation of the hydroxyl sites in 18 was next undertaken. We required a hydroxyl protecting group that would be acid-stable (during t-butyl ether cleavage at C-4), yet easily removable with non-nucleophilic bases, so as to avoid unwanted conjugate addition to the α-methylene-γ-lactone site in 18 and later intermediates. Trifluoroacetylation was chosen and, after much experimentation,[14] we were able to monoacylate 18 cleanly at C-9. Structure 19 was confirmed by a downfield-shifted C-9 quartet at δ5.28 (J=5, 2 Hz). Reaction of 19 with β,β-dimethylacryloyl chloride led smoothly to 20, in which the seven-membered ring now has a chair conformation[18] (C-6 proton at δ4.65 with $J_{6,7}$=2.5 Hz). This conformational change is apparently due to loss of hydrogen bonding between the C-6 hydroxyl and C-4 oxygen atoms, as in 13 and the large steric requirement of the newly-introduced senecoiate ester. t-Butyl ether cleavage in 20 occurred without C-6→C-4 acyl migration,[14,19] followed by pyridinium chlorochromate oxidation to generate the C-4 ketone 21. Careful saponification of the C-9 trifluoroacetate group with aqueous sodium bicarbonate gave 2,3-dihydrofastigilin C(22), mp 165-166°. Both 21 and 22 proved totally inert to the selenylation-selenoxide elimination protocol that had served us well in securing 16 and previously in the final stages (cyclopentenone generation) of synthesizing aromatin[10b] and aromaticin[10a] (no C-6 substituents). It appears that the large "axially" oriented senecoiate ester group in 21 and 22 (depicted below) shields the α-face of the neighboring cyclopentane ring, which already is hindered on the β-side by the C-5 methyl group. These combined steric effects

Scheme VI



reagents: a) excess LDA, -78°, then CO_2; b) $CH_2{=}NMe_2I^-$; c) 1eq. TFAA, Py-THF, -5°; d) $Me_2C{=}CHCOCl$, C_6H_6, reflux; e) p-TSA, C_6H_6, Δ, then PCC/CH_2Cl_2; f) $NaHCO_3$, THF-H_2O.

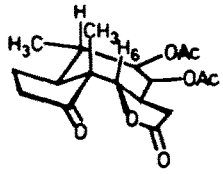
apparently prevent intermolecular enol selenylation that occurred satisfactorily enroute to 16. The precursor ketone 15, with a seven-membered boat conformation enforced by the C-6,7 lactone, does not experience steric hinderance to α-side access at the C-3,4 enolic π bond. Several



R

21 $COCF_3$

22 H



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alternative reagents and/or strategies were investigated,[14] in order to overcome the challenge of introducing the remaining 2,3-double bond into 19 or 20. For example, we deprotected the C-4 hydroxyl group in 19 prior to C-6 acylation and selectively oxidized C-4 to the cyclopentanone, albeit in only 40% yield. However we were again unable to selenylate this compound as we had in generating 16. Finally, a sample of 22 was reacted with cupric bromide to give an α-bromoketone of undefined C-3 stereochemistry. HBr elimination was not observed during electron-impact mass spectroscopy (-Br• instead of -HBr) and vigorous dehydrohalogenation experiments[20] failed to produce detectable amounts of 1 (by TLC, using authentic 1).

Experimental

General: Melting points are uncorrected. ^{1}H NMR spectra were obtained on Varian EM-390 and JEOL FX-90Q Fourier transform spectrometers. Infrared spectra were obtained with a Perkin-Elmer 727B prism instrument; spectra were calibrated using the 1602 cm^{-1} band of polystyrene and were run neat (for oils) or in methylene chloride or chloroform solution (for solids). Routine mass spectral analyses (EI, CI) were obtained at the Cornell University mass spectroscopy facility. High resolution mass spectra determinations were run at Merck, Sharp & Dohme (Rahway, NJ) on a Finnigan model 212 spectrometer in the EI mode at 90ev, using the peak matching method with Ultramark 1600F as internal standard.

