Stereoselective Total Synthesis of (±)-Invictolide. An Efficient Preparation of a Trisubstituted δ-Lactone from Aldol Precursors

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The stereoselective total synthesis of (±)-invictolide (1), a component of the queen recognition pheromone of *Solenopsis invicta*, is described. The $TiCl_4$-mediated addition of silyl ketene thioacetal 8 to (±)-3-(benzyloxy)-2-methylpropionaldehyde afforded exclusively thioester 10, in 65% yield, which was straightforwardly converted to diol 5 (ca. 31% yield). Diol 5 was also prepared after $LiAlH_4$ reduction of the major aldol formed in the condensation between the lithium enolate of 2,6-di-*tert*-butyl-4-methylphenyl propanoate and (±)-2-methylvaleraldehyde (ca. 50% overall yield). Intramolecular alkylation (*t*-BuOK, THF) of 6 or 7 gave a 40:60 mixture of (±)-1 and its C(3) epimer. Catalytic hydrogenation of unsaturated lactone 17 afforded (±)-1 in 80% yield.

The red imported fire ant (*Solenopsis invicta*) is a native species of South America, and since its introduction from Brazil in 1940, it has attained pest status in the southeastern United States.[1] It is best known for its aggressive behavior and painful sting and has resisted attempts of population control with chlorinated pesticides.[2]

In 1974, Jouvenaz et al.[3] reported on the queen pheromone of this species, and Glancey et al.[4] have shown that pentane extracts of the queens are highly attractive to workers and that the behavior patterns observed suggested that the pheromone might have potential for the development of specific control methods. The composition of the queen recognition pheromone was established by Rocca et al.,[5] and the relative configuration of one of its components, namely tetrahydro-3,5-dimethyl-6-(1′-methylbutyl)-2*H*-pyran-2-one (1, invictolide), was determined by total synthesis.[6] The absolute configuration of its natural form was established to be (3*R*,5*R*,6*S*,1′*R*)-1 by Mori and Nakazono in 1986.[7]

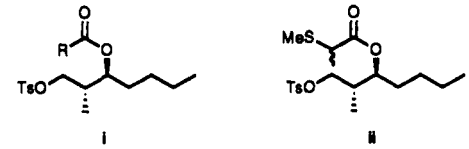
Since both the levorotatory and the racemic forms of invictolide (1) display pheromone activity, several syntheses have been described in the literature.[6-8] Despite its conceivable origin in the polypropionate biosynthetic pathway, there has been no reported total synthesis of (±)-1 using stereoselective aldol condensations to control the relative stereochemistry of the asymmetric centers present in 1. Furthermore it appeared to us that this approach could benefit from the intramolecular alkylation in the construction of the δ-lactone ring[9] (Scheme I).

Results and Discussion

Our initial attempts to stereoselectively prepare aldol product 4a led us to explore the addition of the lithium enolate of the anti-selective BHT propionate (3)[10] to (±)-2-methylvaleraldehyde (Scheme II). A 2:1 mixture of diastereoisomeric aldols 4a and 4b was obtained in 96% yield after Kugelrohr purification. The Felkin isomer 4a was shown to be the major aldol after its isolation from LiChroprep Si60 (40–63-μm) column (64% yield) and its conversion to the known (2*RS*,3*SR*,4*RS*)-2,4-dimethyl-1,3-heptanediol (5).

The diol 5 was uneventfully converted to the *O*-propionyl tosylate 6 and *O*-propionyl iodide 7 which were employed in our studies on the internal alkylation as a direct route to the target δ-lactone ring. Our initial attempts with 6 and 7 using LDA as base, THF or THF/HMPA as solvent, and reaction temperatures ranging from −78 °C to room temperature met only with failure: either recovery of the starting material (1.5 equiv of LDA, THF, −78 to 25 °C) or its partial deprotection (LDA, THF/HMPA, −78 to 25 °C) was observed. Since we had evidence of formation of the lithium enolate under the conditions described above for a related system,[12] we turned our attention to the nature of the counterion as we reasoned that our failure might be due to a strong ionic pair being formed when LDA was employed. Although no improvement was observed when

