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TOTAL SYNTHESIS OF PSEUDOGUAIANOLIDES—II

(±)-AROMATICIN†

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Abstract—(±)-Aromaticin (**5**), a helenanolide with five chiral centers, has been assembled from 2-methyl-1,3-cyclopentanedione in a linear synthesis characterized by high regio- and stereochemistry at all stages.

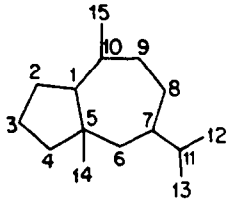
We have recently embarked upon an extended research program which focuses on the total synthesis of hydroazulenic sesquiterpene lactones characterized by the pseudoguaiane skeletal framework. Two major varieties of pseudoguaianolides[1] exist: *ambrosanolides*, which are characterized by a β-oriented C-10 methyl group and exemplified by damsin (I); and *helananolides*, which have the opposite C-10 configuration and are usually more heavily functionalized (and hence more biologically active), as shown in fastigilin C (II). In order to synthesize the structurally challenging helenanolides,[3] we feel it essential to have rapid access to an appropriate bicyclo[5.3.0]decane template, upon which stereocontrolled introduction of functionality could proceed in a rational sequence of operations. Otherwise, such a *linear* strategy would become intolerably long and impractical.

Scheme 1 summarizes the status of our investigations[3] when the present helenanolide synthesis began: solid arrows (→) designate previously completed steps[3] (→**4**) while double arrows (⇒) denote retrosynthetically the chosen route to be followed enroute to aromaticin (**5**).

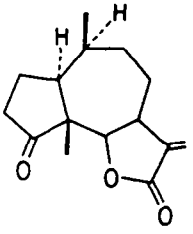
The requirement for an abundant and versatile pseudoguaiane template had been met in selectively-protected diketone **1** (Scheme 1), preparable in only three steps from 2-methyl-1,3-cyclopentanedione.[3] Subsequent functional group manipulations of **1** afforded **2**, whose configuration at carbons 1, 5 and 10 correspond to the natural product damsinic acid (**3**), thus providing the impetus for total synthesis of the latter.

After the necessary correlation of **2** with **3** had been successfully carried out,[3a] epimerization of the unactivated chiral center at C-10 was required. That task was accomplished by temporarily introducing into **2** a "bridging" vinyl group at C-8,9.[3b] This specific perturbation activated the C-10 hydrogen for reversible dienolate formation and eventually afforded the less-strained ketone **4**, without the Me–Me interactions present in **2**, (once the activating α-(phenylthio) vinyl group had been removed by hydrogenation). We were now poised to undertake the present total synthesis of (±)-aromaticin[2d] (**5**), our initial target among the helenanolides.

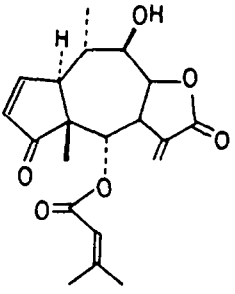
Aromaticin was first isolated by Romo *et al.*[4] from the Chilean plant *Helenium aromaticum* (Hook) Bailey. Structure **5** was correctly deduced from spectroscopic data and correlation with dihydroisotenulin, which permitted rigorous assignment of configuration at all chiral centers except C-7 (tentatively assigned on biogenetic grounds). Subsequently, aromaticin was found to be active *in vitro* against cells derived from human carcinoma of the nasopharnyx (KB) in cell culture (ED_{50} 0.34 mg/ml),[5] a consequence of the



Pseudoguaiane skeleton

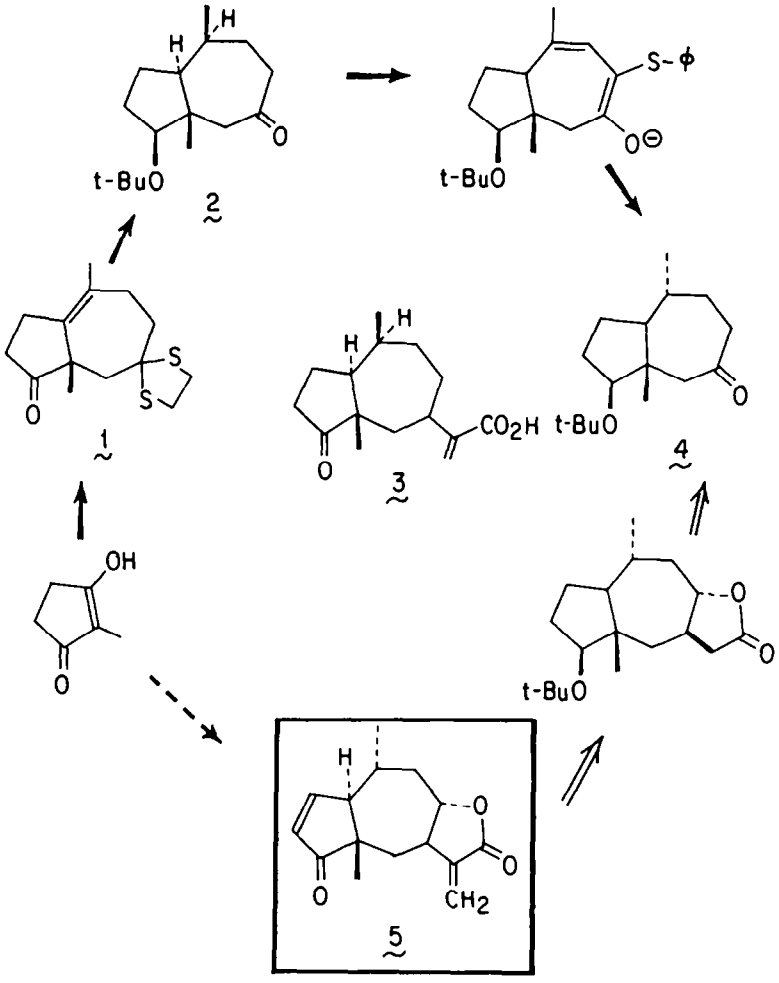


Damsin (I)



Fastiglin C (II)