Column chromatography was performed with Baker 40-140 mesh silica gel or 100-200 mesh Fluorosil. Radial chromatography was carried out on a "Chromatotron" (Harrison Research) with silica gel 60 PF-254 containing gypsum as stationary phase. TLC analyses were carried out with precoated plates of 250 micron thickness, GHLF silica gel (Analtech, Inc.). TLC slides were visualized with iodine, UV light or spraying (sulfuric acid/cobalt chloride or sulfuric acid/sodium dichromate) and then scorching on a hot plate.

All solvent and reagents were purified by appropriate means before use and reactions requiring inert atmospheres were conducted under dried nitrogen or argon. "Standard workup" refers to quenching reactions into aqueous solution, ether and/or methylene chloride extraction of organic material, washing the organic layer(s) with aqueous acid or base as needed, drying over anhydrous magnesium sulfate or sodium sulfate and then removal of solvent by rotary evaporation. Spectral examination and chromatographic purification followed.

Microanalyses were performed by Atlantic Microlabs, Atlanta, Georgia 30366.

Bromination of keto-lactone 4. A solution of lithium hexamethyldisilazide (3.9 mmol) in 5 ml of THF was prepared from 711 mg (4.3 mmol) of hexamethyldisilazane and 3.4 ml (3.9 mmol) of n-butyllithium at -78°. After 20 min, 600 mg (1.95 mmole) of 4 in 2 ml of THF was added, followed by stirring 0.5h at 0°. Excess trimethylsilyl chloride (6.83 mmol) was added, with subsequent stirring for 0.5h. The reaction mixture was then partitioned between pentane and saturated $NaHCO_3$, followed by standard workup. The crude silyl enol ether (0.87g, ~100%), IR(neat) ν_{max} 1785, 1640 cm^{-1}, was taken on to the next step.

A solution of 750 mg (1.95 mmol) of 7 in 30 ml THF was cooled to 0° and 455 mg (2.56 mmol) of N-bromosuccinimide added. After 5 min, the reaction mixture was partitioned between 5% HCl and ether, followed by conventional workup. The crude oily product (720 mg) afforded 525 mg (70%) of pure bromo-ketone 8, mp 159-161°, upon recrystallization from hexane. IR (CH_2Cl_2) ν_{max} 1785, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ4.25-3.80 (3H, m), 3.0 (2H, m) 1.43 (3H, d, J=6.5 Hz), 1.15 (3H,s), 1.06 (3H,s). Anal: calcd. for $C_{18}H_{27}BrO_4$, C, 55,67; H, 6.96. Found: C, 55,83; H, 7.05.

Sodium borohydride reduction of 8. Bromoketone 8 (775 mg; 2 mmol) and $NaBH_4$ (159 mg; 4.20 mmol) were dissolved in 7 ml of THF and 7 ml of ethanol cooled to 0°. After 1h the reaction mixture was partitioned between CH_2Cl_2 and 5% HCl, followed by standard workup to give a quantitative yield of bromohydrin 9, mp 156-158° (from hexane-CH_2Cl_2). IR($CHCl_3$) ν_{max} 1780 cm^{-1}; ^{1}H NMR δ4.13 (1H,d,d, J=10.8, 2.7 Hz), 3.95 (1H,d, J=9.9 Hz), 3.83 (2H,m) 1.15 (9H,s), 1.05 (3H,s), 1.03 (3H,d, J=6.5 Hz). Anal. calcd. for $C_{18}H_{29}BrO_4$: C, 55.38; H, 7.44. Found: C, 55.41; H, 7.55. MS (CI, CH_4) m/e 389, 391 (M^++1); 333,335.

