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TOTAL SYNTHESIS OF PSEUDOGUAIANOLIDES III. (±)-AROMATIN[1]

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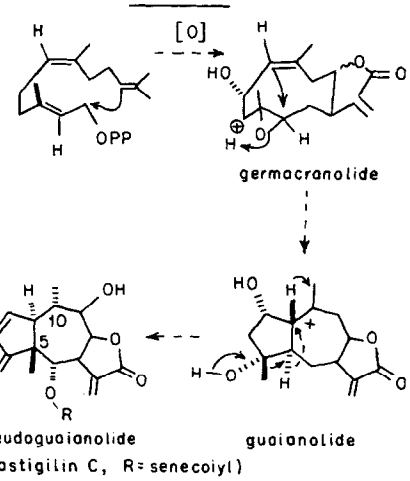
Abstract: (±)-Aromatin (5), has been assembled from 2-methyl-1,3-cyclopentanedione in a linear synthesis characterized by high regio- and stereoselectivity at all stages. Several contributions to organosynthetic methodology are featured.

The pseudoguaianolides are a class of highly functionalized sesquiterpene α-methylene-γ-lactones[2] derived *in vivo* from farnesyl pyrophosphate by two-fold cyclizations, first to germacranes and then guaianes, along with multiple oxidations (summarized in Scheme I). At some stage in their biosynthesis,[2,3] a complex rearrangement sequence occurs, in which 1,2-methyl migration converts the isoprenoid guaiane skeleton into the non-isoprenoid pseudoguaiane. Herz[3a] has postulated that when biogenesis proceeds from *cis, trans*-farnesyl pyrophosphate, the ultimate rearrangement product possesses an α-oriented C-10 methyl group, characteristic of the helenanolides (while the C-10 epimers arising from *trans, trans*-farnesyl pyrophosphate are ambrosanolides). Indeed representatives of each above structural type have been found as cogeners with fastigilin C in the desert marigold (*Baileya multiradiata*, fam. *compositae*)[4]. While the proposed biosynthetic pathway to the helenanolides appears plausible in essence, a biogenetic-type approach to their synthesis seems unfavorable when so much sensitive functionality must be contended with. Moreover, attempts to simulate the guaianolide to pseudoguianolide rearrangement *in vitro* have not been successful.[3b] Such considerations, coupled with the significant biological activity[4b] of these architecturally challenging molecules, have stimulated the efforts of several organosynthetic research groups and significant progress has been made.[5-10]

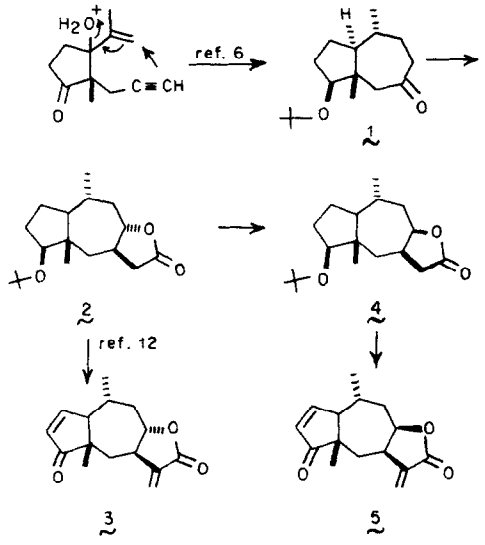
Scheme I



Several years ago, we began work[11] in the helenanolide area by developing an efficient synthesis of the hydroazulenic template 1, which we envisioned would provide ultimate access to fastigilin C and cogeners.[4a] The details for converting 1 into (±) aromaticin (3) were recently published[12] and this report correspondingly discusses our route to (±)-aromatin (5), which proceeds in part along similar lines. Lactone 2, the branch point to

both 3 and 5, is now preparable more directly and with improved steroselectivity as a result of newly developed organosynthetic methodology.