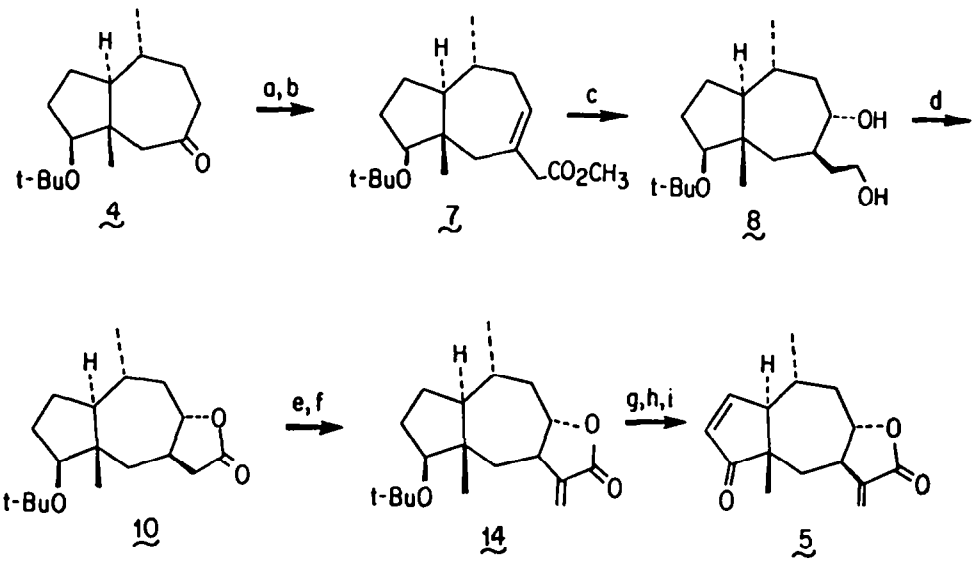
†Dedicated to the memory of Prof. R. B. Woodward, whose artistic creativity and painstaking utilization of strategic planning has inspired and guided our endeavors in the organosynthetic domain.



Scheme I.

presence of two electrophilic α,β-unsaturated carbonyl functions that irreversibly deactivate sulfhydryl enzymes by Michael addition of the latter. The sensitivity of aromaticin and other pseudoguaianolides to *multiple nucleophilic addition* (three sites in fastigilin C) *must be kept foremost in mind when developing a synthetic strategy*. Accordingly, our retrosynthetic analysis of the aromaticin problem (Scheme 1, ⇒) called for unveiling the A-ring cyclopentenone functionality in the final step. Such a structure tends to deconjugate and/or epimerize at C-1, under both acidic and basic conditions,[1a] as well as to undergo nucleophilic addition. The appearance of even the saturated cyclopentanone ring ($pK_a \sim 18$) was to be delayed until α-methylenation of the less acidic γ-lactone ($pK_a \sim 25$) had been completed.[6] The remaining links in the synthetic plan, using **4** as our starting point, were structurally obvious (see below) but their ultimate success hinged on solving the crucial stereochemical questions at C-7 and C-8 as they arose. Numerous rapidly-exchangable conformations are possible for 7-membered rings,[7] assuring that this task would by no means be a trivial one. The successful experiments that culminated in a regio- and stereocontrolled aromaticin synthesis[2d] are outlined in Scheme 2.

The reagent of choice for lactone annelation onto **4** was methyl α-(trimethylsilyl)acetate,[8] which afforded the acrylate **6**, m.p. 69 71 , in quantitative yield. Deconjugation[9] of **6** with LDA–HMPA was expected to occur by regiospecific proton abstraction at the less-hindered γ-site, i.e. C-8, followed by quenching into dilute acetic acid. The β,γ- unsaturated ester **7** isolable from **4** in 80% overall yield after chromatography, showed the anticipated vinyl proton *triplet* at δ 5.56, with J = 5.6 Hz. At this stage, *cis*-hydroboration followed by peroxide oxidation was planned for the introduction of the needed C-8 OH function, and also for establishing the remaining two chiral centers of aromaticin. This desirable outcome would result only if electrophilic attack by a borane occurred from the α-face of the molecule, which seemed to require a chair conformation (based on models). Several reports in the literature[7] supported our expectation that the chair conformation would be the more stable one. Should **7** react via the alternative twist-boat conformer, in which β-face is more accessible, both C-7 and C-8 would have the wrong configuration.