Preparation of unsaturated lactone 10. Two millimoles (770 mg) of bromohydrin 9 was refluxed in 13 ml ethanol and 4 ml of HOAc containing 3.8 g (large excess) of zinc dust. After 18h the reaction was quenched with ether and aqueous $NaHCO_3$, then worked up as usual. Radial chromatography (2 mm plate, hexane/ether) gave 540 mg (93%) of oily 10: IR (neat) ν_{max} 1785 cm^{-1}; ^{1}H NMR δ5.39 (2H,s), 4.03 (1H,d, J=10.5 Hz), 3.88 (1H,m), 1.17 (9H,s), 1.12 (3H,s), 0.94 (3H,d, J=6.5 Hz).

Cis-hydroxylation of lactone 10: "Wet Prevost" reaction. Lactone 10 (0.670 g; 2.29 mmol) was dissolved in 35 ml glacial HOAc and 0.206 ml (11.5 mmol) of H_2O added, followed by 0.765 g (4.58 mmol) of silver acetate and 0.608 g (2.41 mmol) of powdered iodine. After 12h at 60° (oil bath), the mixture was diluted with 2:1 ether-CH_2Cl_2 and filtered through celite. The filtrate was partitioned with saturated $NaHCO_3$ and the organic layer washed and dried over $MgSO_4$. The

crude hydroxy-acetates (0.84 g, ~100%) were dissolved in CH_2Cl_2 (50 ml) and treated with triethylamine (2 ml, 14.3 mmol), acetic anhydride (1 ml, 10.6 mmol) and a few crystals of 4-dimethylaminopyridine. After 1h, the reaction mixture was poured into 10% HCl and the organic products extracted into 2:1 ether-CH_2Cl_2 and worked up as usual. Silica gel chromatography gave three fractions, the major (R_f 0.29, 1:1 hexane-ether) consisting of 840 mg (90% yield) of diacetates 11 and 12. NMR analysis revealed a 5:1 ratio of 11 to 12. Purified 11 had mp 126-128° (needles from hexane-ether). IR($CHCl_3$) ν_{max} 1780, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ5.40 (1H, brd, J=3.6 Hz), 4.58 (1H, dd, J=10.2, 3.6 Hz), 4.48 (1H, d, J=10 Hz), 3.85 (1H, m), 2.9-1.3 (9H,m), 2.15 (3H, s), 1.98 (3H, s), 1.18 (9H, s), 1.14 (3H, s), 0.79 (3H, d, J=7 Hz); HRMS, M^+ calcd. for $C_{22}H_{34}O_7$, 410.2305; found, 410.2306.

Diacetate 12 had mp 140-143° (lumpy crystals, from hexane-ether). Salient NMR data appear in text.

Transposition of lactone 11 into 13. Lactone 11 (267 mg, 0.65 mmol) was refluxed for 2h in 3 ml of ethanol and 3 ml of 5% aqueous NaOH at which time TLC revealed complete saponification. After cooling, the aqueous layer was acidified (10% aqueous HCl) and extracted with CH_2Cl_2 and ether. Standard workup afforded 230 mg (108%) of lactonic product, along with some hydroxy acids. After brief reflux in benzene (to complete lactonization), the residual material, after solvent evaporation, was chromatographed on silica gel (1:1 hexane-ether, then ether) to afford first 190 mg (89%) of dihydroxylactone 13, R_f 0.64, mp 209-209.5° (white needles from ether). IR ($CHCl_3$) ν_{max} 3520, 3420, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ4.5 (2H, m) 3.97 (2H, m), 2.8 (2H, m), 2.5-1.0 (9H, m), 1.22 (9H, s), 1.1 (3H, s), 0.93 (3H, d, J=7 Hz). A single crystal X-ray analysis of this material was carried out by Dr. J. F. Blount (Hoffmann-LaRoche). A second fraction from the above chromatogram (R_f 0.52, ether) was lactone 14, whose structure was established by reconversion to 11 upon acetylation.