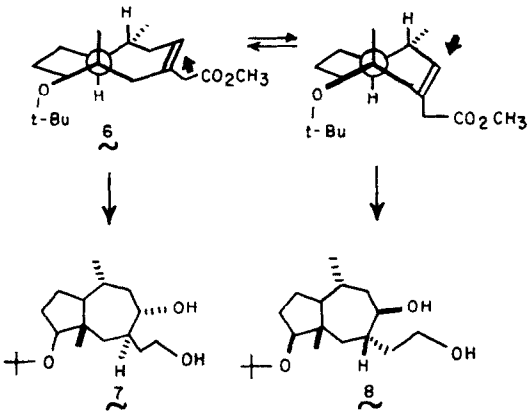
Scheme II



The following discussion is divided into distinct segments (Scheme II) that incorporate new synthetic strategies: 1) a stereospecific γ-lactone annulation for converting 1 to 2 via intramolecular reduction; 2) a "one-pot" carbinol inversion of trans- to cis-fused γ-lactones, e.g. 2 → 4; and 3) improved procedures for α-methylenation of γ-lactones such as 4.

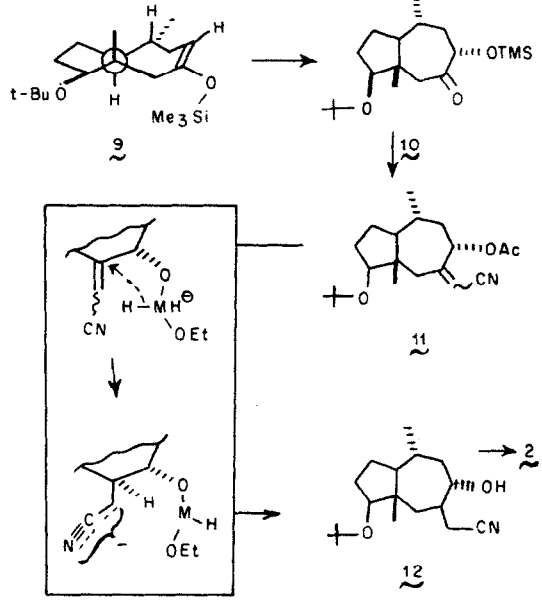
DISCUSSION

A. Selective trans-lactone annulation: Originally[1,12], lactone 2 was approached by the hydroboration-oxidation of the β,γ-unsaturated ester 6 derived from 1. Because of steric hindrance about the double bond, (with both sides accessible due to conformational flexibility), borane rather than dialkylboranes was required to achieve appreciable conversion to hydroboration product. However, despite using low temperatures, unavoidable intramolecular ester reduction also occurred and the overall stereoselectivity (i.e. 7:8) was only 4:1 at best. Thus, diol 8 had to be removed by tedious fractional crystallization before 7 was oxidized back[12] to 2. The above-noted lack of stereo- and chemoselectivity during elaboration of 1 into 2 can now be completely circumvented



by using our newly-developed γ-lactone annulation.[13] In this process, stereospecific hydride transfer to the β-position of an α,β-unsaturated nitrile appendage is accomplished intramolecularly by a neighboring alkoxymetallohydride. The latter species is generated in situ by lithium borohydride or aluminohydride reduction of a previously introduced acetoxy group, as illustrated in Scheme III.

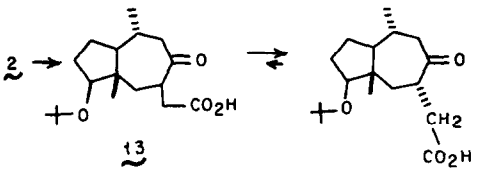
Scheme III



Experimentally, one first had to introduce the crucial directing group at the C-8α position of ketone 1. Accordingly, the kinetic enolate of 1 was formed at C-8 as desired, and then silyated (→9, with vinyl proton multiplet at δ4.92). Although ring inversion among the various conformational forms of cycloheptenes