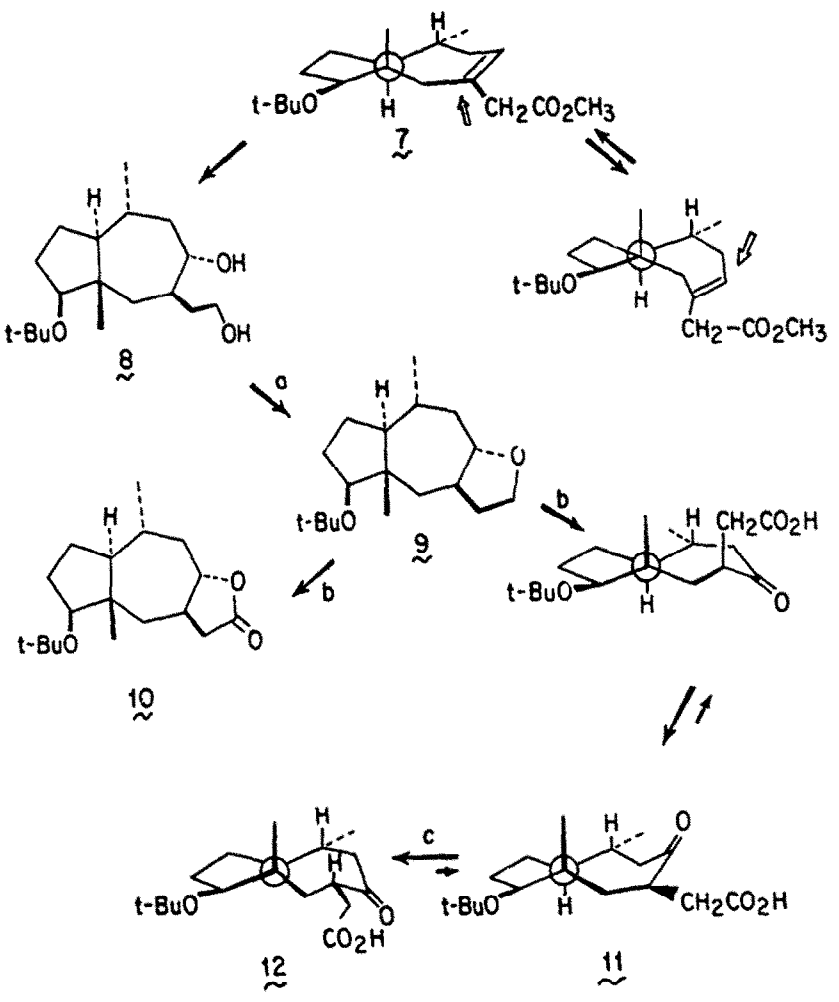


a) LDA, $(CH_3)_3$ $SiCH_2CO_2CH_3$, THF, -78° → 25°; b) LDA-HMPA, THF, -78°, then CH_3CO_2H;
c) BH_3-THF, -78° → 25°, H_2O_2, OH^-; d) Pt, O_2, H_2O-acetone;
e) LDA-HMPA, $BrCH_2OCH_3$, -78° → -5°; f) 3 eq. KOt-Bu, 1 eq. H_2O, THF;
g) TFA, 0°/3 h, then NaOH/i-PrOH-H_2O, 25° 2h; h) PCC, CH_2Cl_2;
i) C_6H_5SeCl, EtAc, HCl, then $NaIO_4$, THF-H_2O, 25°/7 h.

Scheme II.

Before addressing this intriguing stereochemical question, we note that 9-borabicyclononane and related dialkylboranes, which exhibit high regioselectivities in many hydroborations of unsymmetrical alkenes[10] and have no "excess" hydrides for intramolecular ester reduction, were virtually useless for the task at hand. Essentially no hydroboration of the hindered π-bond occurred. After much experimentation, we reverted to borane (BH_3.THF) to achieve efficient, low temperature hydroboration (−78 → 0°); this in turn, meant that unavoidable ester reduction[11] to the diol (after peroxide oxidation) would also take place and a "back oxidation" would subsequently be needed. Once the conversion of **7** to **8** was achieved in virtually quantitative yield, the first concern was to establish its steric course (Scheme 3). A portion of crude diol **8**, provisionally formulated as the desired stereoisomer, was cyclized via the primary monotosylate to the tetrahydrofuran derivative **9**, in order to facilitate analysis, as well as further transformations (see below). Gas chromatography of the cyclic ethers revealed a ~4:1 mixture of isomers but the identity of the major isomer was still unresolved. We had also planned to utilize ruthenium tetroxide oxidation[12] of **9** to generate the lactone ring in **10**. However, a fortuitous observation,† namely strong infrared carbonyl absorption at *ca* 1715 cm^{-1} in the IR spectrum of the crude product (in addition to the γ-lactone CO stretch at 1780 cm^{-1}) proved to be ultimately much more significant and led to unambiguous proof of the relative configuration of **8**! According to literature precedent,[12] ruthenium tetroxide oxidation of tetrahydrofurans such as **9** should occur mainly at the less-substituted carbon, producing the expected lactone **10**, but we obtained a ~1:1 mixture of **10** and keto-acid **11**. Since **10** is itself oxidized to **11** under our conditions (catalytic RuO_4 in acqueous acetone), it is not clear to what extent **9** is the source of **11**, but that question does not affect the role of this keto-acid in elucidating stereochemistry, as we shall now see. It is known that when RuO_4 oxidations generate ketonic groups adjacent to a chiral center, epimerization does *not* occur.[13] Ketoacid **11**, while not of apparent value as an intermediate for aromaticin, contains two sterically compressed alkyl groups (at C-5 and C-7) *if the* C-7 *acetic acid side chain is β-oriented* and should therefore, be prone to epimerization *via* reversible formation of the C-7 enolate. Apparently such "1,3-diaxial" strain is somewhat alleviated in **11** by a conformational adjustment (Scheme 3) in which the C-5 methyl group (δ 0.53) is placed in the C-8 carbonyl shielding cone. Nevertheless, intentional equilibration of **11** was readily achieved (DBN/CH_2Cl_2/25°) and produced an isomeric ketoacid (**12**), m.p. 85–87°, in *ca* 80% yield. In **12** the resultant α-oriented side chain allows a conformational change in the 7-membered ring (compared

†In his philosophical discussion of the paramount importance of careful and rigorous planning in multi-step synthesis, Woodward did not disregard the importance of serendipity, stating "The routine (IR) examination of virtually every reaction mixture, however crude, or lacking in tangible prospect of yielding a desired product, often provides a clue to important developments which could not otherwise be made". R. B. Woodward, *Perspectives in Organic Chemistry* (Edited by A. Todd), pp. 155–184. Interscience, New York (1956).



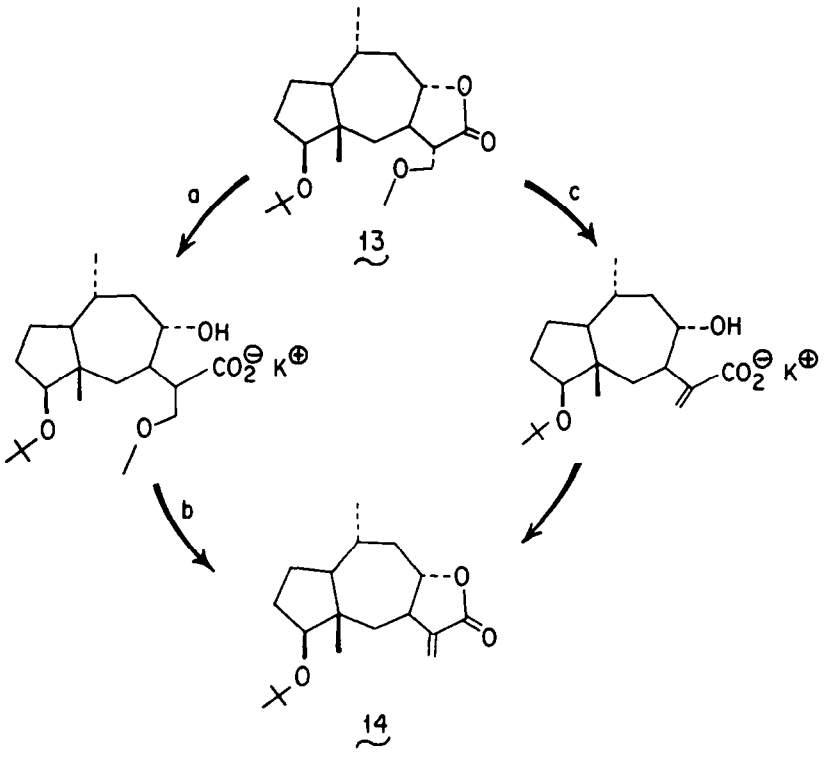
a) TosCl, C_5H_5N, 0° → 60°/56 h; b) RuO_4, acetone-H_2O, 25°/8 h;