(1) Lofgren, C. S.; Banks, W. A.; Glancey, B. M. *Ann. Rev. Entomol.* **1975**, *20*, 1.
(2) Summerlin, J. W.; Hung, A. C. F.; Vinson, S. B. *Environ. Entomol.* **1977**, *6*, 193.
(3) Jouvenaz, D. P.; Banks, W. A.; Lofgren, C. S. *Ann. Entomol. Soc. Am.* **1974**, *67*, 442.
(4) Glancey, B. M.; van der Meer, R. K.; Lofgren, C. S.; Glover, A.; Tumlinson, J. H.; Rocca, J. R. *Ann. Entomol. Soc. Am.* **1980**, *73*, 609.
(5) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1889.
(6) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1893.
(7) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459.
(8) For racemic total synthesis of (±)-1, see: (a) Reference 6. (b) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618. (c) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. (d) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303. (e) Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429. For total syntheses of its natural form, see: (f) Ziegler, F. E.; Stirchak, E. P.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1229. (g) Reference 7. (h) Mori, K.; Senda, S. *Agric. Biol. Chem.* **1987**, *51*, 1379. (i) Wakamatsu, T.; Nishikimi, Y.; Kikuiri, H.; Nakamura, H. *Heterocycles* **1987**, *26*, 1761. (j) Hoffman, R. W.; Ditrich, K.; Koster, G.; Sturmer, R. *Chem. Ber.* **1989**, *122*, 1783.
(9) Nakai, E.; Kitahara, E.; Sayo, N.; Ueno, Y.; Nakai, T. *Chem. Lett.* **1985**, 1725.
(10) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Montgomery, S. H. *Tetrahedron* **1981**, *37*, 4087.
(11) Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442.
(12) Similar results were observed when the tosylate i (R = CH_3) was employed:



i ii

Enolization (LDA/THF, −78 °C) of compound i (R = CH_2CH_3) and trapping with $CH_3SSO_2CH_3$ (−78 °C to rt) afforded tosylate ii, in 55% yield.

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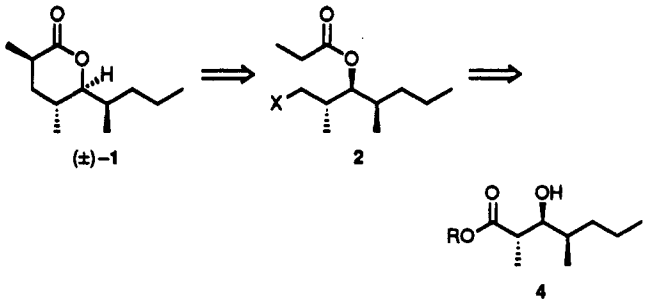
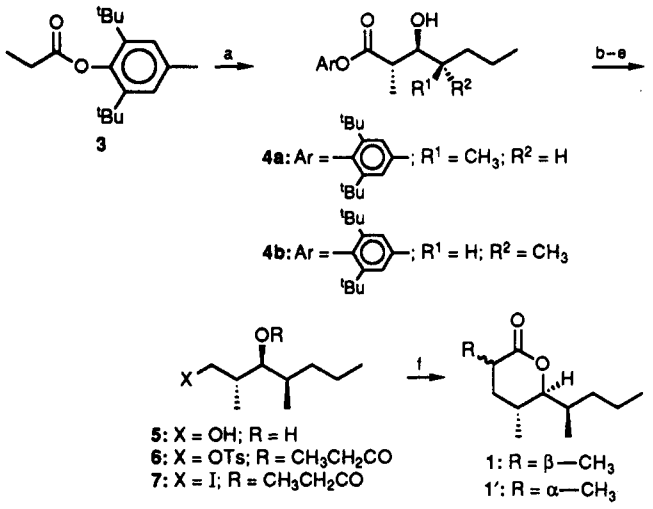
Scheme I



Scheme II[a]