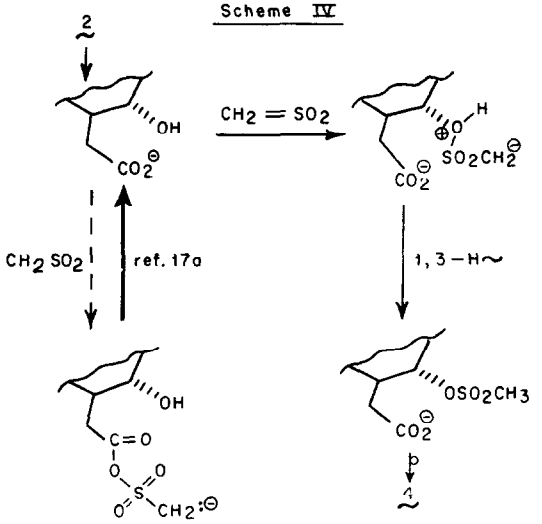
is very rapid, we anticipated that the sterically demanding m-chloroperoxybenzoic acid[14] would react at low temperatures preferably from the α-side of 9, via the chair form shown, in accord with the Curtin-Hammett hypothesis. Certainly stereoselectivity should be more pronounced than was observed previously with borane[12]. Indeed a single, isomeric C-8 trimethylsiloxyketone[14] (10) resulted; the stereochemical control element for the upcoming intramolecular reduction was now in place. When the Wadsworth-Emmons reaction[15] was applied directly to 10, inadvertent hydrolytic desilylation consumed the Z-conjugated nitrile, forming an iminolactone that was valueless for the upcoming conjugate reduction sequence. Hence, the trimethylsilyl group in 10 was directly replaced by acetyl (96% yield) and the resulting α-acetoxyketone converted to the E, Z mixture of α,β-unsaturated nitriles 11. Initial efforts to reduce 11 intramolecularly with relative asymmetric induction utilized lithium borohydride in refluxing tetrahydrofuran,[13] but even after seven hours, there was incomplete reduction (IR showed remaining conjugated nitrile at 2220 cm^{-1}), along with ca. 60% yields of 12. Significant improvements were noted when lithium aluminum hydride was used, with the rationale[13] that α-cyano-stabilized carbanionoid species resulting from hydride transfer (e.f. Scheme III) would have some measure of "electronic protection" from further reduction. Purified 12 was obtained in 75% yield (unoptimized) after 20 min. reaction with $LiAlH_4$ in THF at 0°→20°. Alkaline hydrolysis of 12, followed by acidification led directly to lactone 2, identical in all respects with material prepared previously[1,12]. The overall yield for six steps commencing with 1 was 36% and could doubtless be further optimized if desired. This sequence illustrates the feasibility of trans-fused lactone annulation with complete site- and diastereoselectivity onto any cycloalkanone template provided that the α-oxymetallohydride control element can be introduced as required.[13] Moreover, the completely stereoselective lactone construction leading from 1 to 2 retrospectively enhances the overall specificity of our aromaticin synthesis.[12]

B. Trans→cis-γ-lactone inversion: In considering ways to convert the trans-fused lactone 2 into the cis-fused precursor 4 for aromatin, we avoided the keto-acid 13, having previously observed its facile epimerization,[12] which destroys the hard-won, kinetically acquired chirality of the "pre-lactonic" side chain.



Such a stereomutation poses danger to any redox sequence wherein carbinol inversion proceeds through a ketone intermediate. Moreover, seemingly appropriate reactions for direct intramolecular carbinol inversion, e.g. the Mitsunobu reaction,[16] failed because the hydroxy-acid from 2 relactonized faster than combining with the azoester-triphenylphosphine adduct, even when the carboxylate salt from 2 was neutralized in the presence of the latter reagents. In order to activate the C-8 hydroxyl group for intramolecular displacement without concomitant acyl activation (→2), the following seemingly rational strategy[17a] was pursued (Scheme IV depicts a plausible but unverified mechanistic pathway).

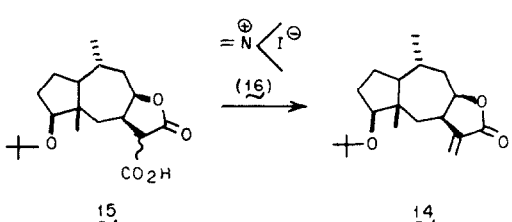
Scheme IV



The dried potassium salt from saponification of 2 was treated with excess mesyl chloride and triethylamine in tetrahydrofuran, conditions

wherein sulfene is generated.[17b] We hoped that any reaction of that species with carboxylate would be reversible[17a] while combination with the hindered C-8 hydroxyl group would not be.[18] Once the latter reaction had proceeded, aqueous hydroxide was directly added (to hydrolyze any mixed anhydride) so that intramolecular SN2 carboxylate displacement at C-8 could become optimized. In the event, workup provided a lactone mixture containing 85% of cis-lactone 4 (carbinol proton multiplet at δ 4.80) and 15% of starting lactone 2 (carbinol proton at δ 4.20). This pleasing outcome was buttressed by the subsequent finding (next section) that of the pair only 4 could be carboxylated by Stiles' reagent (methyl methoxymagnesium carbonate) and this clearly separated 4 as the α-carboxylactone from 2, which was recyclable in the lactone inversion process.