Scheme III.

with **11**) which removes the C-5 Me group (now observed at δ 0.80) from the C-8 CO shielding cone (Scheme 3). These results fully establish the β-orientation of C-7 substituents in compounds **8–11**, and the C-8 oxygen substituent in **8–11**, originating from *cis*-hydroboration of **7**, must accordingly be alpha. For synthetic purposes, pure **10**, m.p. 88.5–89°, which possesses all the chirality in aromaticin, was prepared by catalytic oxidation[14] (Pt/O_2) of the major isomer of **8**. In this reaction **11** was not an observed by-product. It was found that improved yields can be achieved when the heterogeneous reaction is conducted in an ultrasonic bath.

We were now ready to introduce the α-methylene group into the γ-lactone ring of **10** and certainly aware of the plethora of methods available.[15] However, much of this methodology has been developed only with simple model compounds, notable exceptions being the work of Danishefsky,[16] Grieco[2a,15] and Johnson.[17,2b] It was soon apparent that enolate alkylations of **10** with alkyl halides containing potential leaving groups (e.g. $C_6H_5S-CH_2I$) proceeded in only modest yields as did the Parker–Johnson procedure;[17] moreover the known tendency of α-methylene-γ-lactones to undergo destruction by nucleophiles, if generated in their presence concerned us from the beginning. These two problems were solved concurrently by alkylating with methoxymethyl bromide, an excellent S_N2 substrate, which gave **13** (along with some dialkylation product), whose side chain resembles that encountered, via base-catalyzed methanol addition, in earlier structural investigations of sesquiterpene lactones.[1] Such a side chain is, in fact, a sturdily-protected, latent α-methylene group, capable of withstanding a variety of neutral or acidic transformations elsewhere in the molecule, but presumably susceptible to deblocking by appropriate basic reagents when desired. It was originally intended to remove the poor leaving group (–OMe) in **13** by employing excess "unsolvated" KOt–Bu/KOH in tetrahydrofuran,[18] under which conditions the more protected acrylate *anion* (from concomitant saponification) would be formed in one operation (Scheme 4). Quenching the above mixture *into* dilute acid led to isolation of **14** in satisfactory yield (*ca* 30% from **10**), as judged by IR and NMR.

Alternatively, the two steps could be experimentally separated. Methanolic potassium hydroxide effected



a) KOH/CH_3OH b) KOt-Bu/THF, then H_3O^+ c) Scheme II, steps e, f, then H_3O^+.

Scheme IV.

only saponification to give the potassium γ-hydroxycarboxylate (IR) from which solvent was removed *in vacuo*; subsequently, KOt-Bu in anhydrous THF transformed the above salt into the acrylate, followed by acid quench and work-up. This slightly longer procedure raised the yield for the **10** → **14** conversion to *ca* 60%. The crude non-crystalline α-methylene-γ-lactone **14** was directly subjected to dealkylation and oxidation at C-4, using Marshall's sequence,[19] and there was subsequently isolated pure, crystalline 2,3-dihydroaromaticin (**15**), m.p. 123–124°. At the time we were completing this research, Bohlmann[20] reported the isolation of (+)-**15**, m.p. 151°, as a constituent of *Telekia speciosa* and provided detailed 270 MHz NMR and MS Data for this natural product. Our synthetic (±)-**15** had identical spectral properties with those reported for the natural product and its successful conversion to (±)-aromaticin (see below) further confirmed its structure and relative configuration.

In order to complete the total synthesis of aromaticin from **15**, we needed only to insert a 2,3-double bond under essentially neutral conditions. Following Grieco's procedure, **15** was treated with phenylselenenyl chloride in ethyl acetate containing some hydrogen chloride (to initiate enolization). The crude selenylated **15** was oxidized with sodium metaperiodate in THF-water, heating briefly to complete selenoxide elimination. (±)-Aromaticin (**5**), prepared in ~75% crude yield from **14**, was recrystallized several times to give pure product, m.p. 178–181°, which was identical in all respects, except for optical rotation, with authentic (+)-**5** by tlc, ^1H NMR, IR and MS.

With the completion of this total synthesis, in twenty-two steps from 2-methyl-1,3-cyclopentandine, the remaining uncertainty in the configurational assignment of aromaticin, namely C-7 chirality, had been resolved. Moreover, concurrent investigations in our group have established the feasibility of inverting *trans*-fused lactones[2d] such as **10** at the carbinol position. This methodology has provided an entry to aromatin,[2d] a cogener and C-8 epimer of **5**, and should have useful ramifications in our continuing efforts to prepared *cis*-fused lactones such as fastigilin C.

EXPERIMENTAL[22]

General considerations. All of the reactions described herein were run under a blanket of dry argon. The phase "was concentrated" or "concentration gave" refers to removal of the solvent on a rotary evaporator under reduced pressure. M.ps were determined with a "Mel-Temp" capillary tube apparatus and are uncorrected. B.ps refer to the oven temps during Kugelrohr distillations and to the vapor temps during fractional distillations.

Glc was performed on either a F and M Scientific 720 dual-column gas chromatograph or a Hewlett-Packard 573A instrument. The packings used were: 10% Apiezon L, 10% and 5% Carbowax 20 M, and 3% OV-1 on Chromosorb W (mesh size 30/60). All of the columns were 0.125 in. inner diam and 6 ft long, except for the 3% OV-1 column which was 4 ft long. The carrier gas (He) flow rate was 60 cm^3/min. Peak areas were used to estimate the relative proportions of compounds in mixtures.

Adsorption chromatography was performed with silica gel GF-254 (type 60) for tlc, silica gel 60 PF254 (containing gypsum) for preparative layer chromatography, and silica gel 60 (particle size 0.063–0.200 mm) or 100–200 mesh Florisil for column chromatography. The tlc slides and preparative layer plates were generally visualized with UV light, Iodine staining, and charring (30% sulfuric acid, then heat on a hot plate), were also used on occasion.