α-Methylenation of lactone 13 to 18. A solution of lithium diisopropylamide (3.6 mmol) in 16 ml of 4:1 THF-hexane was prepared from equivalent quantities of diisopropylamine and n-butyllithium at -78°. After 0.5 h stirring, 180 mg (0.55 mmol) of lactone 13 was added, followed after 45 min by a stream of dried CO_2 during 50 min while the reaction temperature gradually rose to -20°. After dilution with ether and quenching with 10% aqueous hydrochloric acid, the organic material was isolated, along with additional salting out and extraction of the aqueous layer. Concentration of the dried organic layer afforded 177 mg (87%) of crude carboxy-lactone, which was immediately carried on to the next stage.

The above carboxylactone (177 mg) was dissolved in 25 ml of acetonitrile, followed by addition of 180 mg (0.97 mmol) of N,N-dimethylmethyleneimmonium idodide (Eschenmoser's salt). After 3h at 95°, the reaction mixture was cooled and partitioned between ether-CH_2Cl_2 (2:1) and 5% aq. hydrochloric acid. Standard workup afforded 139 mg (86%) of α-methylene-γ-lactone 18, mp 180-182° (pellets from ether-hexane). ^1H NMR ($CDCl_3$) δ6.29 (1H, m), 5.99 (1H, m), 4.67 (1H, dd, J=8.8, 2.2 Hz), 4.43 (1H, d, J=9.3 Hz), 4.1-3.9 (2H, m), 3.3 (1H, m), 2.1-1.0 (8H, m), 1.3 (9H, s), 0.98 (3H, s) 0.98 (3H, d, J=7 Hz); HRMS, M^+ calcd. for $C_{19}H_{30}O_5$, 338.2093; Found, 338.2094.

Selective acylations of α-methylene-γ-lactone 18 to 20. A THF solution (5 ml) of 18 (75.4 mg, 0.223 mmol) containing 0.036 ml (0.44 mmol) of pyridine was cooled to -5° and then 0.0385 ml (0.27 mmol) of trifluoroacetic anhydride added gradually (0.1 ml syringe) until starting material was consumed (TLC: R_f 0.06 for diol 18 and 0.35 for C-9 trifluoroacetate 19 in 1:1 hexane-ether). Quenching into ether-CH_2Cl_2 (2:1) and 1% aqueous hydrochloric acid, followed by standard workup gave 86 mg (89%) of 19: ^1H NMR ($CDCl_3$) δ6.33 (1H, d, J=2.9 Hz), 6.00 (1H, d, J=2.7 Hz) 5.28 (1H, dd, J=4.8, 2 Hz), 4.77 (1H, dd, J=9, 2 Hz), 4.10 (1H, d, J=8 Hz), 4.0 (1H, m), 3.4 (1H, m), 2.1-1.1 (7H, m), 1.2 (9H, s), 1.01 (3H, d, J=7 Hz), 0.83 (3H, s).

Twelve mg (0.3 mmol) of the crude 19 was refluxed for 24 h with excess 3,3-dimethylacryloyl chloride (0.7 mmol) in benzene. Cooling and hydrolysis (aq $NaHCO_3$), followed by extraction and workup afforded 20 mg. of the C-9 protected C-6 senecoiate 20, mp 168-172° (from hexane). NMR ($CDCl_3$) δ6.37 (1H, d, J=2.5 Hz), 5.98 (1H, d, J=2.0 Hz), 5.72 (1H, m), 5.21 (1H, dd, J=10, 2 Hz), 4.85 (1H, d, J=2.5 Hz), 4.68 (1H, dd, J=9, 2 Hz), 3.7 (2H, m), 2.16 (3H, d, J=1 Hz), 2-1 (6H, m), 1.92 (3H, d, J=1 Hz), 1.02 (9H, s), 0.93 (3H, d, J=7Hz), 0.65 (3H,s).