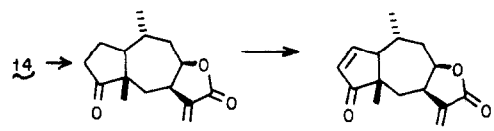
C. α-Methylenation of γ-lactone 4: In our preliminary report[1] we described the conversion of 4 into the α-methylene-γ-lactone 14 by means of Parker and Johnson's methodology,[19] wherein the lactone is first carboxylated and then subjected to decarboxylative Mannich reaction with formaldehyde and diethylamine. The 40% overall yield for these two steps suggested that improvement was possible. However, preferential carboxylation of 4 with Stiles reagent in the presence of 2 remained a component of any revised sequence since it allowed isolation of pure α-carboxyl-cis-lactone 15. We next treated 15 in acetonitrile with Eschenmoser's salt (16), which Danishefsky et al[20] had used for lactone enolate alkylation (and subsequent elimination of the derived quaternary methiodide salt). α-Methylene-γ-lactone 14 was now produced directly in 75% yield; moreover we have since found this procedure to be quite efficient in more highly functionalized



15 14

pseudoguaianolides wherein the original Parker-Johnson method[19] failed in our hands. The smaller steric requirement of cation-16 is no doubt responsible for the improved yields.

The remaining steps for conversion of 14 into aromatin (5) in 40% overall yield, are basically those we have already reported.[1]



17 5

Removal of the C-4 t-butyl ether protecting group followed by pyridinium chlorochromate oxidation gave 2,3-dihydroaromatin[21] (17), mp 113-114°, which showed the expected IR carbonyl bands at 1765 and 1740 cm^{-1}. Phenylselenylation of 17 and periodate oxidation of the derived α-selenylated ketone, with warming to ensure optimum selenoxide elimination, gave rise to (+)-aromatin, mp 125-126°, whose IR and PMR spectra agreed with those reported.[22]

In summary, the total synthesis presented herein includes three potentially general sequences for use by organosynthetic practitioners: 1) a site- and stereoselective γ-lactone annulation (1→2); 2) a "one-pot" procedure for lactone inversion at the carbinol center; and 3) improved technology for α-methylenation of lactones that may be appropriate when other methods[23] are unsatisfactory.

EXPERIMENTAL[24]

Preparation of [c-2, t-7-dimethyl-c-4-hydroxy-t-8-(tert. butyloxy)-r-1H-bicyclo[5.3.0]dec-t-5-yl] acetic acid-γ-lactone (2):

To a solution of LDA prepared at -78°C from 0.042 mL (0.30 mmol) of diisopropylamine and 0.190 mL of 1.4 M n-butyllithium solution (0.26 mmol) in 1.0 mL of tetrahydrofuran (THF) was added 50 mg (0.20 mmol) of 1[11] in 0.30 mL THF. After 40 min. at -78°, warming to 0° and addition of 0.15 mL of HMPA, 0.075 mL (0.60 mmol) of chlorotrimethylsilane was added and the mixture stirred for 30 min., then partitioned between pentane and aqueous $CuSO_4$. Standard workup, drying (Na_2SO_4), and solvent evaporation yielded 60 mg (93%) of 9, as a pale yellow oil. IR(neat) ν_{max}: 1660, 1260, 1210, 910, 880, 850 cm^{-1}; ^1H NMR δ 4.92 (1H, dd, J=8.0, 5.0 Hz), 3.30 (1H, t, J=7.0 Hz), 2.11 (2H,s), 1.13 (9H,s), 0.76 (3H,s), 0.76 (3H, d, J=6.5 Hz), 0.18 (9H,s).