All solvents were dried and distilled prior to use. IR spectra were run on a Perkin Elmer 467 grating spectrophotometer and calibrated with the 1602 cm^{-1} band of polystyrene.

NMR spectra were run on a Jeol JNH-MH-100 spectrometer at 100 megahertz (MHz). With samples less than 5 mg, spectra were taken on a Varian Associates XL-100 (100 MHz) spectrometer using the Fourier Transform (FT) mode. Unless noted otherwise, the spectra were taken into $CDCl_3$ soln utilizing TMS as the internal standard. The spectra are reported in ppm as δ values. The coupling constants (J) are reported in hertz (Hz). Multiplicities of the peaks are abbreviated as s, singlet; d, doublet; t, triplet, q quartet; m, multiplet; and br, broad.

UV spectra were run on a Perkin Elmer 202 UV-visible spectrometer and the absorptions are reported in nanometers (nm).

Mass spectra were run on a Perkin Elmer RMU-6E instrument operating at an ionization potential of 70 eV. A reservoir inlet technique was used unless the direct probe technique is specified. Relative peak intensities were obtained using a Gerber variable scale.

Microanalysis were performed by: Atlantic Microlab, Inc., P.O. Box 80569, Atlanta, GA, 30366, U.S.A.

Methyl 2-[c-2,t-7-*dimethyl*-t-8-(*t-butyloxy*)-*r*-1*H*-*bicyclo*[5.3.0] *dec*-4,5-*en*-5-*yl*] *acetate* (**86**). In a flame dried 10 ml flask, fitted with a side arm and rubber septum, was placed 0.261 ml (1.86 mmol) dry diisopropylamine and 2.9 ml dry THF. The agitating soln was cooled to −78°, then 0.692 ml (1.49 mmol) of n-BuLi in pentane (2.15 M) was added dropwise. After 30 m, a soln of 0.2903 g (1.984 mmol) methyl trimethylsilylacetate in 0.93 ml dry THF was added dropwise. After 30 m, a soln of 0.2500 g (0.9921 mmol) of **4** in 3.50 ml dry THF was added dropwise. The reaction was kept at −78° for 1 hr, then allowed to warm to 25°. After 2 hr at 25°, the reaction was poured into 40 ml 10% HCl. The resulting mixture was extracted with ether (3 × 40 ml). The combined extracts were washed with water (2 × 100 ml), sat $NaHCO_3$aq (1 × 100 ml), brine (1 × 100 ml), dried over $MgSO_4$ and concentrated to give 0.3361 g (>100%) of a light yellow solid. A glc analysis (3% OV-1 column, 230° oven temp) indicated that **6** had been obtained as two isomers in a ratio of ~19:1. An analytical sample, m.p. 69–71°, was obtained by recrystallization from MeOH. Generally, the crude product was carried on further without purification. ^1H NMR: τ 5.57 (1 H, broad s), 3.63 (3 H, s), 3.50–1.20 (complex), 1.14 (9 H, s), 0.85 (3 H, d, J = 6 Hz), 0.66 (3 H, s). IR (neat) ν_{max}: 1715, 1620 cm^{-1}. UV $\lambda_{max}^{95\%\ C_2H_5OH}$ (ε): 232 (13,800) nm. (Found: C, 74.02; H, 10.44. Calc. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%).

The crude **6** was deconjugated as described below.[9] In a flame dried 50 ml flask, fitted with a side arm and rubber septum, was placed 0.135 ml (0.965 mmol) dry diisopropyl amine and 1.3 ml dry THF. The agitating soln was cooled to −78°, then 0.365 ml (0.804 mmol) n-Buti in pentane (2.20 M) was added dropwise. After 30 m, the soln was warmed to −40° and 0.032 ml (1.85 mmol) dry hexamethylphosphoramide (HMPA) was added. The reaction was held at −40° for 20 min then −78° for 15 mins. A soln of **6** (0.1650 g, 0.5357 mmol) in 1.8 ml dry THF was added gradually (over a 10 min period) at −78°. After 1 hr at −78°, the reaction was inversely quenched into vigorously stirring 20% AcOH (20 ml) at 25°. The aqueous mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with water (1 × 60 ml), sat $CuSO_4$aq (2 × 50 ml), sat $NaHCO_3$aq (2 × 50 ml), brine (1 × 50 ml) and dried over $MgSO_4$. Concentration gave 0.1491 g (98%) of a light yellow oil. The crude product was suitable for subsequent steps without purification. If desired, the ester **7** can be purified by chromatography on silica gel (4% ethyl acetate/methylene chloride, R_f ~ 0.7) resulting in an 80% overall isolated yield from **4**. ^1H NMR: δ 5.56 (1 H, br t, J = 5.6 Hz), 3.56 (3 H, s), 3.28 (1 H, t, J = 6 Hz), 2.90 (2 H, s), 2.3–1.2 (complex), 1.10 (9 H, s), 0.77 (3 H, d, J = 6 Hz), 0.61 (3 H, s). IR (neat) ν_{max}: 1740, 1200 cm^{-1}. (Found: C, 74.02; H, 10.46. Calc. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%).

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H*-*bicyclo*[5.3.0] *dec*-*t*-5-*yl*] *ethanol* (**8**). In a flame dried 10 ml flask was placed 0.1880 g (0.6104 mmol) of crude **7** and 1.0 ml dry THF. The stirring soln was cooled to −78°, then 1.83 ml (1.83 mmol) of BH_3·THF complex (1 M) was added dropwise. The resulting mixture was held at −78° for 4 hr, then allowed to slowly warm to −50° over a 2 hr period. The reaction was further warmed gradually to 0° over a 2 hr period and finally held at 0° to +5° for 4 hr. A small amount of MeOH was added (until H_2 evolution ceased) to quench excess BH_3·THF. A 3 N NaOH was added (1.22 ml, 3.66 mmol) followed by 0.81 ml (7.29 mmol) of a 30% H_2O_2 soln. The resulting mixture was stirred at 45° for 2 hr then cooled. The reaction was diluted with 40 ml ether and washed with 5% HCl (1 × 40 ml), water (2 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. Concentration gave 0.1823 g (>100%) of a white solid, mp 74–96°. Recrystallization from hexane–CH_2Cl_2 gave 0.118 g (65%) pure **8**, m.p. 114–115°, as the first crop. Further crops raised the isolated yield to the 70–75% range overall from **4**. ^1H NMR δ 4.0–3.3 (~5 H, m), 3.23 (1 H, t, J = 8 Hz), 1.90–1.2 (complex), 1.12 (9 H, s), 0.90 (3 H, d, J = 5 Hz), 0.82 (3 H, s). IR (neat) ν_{max}: 3325, 1200 cm^{-1}. (Found: c, 72.59; H, 11.22. Calc. for $C_{18}H_{33}O_3$: C, 72.68, H, 11.18%)