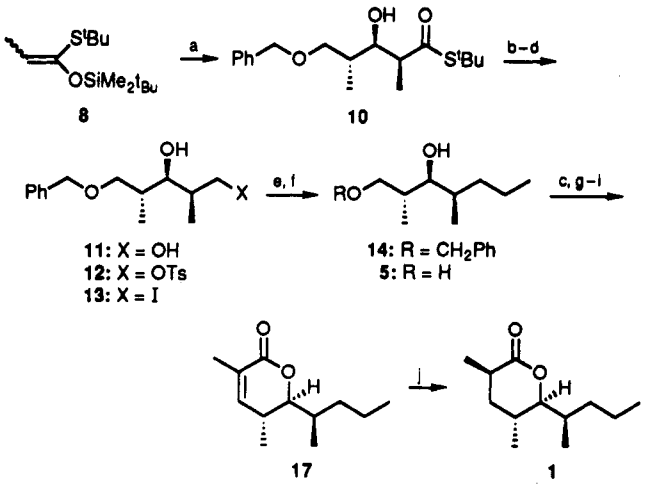
[a] (a) (i) LDA, THF, −78 °C; (ii) (±)-2-methylvaleraldehyde; (b) chromatography (64% yield); (c) $LiAlH_4$, THF, rt (78% yield); (d) (i) TsCl, CH_2Cl_2, Et_3N, −15 °C; (ii) $(CH_3CH_2CO)_2O$, CH_2Cl_2, Et_3N, DMAP (cat.), rt (92% overall yield); (e) NaI, acetone, reflux (73% yield); (f) *t*-BuOK, THF, 0 °C (75–78% yield).

NaH/HMPA[13] or NaHMDS/C_6H_6[14] was employed, the desired δ-lactones 1/1′ were isolated in good yields (75–78%) when *t*-BuOK (4 equiv) in THF was used. The 40:60 ratio of δ-lactones 1:1′ observed in the internal alkylation of **6** and **7** correlates well with the ratio reported by Nakai et al.[9] in the synthesis of the Prelog–Djerassi lactone.

With a short route to the desired skeleton secured we turned our attention to the control of the relative configuration of the four asymmetric centers present in **1**. Among the methodologies available in the literature for the stereoselective construction of intermediate **6**, we decided to employ the one developed by Gennari and coworkers[15] (Scheme III) which features the $TiCl_4$-promoted addition of the silyl ketene thioacetal **8** to (±)-3-(benzyloxy)-2-methylpropionaldehyde (**9**). The guidelines for our choice were the high yields reported for this transformation, the advantage of using a mixture of the *E* and *Z* thioacetals without any deleterious effect in the stereochemical outcome of the reaction and the possibility of access to the natural form of invictolide from commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate.

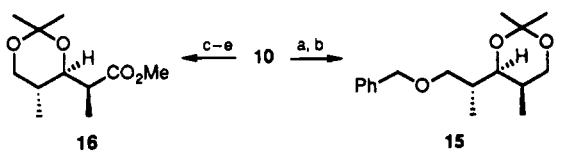
The addition of silyl ketene thioacetal **8** (*E*/*Z* ratio = 87:13), prepared in 66% yield from *tert*-butyl thiopropionate, to an equimolar mixture of (±)-**9** and $TiCl_4$, in CH_2Cl_2 at −78 °C, afforded thioester **10** (65% yield) diastereomerically homogeneous by ^1H- and ^{13}C-NMR analyses. Its relative stereochemistry was unambiguously assigned[16] after its conversion to the corresponding acetonides **15** and **16** (Scheme IV); vicinal coupling constants of 2.1 and 10.2 Hz between H-3 and H-4 in **15** and **16**, respectively, were fully consistent with the relative configuration of the three contiguous chiral centers present in (±)-**1**.