To 60 mg (0.18 mmol) of crude 9 in 1.0 mL of methylene chloride (CH_2Cl_2) at -10° was

added 50 mg (0.23 mmol) of MCPBA dissolved in 0.50 mL CH_2Cl_2. After 20 min., the mixture was poured into 20 mL pentane, washed with 10% sodium sulfite (2x15 mL), saturated $NaHCO_3$, dried and concentrated to yield 50 mg (79%) of oily 10. IR(neat)ν_{max}: 1715, 1260, 1200, 910, 880, 850 cm^{-1}; ^1H NMR δ 4.20 (1 H, dd, J=8.0, 4.0 Hz), 3.30 (1H, t, J=8.0 Hz), 2.40 (2H, AB quartet, J=15 Hz), 0.93 (3H, d, J=6.5 Hz), 0.80 (3H,s), 0.15 (9H,s).

Ketone 10 (93 mg, 0.27 mmol) was dissolved in 5.0 mL of CH_2Cl_2, followed by 0.305 mL (2.19 mmol) of triethylamine, 0.260 mL (2.73 mmol) of acetic anhydride and 3 mg (0.027 mmol) of 4(N,N-dimethylamino)pyridine. After 24 h at RT, the reaction mixture was diluted with 20 mL CH_2Cl_2, washed with 5% HCl (2x30 mL), saturated $NaHCO_3$ (30 mL), dried and concentrated, yielding 82 mg (96%) of 8-acetoxyketone. IR(neat) ν_{max} 1740, 1715, 1240, 1200 cm^{-1}. ^1H NMR δ 5.17 (1H, dd, J=11.5, 4.0 Hz), 3.33 (1H, t, J=8.0 Hz), 2.70 (1H, d, J=18 Hz), 2.20 (1H, br d, J=18 Hz), 2.06 (3H,s), 1.09 (9H,s), 0.91 (3H, d, J=6 Hz), 0.88 (3H,s).

Sodio diethyl cyanomethylphosphonate (0.344 mmol) was generated from 16 mg of NaH (50% in oil) and 65 mg of diethyl cyanomethylphosphonate in 2 mL of dimethoxyethane (DME). After 40 min. at R.T, a solution of 82 mg of the 8-acetoxyketone in 10 mL of DME was added and the reaction run for 45 min., then quenched into 30 mL of 5% HCl and extracted with ether (2x30 mL). The combined ether extracts were washed, dried and concentrated to yield 100 mg (98%) of oily acetoxynitrile 11 (E,Z mixture). IR(neat)ν_{max} 2220, 1750, 1620, 1240, 1200 cm^{-1}. ^1H NMR δ 2.03, 2.06 (isomeric acetates), 0.87 (C-10 methyls, 0.75, 0.53, d, J=7Hz) 0.75, 0.53 (C-5 methyls).

Lithium aluminum hydride (15 mg, 0.4 mmol) was added to a solution of 11 (88 mg, 0.27 mmol) in 5.0 mL of THF. After 20 min. at RT, the reaction was quenched into 30 mL 5% HCl, the product extracted into ether and worked up conventionally, yielding 59 mg (75%) of oily hydroxynitrile 12. IR(neat)ν_{max} 3500, 2250 cm^{-1}. ^1H NMR δ 3.70 (1H,m), 3.27 (1H, t, J=8 Hz), 1.10 (9H,s), 0.82 (3H, d, J=6.5 Hz), 0.66 (3H,s).

Crude 12 (59 mg, 0.20 mmol) was dissolved in 5.7 mL of ethanol and 1.44 mL (2.0 mmol) of 5% NaOH added. After 4h reflux, ammonia evolution had ceased and the mixture diluted with 20 mL H_2O and washed with ether (2x15 mL) to remove any neutral by-products. Acidification, ether extraction and standard workup afforded 40 mg (66%) of oily lactone 2, which gave crystals, mp 87-8°, from hexane (reported,[12] mp 88.5-89°). IR and ^1H NMR data were identical with those reported.[12]

Preparation of [c-2,t-7-dimethyl-t-4-hydroxy-t-8[tert. butyloxy]-r-1H-bicyclo[5.3.0] dec-t-5-yl]acrylic acid-γ-lactone (14):