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H*-*bicyclo* [5.3.0]-*dec*-*t*-5-*yl*] *ethanol tetrahydrofuran* (**9**). In a flame-dried 10 ml flask was placed 0.0741 g (0.2487 mmol) of the crude **8** and 1.3 ml dry pyridine. The stirring soln was cooled to 0°, then a mixture of 0.0522 g (0.2735 mmol) *p*-toluene sulfonyl chloride in 0.9 ml dry pyridine was added. The reaction was stirred at 0° for 8 hr, then allowed to warm to 25° over a 14 hr period. The temp was held at 25° for 25 hr, then raised to 60° for 5 hr. After cooling, the reaction was diluted with 40 ml ether and washed with sat $CuSO_4$aq (3 × 40 ml), water (1 × 40 ml), sat $NaHCO_3$aq (1 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. After concentration, 0.0569 g (82%) of a light yellow oil was obtained. A glc analysis of the crude **9** (10% Apiezon L column, 250° oven temp) indicated that this material consisted of an 8:2 ratio of two isomeric tetrahydrofurans. These isomers reflect an 8:2 preference for hydroboration of **7** from the α-face versus the β-face. ^1H NMR δ 3.9–3.1 (4 H, complex), 2.5–0.75 (complex), 1.13 (9 H, s), 0.87 (3 H, d, J = 7 Hz), 0.81 (3 H, s). IR (neat) ν_{max}: 1200, 1100, 1090, 1050 cm^{-1}, no OH band. (Found: C, 76.87; H, 11.49. Calc. for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50%).

Ruthenium tetroxide oxidation of 2-[c-2,t-7-*dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H*-*bicyclo* [5.3.0]-*dec*-*t*-5-*yl*] *ethanol tetrahydrofuran* (**9**). In a 25 ml flask was placed 0.0126 g (0.0516 mmol) RuO_2 (54.5%, Engelhard Ind. Inc.) and 3.2 ml acetone. A soln of 0.1739 g (0.8128 mmol) sodium periodate in 1.8 ml water was added to the stirring RuO_2 dispersion at 25°. After about 10 min the reaction had changed from a black dispersion to a bright yellow color, indicating RuO_4 was present. A soln of **9** in 3.6 ml acetone was added to the reaction. After 8 hr, 1.0 ml i-PrOH was added to the grey dispersion. After 15 min, the reaction was filtered through Celite which was subsequently rinsed with 100 ml hot acetone. The filtrate was concentrated then diluted with 40 ml pentane-CH_2Cl_2 (2:1). This soln was washed with water (3 × 40 ml), brine (1 × 40 ml) and dried over Na_2SO_4. Concentration gave 0.0501 g (84%) dark brown oil (contaminated with RuO_2?). The ^1H NMR and IR of the crude product indicated that it consisted largely of a 1:1 mixture of **10** and **11** with a small amount of keto-lactone also being present. The mixture was separated by preparative layer chromatography (silica gel, 4% EtOAc/95% CH_2Cl_2). The lactone **10** (R_f ~ 0.6, 10 mg) was isolated and

recrystallized from hexane (25 to −20) to give an analytical sample with m.p. 88.5–89.0 . A small amount of keto-lactone ($R_f \sim 0.2$, 5 mg) was also isolated. The keto-acid **11** ($R_f \sim 0.1$, 20 mg) was recrystallized from hexane (25 to −20) to give white cubes, m.p. 119 120 .

Lactone **10**. ^{1}H NMR δ 4.4–4.1 (1 H, m), 3.45 (1 H, t, J = 7 Hz), 2.7–0.7 (complex, 1.12 (9 H, s), 0.89 (3 H, d, J = 6 Hz), 0.84 (3 H, s). Ir (neat) ν_{max}: 1780, 1200 cm^{-1}. (Found: C, 73.38; H, 10.26. Calc. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%).

Keto-acid **11**. ^{1}H NMR δ 9.7–9.1 (1 H, br, s), 3.4–0.7 (complex), 1.12 (9 H, s), 0.94 (3 H, d, J = 6 Hz), 0.53 (3 H, s). IR (neat) ν_{max}: 2900 (broad), 1715, 1690, 1190 cm^{-1}.

Equilibration of 2-[c-2,t-7-*Dimethyl*-t-8-(*t-butyloxy*)-r-1*H-bicyclo*[5.3.0] *decan*-4-*one*-*t*-5-*yl*] *acetic acid* (**11**). In a 10 ml flask was placed 12.4 mg (0.0400 mmol) of crystalline **11** and 1.0 ml CH_2Cl_2. To this stirring soln was added 9.9 μl (0.0800 mmol) 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). After stirring for 1 week at 25 , the reaction was diluted with 40 ml pentane CH_2Cl_2 mixture (2:1). This soln was washed with 25% AcOH (2 × 40 ml), water (3 × 40 ml), dried over Na_2SO_4 and concentrated to give 0.0112 g (90%) of a clear colorless oil. The ^{1}H NMR of the crude product indicated that **11** had now epimerized so that **12** is the major constituent. The ratio of **11** to **12** was 1:4, respectively, as determined by comparing the intensities of the C-5 Me groups. A sample of purified epimerized **12** was obtained by fractional crystallization from hexane (25 to −20), whereupon 4.5 mg white crystals with m.p. 85 87 were collected: ^{1}H NMR: δ 8.4 7.9 (1 H, br, s), 3.4 0.7 (complex), 1.12 (9 H, s), 0.93 (3 H, d, J = 6 Hz), 0.80 (3 H, s). IR (neat) ν_{max}: 3000 (broad), 1740–1700 (broad C=O stretch, 1200 cm^{-1}. Mass spectrum (direct probe): *m/e* 310 (1), 292 (10), 254 (18), 236 (33), 218 (25), 168 (30), 124 (85), 57 (100).