Scheme III[a]



[a] (a) **9**, CH_2Cl_2, $TiCl_4$, −78 °C (65% yield); (b) $LiAlH_4$, THF, rt (97% yield); (c) TsCl, CH_2Cl_2, Et_3N, −15 °C (85% yield); (d) NaI, acetone, reflux (73% yield); (e) Et_2CuLi, Et_2O, −78 °C → rt (55% yield); (f) Li, NH_3(l), −78 °C (94% yield); (g) $(CH_3CH_2CO)_2O$, CH_2Cl_2, Et_3N, DMAP (cat.), rt (95% yield); (h) *t*-BuOK, THF, 0 °C (78% yield); (i) LDA, THF, −78 °C, then PhSeBr, −78 °C → 0 °C and 30% H_2O_2/HOAc (50% yield); (j) H_2, EtOH, Pd/C (80% yield).

Scheme IV[a]

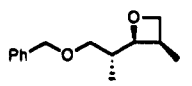


[a] (a) $LiAlH_4$, THF, rt (97% yield); (b) acetone, C_6H_6, PPTS, reflux (97% yield); (c) $Hg(OAc)_2$, MeOH; (d) H_2, Pd/C, EtOH, HCO_2H; (e) acetone, C_6H_6, PPTS, reflux (42% yield, 3 steps).

Thioester **10** was uneventfully converted to the iodide **13** in 60% overall yield, which was chain elongated with an excess of lithium diethylcuprate[17] (**13** → **14**, 55% yield[18]) followed by hydrogenolysis of the benzyl group (Li/NH_3(l)) to afford (±)-**5** in 94% yield. Lactonization of the *O*-propionyl tosylate **6**, as depicted in Scheme II, led to a 40:60 ratio of (±)-invictolide (**1**) and its C(3) epimer (**1′**). Access to the correct stereochemistry at C(3) of (±)-**1** was

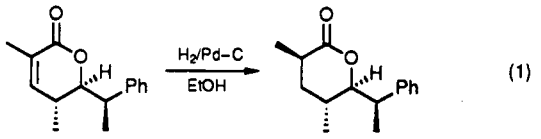
(13) Takahashi, T.; Hashigushi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424.
(14) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945.
(15) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 909.

(16) See also: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873 for the assignment of the relative stereochemistry of (±)-**11** and its stereoisomers.
(17) Ethyllithium was prepared from ethyl bromide and lithium wire in ether at −30 °C under sonication (40 kHz) and transferred with cannula to the reaction flask. The use of ethylmagnesium bromide catalyzed by Kochi's reagent (Li_2CuCl_4) did not yield the coupling product **14**.
(18) Oxetane **iii** was the major product (49% yield) when tosylate **12** was employed while the desired alcohol **14** was formed only in 21% yield. With iodide **13**, oxetane **iii** was formed as a byproduct in 20% yield.



iii

gained through the catalytic hydrogenation of the unsaturated δ-lactone 17, the major product isolated after α-selenylation, oxidation, and elimination of the mixture of epimeric δ-lactones 1/1′ (Scheme III). (±)-Invictolide (1) was obtained as the major epimer (6:1 ratio by GC), and it could be easily distinguished from its C(3) epimer both by ^{1}H- and ^{13}C-NMR (see the Experimental Section). The same sense of diastereoselection was observed in the catalytic hydrogenation of the exo δ-lactone, but the diastereoisomeric ratio observed in this case was only moderate. Although a clear rationalization for these results is still lacking, they are in accordance with those described by Danishefsky et al.[19] in the reduction of the unsaturated lactone 19 (eq 1).