Twenty mg (0.068 mmol) of 2 was refluxed for 3h in 1.0 mL of 95% aqueous methanol containing 5 mg (0.082 mmol) of KOH. Solvent was then removed in vacuo and residual water removed by repeated azeotroping with benzene. The residual salt ($\nu_{C=O}$ 1580 cm^{-1}) was suspended in 1.0 mL of THF, cooled to 0°, and treated with 0.045 mL (0.3 mmol) of triethylamine, followed by 0.020 mL (0.24 mmol) of methanesulfonyl chloride. After 45 min., 2.2 mL (0.3 mmol) of 0.13 N NaOH solution was added and the mixture warmed at 50° for 1h. After acidification with 20 mL of 5% HCl and extraction with ether, workup proceeded to yield 20 mg (~100%) of oily 4 + 2 in an 85:15 ratio (estimated by NMR integration of C-8 proton multiplets in 4, at δ 4.8, and in 2, at δ 4.2). For lactone 4: IR(neat)ν_{max} 1780, 1190, 1100, 1000, 900 cm^{-1}. ^1H NMR δ 4.80 (1H,m) 3.4 (1H, t, J=7.0 Hz), 1.16 (9H,s), 0.98 (3H, d, J=6.0 Hz), 0.80 (3H,s).

A crude sample of lactone 4 (58 mg, 0.197 mmol, containing ca. 25% of lactone 2, from the above inversion sequence inter alia) was heated with 1.65 mL (3.94 mmol) of 2N methyl methoxymagnesium carbonate in DMF[19] at 140° for 40 min. After cooling, the solution was partitioned between ether and 6 N HCl. The ether layer was extracted with 5% NaOH (2x30 mL) and worked up to provide 30 mg of a 1:1 (NMR) mixture of 4 and 2. The combined basic washes from above were acidified and worked up to provide 26 mg of 15 as a crystalline foam (87% yield, based on recovered 4). IR(neat)ν_{max} 3450-2700 (br), 1780, 1720, 1200, 1060, 1040, 1010 cm^{-1}. ^1H NMR δ 4.90 (1H,m), 3.75 (1H,m), 3.48 (1H, t, J=7.0 Hz), 3.20 (1H, br s), 1.14 (9H,s), 0.98 (3H, d, J=7 Hz), 0.76 (3H,s).

Crude 15 (22 mg, 0.065 mmol) and Eschenmoser's salt (24 mg, 0.13 mmol) were refluxed for 2h in 2 mL of acetonitrile. After cooling, the solution was partitioned between ether and 5% HCl, then the ether layer washed with 10% Na_2SO_3 (15 mL), brine (15 mL), dried and concentrated to give 20 mg (90%) of 14, mp 95-97° (from hexane). IR($CHCl_3$)ν_{max} 1770, 1660, 1200, 1130, 1060, 1040, 1010, 950, 900, 830 cm^{-1}. ^1H NMR δ 6.28 (1H, d, J=2 Hz), 5.50 (1H, d, J=2.0 Hz), 4.80 (1H,m), 3.52 (1H, t, J=8.0 Hz), 3.12 (1H,m), 1.20 (9H,s), 1.00 (3H, d, J=6.5 Hz), 0.80 (3H,s). MS: m/e 306 (M^+, <1%), 250 ($M^+-C_4H_8$; 100%), 232 (15%); Exact mass. Calculated for $C_{15}H_{22}O_3$ (base peak): 250.1569. Found: 250.1602.

Preparation of 2,3-dihydroaromatin (17):

Twenty milligrams of 14 (0.065 mmol) and 4 mg of p-toluenesulfonic acid monohydrate were refluxed for 1.5 h in 2 mL of benzene. After cooling, 25 mL of ether was added and the solution washed with $NaHCO_3$ (2x20 mL), dried and concentrated to give 14 mg (86%) of the C-4 alcohol (oil). IR(neat)ν_{max} 3450, 1760, 1660 cm^{-1}. ^1H NMR δ 6.30 (1H, d, J=2.0 Hz), 5.68 (1H, d, J=2.0 Hz), 4.76 (1H,m), 3.84 (1H, t, J=8 Hz), 3.14 (1H,m), 0.96 (3H, d, J=6.5 Hz), 0.80 (3H,s).