Platinum oxidation route to [c-2,t-7-*dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H-bicyclo*[5.3.0] *dec*-*t*-5-*yl*] *acetic acid* γ-*lactone* (**10**). In a 250 ml 3-necked flask fitted with two fritted disc gas bubblers, a dry ice reflux condenser (with a bubbler attached to monitor the O_2 flow rate), and an ultrasonic bath (filled with water, in which the flask was immersed) was placed 0.497 g PtO_2 (Adams' catalyst, Aldrich Chemical Co.) and 13 ml water. The PtO_2 was reduced to Pt metal by bubbling H_2 through the dispersion while agitating with the ultrasonic bath for 1 hr. N_2 was then flushed through the reaction vessel to remove the H_2. Acetone (*reagent grade*, 30 ml) was added to the reaction, followed by a soln of 0.250 g (0.839 mmol) of **8** in 35 ml acetone. O_2 was then bubbled vigorously through the agitating dispersion which had been heated to 50 . After 10 hr, the reaction was filtered through Celite which was subsequently rinsed with copious amounts of hot acetone. The combined filtrates were concentrated, then diluted with 50 ml ether. The organic layer was washed with 50 ml water, then dried with $MgSO_4$ and concentrated to give 0.266 g of a viscous oil. A ^{1}H NMR, IR and tlc analysis of this oil indicated that it consisted of the desired **10** (IR: 1780 cm^{-1}, R_f^* ~ 0.7), a lactol (IR: 3375 cm^{-1}, R_f^* ~ 0.3) and starting material **8** (IR: 3375 cm^{-1}, R_f^* ~ 0.1). The oil was dissolved in hexane and cooled to −20 whereupon 0.093 g of starting **8** crystallized out cleanly, and the mother liquor (0.173 g) was free of **8**. The mother liquor was concentrated then placed in a 10 ml flask fitted with a magnetic stirrer. CH_2Cl_2 (3 ml) was added followed by 0.258 g (excess) pyridinium chlorochromate. After stirring for 2 hr, the reaction was filtered through Florisil. After rinsing the Florisil with copious amounts of CH_2Cl_2, the combined filtrates were concentrated to give 0.147 g (95% yield, 63% conversion) of pure **10**. The lactone was recrystallized from hexane (25 to −20) to give crystals with m.p. 88.5 89.0 . The spectral properties were identical with those obtained from **10** in the ruthenium tetroxide oxidation of **9** described earlier.

The overall yield of **10** from **4** (five steps) is about 45 50% when purification is postponed until diol **8**.

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H-bicyclo*[5.3.0]*dec*-*t*-5-*yl*]-3-*methoxypropionic acid* γ-*lactone* (**13**). In a flame dried 5 ml flask fitted with a side arm, and rubber septum, was placed 0.062 ml (0.442 mmol) dry diisopropylamine and 0.61 ml dry THF. The starting soln was cooled to −78°, then 0.210 ml (0.408 mmol) on n-BuLi (1.94 M) was added dropwise. After stirring for 40 min, a soln of 0.1000 g (0.340 mmol) of **7** in 0.74 ml of dry THF was added dropwise. After 2.2 hr, 0.128 ml dry HMPA was added and the reaction was allowed to warm to −40° gradually over 50 min, then cooled back to −78°. After 30 min, a soln of bromomethyl methyl ether (0.037 ml, 0.4421 mmol) in 0.62 ml dry THF was added. The temp was slowly allowed to rise to −20° during 2.5 hr, then to −5° in 2 hr more. The reaction was then poured into 40 ml 10% HCl and 40 ml ether. After mixing and separation, the organic layer was washed with water (1 × 4 ml), $CuSO_4$aq (2 × 40 ml), water (1 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. Concentration gave 0.1123 g (98%) light yellow oil. A spectral analysis of the crude indicated that it was essentially pure alkylated lactone (one epimer?) **13**. The material was suitable for subsequent reactions without purification. ^{1}H NMR δ 4.5–4.0 (1 H, m), 3.9 3.4 (3 H, m), 3.32 (3 H, s), 2.8–0.7 (complex), 1.16 (9 H, s), 0.93 (3 H, d, J = 6 Hz), 0.84 (3 H, s). IR (neat) ν_{max}: 1780, 1200 cm^{-1}.

(±)-2,3-*Dihydroaromaticin* (**15**). In a flame dried 10 ml flask was placed 0.0872 g (0.713 mmol) of BuOK, 1.50 ml dry THF and 5.4 μl (0.300 mmol) water. To this agitating mixture was added a soln of 0.0998 g of **13** (contaminated with about 15% *non*-alkylated lactone **10**) in 0.97 ml dry THF. After 19 hr at 25°, the reaction was poured into 40 ml 10% HCl and 40 ml ether. After mixing, the layers were separated and the organic layer was washed with 10% HCl (3 × 40 ml), brine (1 × 40 ml), and dried over $MgSO_4$. Concentration gave 0.0854 g (93%) light yellow solid. This material was estimated to contain about 30% of **6** based upon the ^{1}H NMR integration of the vinyl protons [δ 6.00 (1 H, d, J = 3 Hz), 5.26 (1 H, d, J = 3 Hz)] versus the C-8 lactone proton [δ 4.3–3.9 (1 H, m)]. The reaction was judged complete by the total disappearance of the OMe adsorption at δ 3.32. The IR (neat) shows an absorption at 1760 cm^{-1} for the α-methylene lactone. This material was carried on to **19** as described below without purification.

In a flame dried 10 ml flask was placed 0.0718 g of the crude **14** above and 1.3 ml dry trifluoroacetic acid (distilled from P_2O_5). The resulting soln was immediately cooled to 0 . After 3 hr, the trifluoroacetic acid was removed at 0 under vacuum. The residue was dissolved in 5.2 ml i-PrOH and then 1.3 ml 15% NaOHaq was added. The resulting mixture was warmed to 25 . After 2 hr, the i-PrOH was removed on a rotary evaporator and the residue was diluted with 40 ml ether. This was followed by washing with 10% HCl (1 × 40 ml), water (2 × 40 ml), brine (1 × 40 ml) and drying over $MgSO_4$. Concentration gave 0.0411 g (70%) of a glassy solid. The IR (neat) showed a large OH absorption (3450 cm^{-1}) and the absence of a t-butyloxy absorption (1200 cm^{-1}). The ^{1}H NMR indicated that the vinyl protons were still present [δ 6.13 (1 H, d, J = 3 Hz), 5.46 (1 H, d, J = 3 Hz)] and that the t-butyloxy peak [δ 1.14 (9 H, s)] had disappeared. A strong, broad, CO absorption in the IR (1780–1760 cm^{-1}) indicated that the lactone(s) was still present. The crude product containing hydroxylactone was carried on as described below without purification.