Formation of 2,3-dihydrofastigilin C (22). Heating a benzene solution of 20 (14.4 mg in 0.3 ml) containing a crystal of p-toluenesulfonic acid for 2h at 75 (oil bath) sufficed to remove the t-butyl ether protecting group at C-4. Product workup, using ether-CH_2Cl_2 (2:1) and aqueous $NaHCO_3$, afforded 15 mg of crude, oily carbinol. NMR showed loss of t-butyl group signal at δ1.02. This material was reacted with excess pyridinium chlorochromate (17 mg, 0.081 mmol) in 0.20 ml of CH_2Cl_2. After 3h, the oxidation was complete (TLC) and the reaction mixture worked up to provide 2,3-dihydrofastigilin C trifluoroacetate (21). ^{1}H NMR ($CDCl_3$) δ6.42 (1H, d, J=2.2 Hz), 6.16 (1H, d, J=1.7 Hz), 5.54 (1H, m), 5.23 (1H, brd), 5.18 (1H, brd, J=10 Hz), 4.7 (1H, dd, J=8, 2 Hz), 3.69 (1H, m), 2.4-1 (6H, m), 2.12 (3H, d, J=1 Hz), 1.85 (3H, d, J=1.2 Hz), 1.1 (3H, d, J=6 Hz), 0.72 (3H, s).

The above material was stirred for 3h in 1:1 THF-aqueous sodium bicarbonate, then extracted with ether-CH_2Cl_2 and worked up in the usual manner. Silica gel chromatography gave 7 mg of 2,3-dihydrofastigilin C (22), R_f = 0.29 (1:1 ethyl acetate-hexane), which had mp 165-166° (from hexane-ether). IR ($CHCl_3$) ν_{max} 3460, 1765, 1745, 1720, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ6.39 (1H, d, J=2.4 Hz), 6.12 (1H, d, J=2.4 Hz), 5.49 (1H, m), 5.21 (1H, d, J=2 Hz), 4.93 (1H, dd, J=9,2 Hz), 3.7-3.4 (2H, m), 2.14 (3H, brs), 1.87 (3H, brs), 2-1 (7H, m), 1.2 (3H brd), 0.75 (3H, s); HRMS, M^+, calcd. for $C_{20}H_{26}O_6$, 362.1729; Found, 362.1710.

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16. A similar preponderance of 13 over 14 was observed when lactone 11 was subjected to equilibrium trans-esterification with $NaOCH_3$ in methanol (P. T. Lansbury and D. J. Mazur, unpublished results).

17. This study was carried out by Dr. J. F. Blount, Hoffmann LaRoche, Inc., to whom we are most appreciative. The crystals were monoclinic, space group $P2_1/a$, with a = 11.899(5), b = 12.974(4), c = 11.503(4)A, β = 103.85(3)°, and d_{calcd} = 1.258 g cm^{-3} for Z = 4 ($C_{18}H_{30}O_5$, M = 326.43). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ -2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.12 x 0.20 x 0.75 mm. A total of 1616 independent reflections were measured for θ < 48°, of which 1485 were considered to be observed [I > 2.5σ(I)]. The structure was solved by a multiple-solution procedure and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.045 and wR = 0.056 for the 1485 observed reflections. The final difference map has no peaks greater than ±0.2 e A^{-3}. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

18. In such boat conformations, C-6 and C-7 trans-substituents are diequatorial, hence the trans-protons at these positions are anti-parallel and $J_{6,7}$ is large, usually 9-11 Hz. When the seven-membered ring adopts a chair conformation, the hydrogens at C-6 and C-7 in these compounds (e.g. 20-22) are diequatorial and $J_{6,7} \leq 3$ Hz.

19. We observed that when the C-6 α-hydroxyl group was esterified with acetate or trifluoroacetate groups, C-6→C-4 acyl migration occurred during acid-catalyzed removal of the β-oriented C-4 t-butyl ether group.

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