The above hydroxy-lactone (14 mg, 0.056 mmol) was dissolved in 2 mL of CH_2Cl_2 and treated with 15 mg (0.07 mmol) of pyridinium chlorochromate. After 2h, the slurry was diluted with CH_2Cl_2 and filtered thru silica gel. Dihydroaromatin (17) was recovered by ethyl acetate elution, followed by further purification on SilicAR (with 9:1 CH_2Cl_2: ethyl acetate), to give 9 mg (64%) of pure 17, mp 113-114, whose NMR spectrum showed the

absence of 2,3-dihydroaromaticin.[12] IR (CH_2Cl_2)ν_{max} 1765, 1740, 1660 cm^{-1}. ^1H NMR δ 6.20 (1H, d, j=2.5 Hz), 5.67 (1H, d, J=2.5 Hz), 4.70 (1H,m), 3.08 (1H,m), 1.05 (3H, d, J=6.5 Hz), 0.88 (3H,s). MS: m/e 248 (M^+, 100%), 204 (M^+-CO_2); Exact mass. Calculated for $C_{15}H_{20}O_3$: 248.1413. Found: 248.1449.

Some time after this work was completed,[1] a sample of 17 was sent to Prof. F. E. Ziegler (Yale) who compared its 270 mHz NMR spectrum with his material prepared by another route (ref. 8); the two spectra were identical.

Preparation of (+)-Aromatin (5):

Eight milligrams (0.032 mmol) of 17 in 1 mL of ethyl acetate was "spiked" with 0.20 mL of ethyl acetate containing HCl gas. Phenylselenyl chloride (7.0 mg, 0.036 mmol) was added and the orange solution stirred at RT for 14 h (changing to pale yellow). At this stage, selenylated ketone (R_f 0.80, 8% ethyl acetate/CH_2Cl_2) was present to the virtual exclusion of 17 (R_f = 0.40). The reaction mixture was taken up in 20 mL ether, extracted with $NaHCO_3$ (2x20 mL), dried and concentrated to give 15 mg of crude selenylated ketone, which was further purified by chromatography (5 g. SilicAR, 4% ethyl acetate/CH_2Cl_2) to give 11 mg (85%). IR(neat)ν_{max} 1765, 1935, 740, 690 cm^{-1}. ^1H NMR δ 7.64-7.30 (5H, complex), 6.30 (1H, d, J=2.5 Hz), 5.68 (1H, d, J=2.5 Hz), 4.60 (1H,m), 4.06 (1H,m), 2.65 (1H,m), 0.94 (3H, d, J=6.5 Hz), 0.90 (3H,s).

Six milligrams (0.015 mmol) of the purified selenyl ketone was dissolved 0.60 mL THF and 0.10 mL H_2O, along with 10 mg (0.045 mmol) of $NaIO_4$. After 2h at RT, starting material was consumed (by TLC). After 30 min. at 50°, the reaction mixture was cooled, diluted with 30 mL ether, washed with $NaHCO_3$ (2x15 mL), dried and concentrated to give 4 mg of oily 5. Purification on 2g of SilicAr (4% ethyl acetate/CH_2Cl_2) gave 2.4 mg of crystalline (+)-aromatin (5), mp 125-126° (from hexane/acetone). IR (CH_2Cl_2)ν_{max} 1765, 1715, 1660, 1575, 1200, 1160, 825 cm^{-1}. ^1H NMR δ 7.54 (1H, dd, J=8.0, 2.0 Hz), 6.30 (1H, d, J=2.4 Hz), 6.13 (1H, d,d, J=8.0, 3.0 Hz), 5.7 (1H, d, J=2.4 Hz), 4.80 (1H,m), 3.20 (1H,m), 1.15 (3H, d, J=6.5), 1.05 (3H,s). These spectral data agreed with published values for (-)-aromatin.[22]

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REFERENCES

1. A preliminary account of this research has appeared: Lansbury, P. T.; Hangauer, Jr., D. G.; Vacca, J. P. J. Am. Chem. Soc. 1980, 102, 3964.

2. Fischer, N. H.; Olivier, E. J.; Fischer, H. D. Fort. der Chem. Org. Naturstoffe, 1979, 38, 47-390. This comprehensive review provides complete numbering systems for all classes of sesquiterpene lactones.

3. (a) Herz, W.; Murari, R.; Blount, J. F. J. Org. Chem. 1979, 44, 1873 and references cited therein.
(b) Fischer, N. H.; Wu-Shih, T-F.; Chiari, G.; Fronczek, F. R.; Watkins, S. F. Journal of Natural Products (Llyodia) 1981, 44, 104.