In a 5 ml flask was placed 0.0371 g of the crude hydroxylactone above and 1.2 ml CH_2Cl_2. To this stirring soln was added 0.0633 g (excess) of pyridinium chlorochromate. After 3 hr at 25 , the reaction was filtered through a 17 × 23 mm Florisil plug, which was subsequently rinsed with 250 ml of CH_2Cl_2. Concentration of the filtrate gave 0.0079 g of crystalline **15**. The Florisil was then rinsed with 75 ml EtOAC and this filtrate was concentrated to give 0.0237 g of a yellow glassy solid. A spectral analysis of this solid revealed the presence of a small amount of **15**, but the majority of the material was unidentifiable. Chromatography of this fraction (silica gel, 8% EtOAc/CH_2Cl_2) on a preparative layer plate yielded 0.0022 g more **15** [$R_f \sim 0.4$]. The overall yield of (±) **15** from **10** was 17%. Recrystallization from hexane/CH_2Cl_2

at 25° gave white needles with *m.p.* 123–124°. ^{1}H NMR: Found, δ 2.50 ($H_{6\alpha}$, dd, J = 15, 6), 1.52 ($H_{6\beta}$, dd, J = 15, 11 Hz), 4.28 ($H_{8\beta}$, ddd, J = 10, 9, 3), 6.19 (H_{12}, d, J = 3.5), 5.51 (H_{13}, d, J = 3), 1.10 (C-10 methyl, d, J = 6), 1.03 (C-5 methyl, s). Reported data, which agrees with that above, is in Ref. 20. Mass spectrum (direct probe): *m/e* 248 (100), 233 (16), 204 (45). Reported data, which agreed with that above, is in ref. 20.

(±)-*Aromaticin* (**5**). In a flame dried 5 ml flask was placed 5.4 mg (0.0218 mmol) of (±)-**15** and 0.18 ml dry EtOAc, "spiked" with HCl gas. To this stirring soln was added 4.6 mg phenylselenenyl chloride. After 8 hr at 25°, the reaction was poured into 20 ml of an ether–pentane mixture (1/1) and 20 ml $NaHCO_3$aq. The organic layer was washed with more $NaHCO_3$aq (1 × 20 ml), water (1 × 20 ml), brine (1 × 20 ml) and dried over $MgSO_4$. Concentration gave 8.9 mg (91%) of a yellow oil. This material was carried on to the next step crude. ^{1}H NMR (crude): δ 7.8–7.5 (5 H, complex), 6.18 (1 H, d, J = 3 Hz), 5.47 (1 H, d, J = 3 Hz), 4.4–3.8 (~2 H, m), 3.0–1.1 (complex), 0.98 (C-5 methyl group and the downfield peak of the C-10 methyl doublet), 0.94 (upfield peak of the C-10 methyl doublet).

In a 5 ml flask was placed the crude selenylated ketone above and 0.40 ml of a tetrahydrofuran–water mixture (6/1). To this stirring soln was added 5.0 mg (0.0597 mmol) $NaHCO_3$ then 12.8 mg (0.0597 mmol) sodium periodate. After 15 min a large amount of ppt appeared. After 2 hr, the reaction was poured into 20 ml of an ether–pentane mixture (1/1) and washed with $NaHCO_3$aq (2 × 20 ml), water (1 × 20 ml), brine (1 × 20 ml) and dried over $MgSO_4$. Concentration gave 6.1 mg (>100%) of a yellow oil. An IR analysis of the crude product indicated that it consisted of about a 1:1 mixture of starting material (1730 cm^{-1}) and (±)-**5** (1710 cm^{-1}). Consequently, the crude product was resubjected to the oxidation conditions above except that the $NaHCO_3$ was reduced to 3.3 mg (0.0398 mmol) and the reaction was run for 5 hr. Workup, as above, gave 4.0 mg (75% overall crude) of a yellow oil. The IR now indicated that the reaction had proceeded essentially to completion.

The crude product was chromatographed (silica gel 4% EtOAc/CH_2Cl_2) on two tlc slides using natural (±)-aromaticin as a control. The spot with an identical R_f (0.21) to the natural material was isolated as 0.5 mg of a light yellow oil. The synthetic (±)-**5** was crystallized from acetone to give needles with m.p. 178–181° (taken on a Fisher-Johns apparatus). A ^{1}H NMR comparison (100 MHz, FT) of the synthetic and natural aromaticin showed the samples to be identical. A FT-IR of the natural aromaticin, as a KBr pellet, gave a shift in the cyclopentenone CO band from the reported[3] 1710 cm^{-1} ($CHCl_3$ soln) to 1701 cm^{-1}. The α-methylene lactone CO absorbed at 1762 cm^{-1} as a KBr pellet. The remaining spectral data were in good agreement with that reported and found for our sample of natural (+)-aromaticin. ^{1}H NMR (Found, 100 MHz, FT): δ 7.64 (1 H, dd, J = 6.0, 1.8 Hz), 6.14 (1 H, dd, J = 6.1, 3.0 Hz), 6.20 (1 H, d, J = 3.4 Hz), 5.53 (1 H, d, J = 3.2 Hz), 4.51 (1 H, ddd, J = 11.3, 9.4, 3.2 Hz), 1.26 (3 H, d, J = 6.4 Hz), 1.10 (3 H, s), 3.0–1.3 (complex). ^{1}H NMR (reported,[4] 60 MHZ): δ 7.70 (1 H), 6.20 (1 H), 6.15 (1 H), 5.55 (1 H), 4.53 (1 H), 1.25 (3 H), 1.19 (3 H). IR ($CHCl_3$ soln, FT) ν_{max}: 1763, 1710 (Reported[4] 1760, 1710 cm^{-1}). Mass spectrum (direct probe): for (±)-**5**, *m/e* 246 (100), 231 (23), 218 (19), 204 (21), 175 (23), 159 (26), 136 (40). For (+)-**5**, *m/e* 246 (100), 231 (24), 218 (19), 204 (19), 175 (20), 159 (24), 136 (35).

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