4. (a) Pettit, G. R.; Herald, C. L.; Gust, D.; Herald, D. L.; Vannell, L. D. J. Org. Chem. 1978, 43, 1092.
(b) Pettit, G. R.; Herald, C. L.; Judd, G. F.; Bolliger, G.; Vannell, L. D.; Lehto, E.; Pase, C. P. Lloydia 1978, 41, 29.

5. Grieco, P. A.; Ohfune, Y.; Majetich, G. Tetrahedron Lett. 1979, 3265, and references cited therein.

6. Roberts, M. R.; Schlessinger, R. H. J. Am. Chem. Soc. 1979, 101, 7626.

7. Kok, P.; DeClercq, P. J.; Vandewalle, M. E. J. Org. Chem. 1979, 44, 4553.

8. Ziegler, F. E.; Fang, J-M. J. Org. Chem. 1981, 46, 825.

9. Nagao, K.; Chiba, M.; Yoshimura, I.; Kim, S-W. Chem. Pharm. Bull. 1981, 29, 2733.

10. Ambrosanolides have also received much and earlier attention. Damsin was the first to be synthesized: Kretchmer, R. R.; Thompson, W. J. J. Am. Chem. Soc. 1976, 98, 3379.

11. Lansbury, P. T.; Serelis, A. K.; Hengeveld, J. H.; Hangauer, Jr., D. G.; Tetrahedron 1980, 36, 2701.

12. Lansbury, P. T.; Hangauer, Jr., D. G. Tetrahedron 1981, 37, Suppl. 1, 371.

13. Lansbury, P. T.; Vacca, J. P. Tetrahedron Lett. 1982, in press.

14. Rubottom, G. A.; Vazquez, M. A.; Pelegrina, D. R. Tetrahedron Lett. 1974, 4319.

15. Wadsworth, Jr., W. S. "Organic Reactions" Vol. 25, 73.

16. An efficient δ-lactone inversion has been reported: Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, T. Tetrahedron Lett. 1981, 22, 913. γ-Lactone formation with carbinol inversion occurs best if the γ-hydroxy-acid cannot lactonize directly due to geometric constraints: Trost, B. M., Shuey, C. D.; DiNinno, F. J. Am. Chem. Soc. 1979, 101, 1284.

17. (a) For kinetic studies of concerted E2 and/or E1CB eliminations of aryl methanesulfonates, see Douglas, K. T.; Steltner, A.; Williams, A. J.C.S. Chem. Comm. 1975, 353.
(b) Crossland, R. K.; Servis, K. L. J. Org. Chem. 1970, 35, 3195.

18. With p-toluenesulfonyl chloride in pyridine, the carboxylate is irreversibly sulfonylated and hydroxyl attack upon the mixed anhydride simply reforms lactone 2 (in amounts comparable to 4).

19. Parker, W. H.; Johnson, F. C. J. Org. Chem. 1973, 38, 2489.

20. Danishefsky, S.; Schuda, P. F.; Kitihara, T.; Etheridge, S. J. J. Am. Chem. Soc. 1977, 99, 6066.

21. After our preliminary report,[1] Professor F. Ziegler (Yale) informed us of his synthetic efforts toward aromatin: see ref. 8. A sample of 17 and the corresponding material prepared alternatively by these workers were found to be identical, via 270 mHz NMR analyses at Yale University.

22. Romo, J; Joseph-Nathan, P.; Diaz, F. Tetrahedron 1964, 20, 79-85.

23. (a) Grieco, P. A. Synthesis 1975, 6782.
(b) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. Synthetic Communications 1975, 5, 245.

24. All reactions were run in purified solvents under nitrogen or argon atmospheres. "Standard workup" refers to partitioning reaction mixtures between organic and aqueous phases, washing the former with dilute acid or base as required, then brine solution, drying over Na_2SO_4 or $MgSO_4$, and finally removing solvent by means of a rotary evaporator under reduced pressure. Melting points were taken on a calibrated "Mel-temp" apparatus or Fischer-Johns block and are uncorrected. ^1H NMR spectra were obtained on a Varian EM-390 spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. IR spectra were obtained on a Perkin-Elmer 727B, using neat films or solutions in solvents as indicated.