19 (1)

In summary, (±)-invictolide (1) has been synthesized in 8 steps from 2,6-di-*tert*-butyl-4-methylphenyl propionate (14% overall yield) and in 10 steps from 3-(benzyloxy)-2-methylpropionaldehyde (6% overall yield). The diastereoisomeric excess in the latter case was greater than 70%.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Diisopropylamine, triethylamine, pyridine, hexamethylphosphoric triamide (HMPA), and dichloromethane were distilled from CaH_2 immediately prior to use. All reactions involving organometallic reagents were carried out under a N_2 or an Ar atmosphere. The normal processing of organic extracts consisted of washing the extract with water and brine, drying over $MgSO_4$, filtration, and concentration with a rotary evaporator. Column chromatography were carried out with silica gel, 70–230 mesh, and TLC plates were prepared with silica gel, 35–70 mesh. GC analyses were performed in a HP 5890A chromatograph with a 30-m × 0.53-mm × 1.3-mm fused silica capillary column (cross-linked poly(ethylene glycol) or 5% diphenyl–95% dimethylpolysiloxane as stationary phase) and N_2 as the carrier gas. The GC–MS analyses were performed with a HP 5988A GC/MS system equipped with a 25-m × 0.20-mm × 0.33-mm fused silica capillary column (stationary phases above) and H_2 as the carrier gas. Infrared spectra (IR) were determined as films in KBr with a Perkin-Elmer 399B or Perkin-Elmer 1600 FT-IR spectrophotometer. Mass spectra were measured with a Varian MAT 311A (70 eV) spectrometer. All NMR spectra were measured in $CDCl_3$ solution, unless otherwise noted. ^{1}H-NMR spectra were determined at 300 MHz and ^{13}C-NMR spectra at 75.2 MHz (Varian Gemini), unless otherwise noted. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane; coupling constants are expressed in hertz. ^{1}H-NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qt, quintuplet; m, multiplet; br, broad signal), coupling constants in hertz, and number of protons. Elemental analyses were performed on a Perkin-Elmer 2400 CHN Analyser at Instituto de Química, UNICAMP).

(2*SR*,3*SR*,4*RS*)-2′,6′-Di-*tert*-butyl-4′-methylphenyl 3-Hydroxy-2,4-dimethylheptanoate (4a). To a stirred solution of diisopropylamine (2.23 g, 22 mmol) in 20 mL of THF at 0 °C was added dropwise a solution of *n*-BuLi in hexanes (1.60 M, 12.5 mL, 20 mmol). After 15 min the solution was cooled to −78 °C, and 2,6-di-*tert*-butyl-4-methylphenyl propanoate[10] (3) (5.53 g, 20.0 mmol) was added dropwise during 15 min. After stirring for 45 min, 2-methylvaleraldehyde (2.00 g, 20.0 mmol) was added in one portion. The mixture was then allowed to stirr for 5 min at −78 °C when it was quenched by the addition of 10 mL of saturated aqueous NH_4Cl. After warming up to room temperature, the reaction mixture was diluted with 50 mL of ether, and the organic phase was washed with 1% aqueous HCl (3 × 20 mL) and 5% aqueous $NaHCO_3$ (3 × 20 mL). Normal workup gave a 70:30 mixture of the Felkin aldol **4a** and the *anti*-Felkin aldol **4b** (7.23 g, 19.2 mmol), in 96% yield, after Kugelrohr purification (1.0 mmHg, 110–120 °C). The pure aldols were obtained after medium-pressure column chromatography in silica gel (40–30 μm) and 5% ether in hexanes as the eluent.

***anti*-Felkin aldol 4b**: ^{1}H NMR δ 0.93 (t, *J* = 6.6, 3 H), 1.03 (d, *J* = 6.9, 3 H), 1.32 (s, 9 H), 1.34 (s, 9 H), 1.43–1.48 (m, 5 H), 1.58 (s, br, 2 H), 1.77 (m, 1 H), 2.32 (s, 3 H), 2.92 (qt, *J* = 7.5, 1 H), 3.55 (d, *J* = 4.2, 1 H), 3.66 (m, 1 H), 7.14 (s, 2 H); ^{13}C NMR δ 13.63, 14.39, 17.23, 20.53, 21.55, 31.31, 31.56, 31.63, 34.33, 35.30, 35.41, 43.83, 77.59, 127.51, 127.72, 135.29, 142.32, 142.55, 146.42, 177.68.

Felkin aldol 4a: ^{1}H NMR δ 0.93 (d, *J* = 6.6, 6 H), 1.31 (s, 9 H), 1.32 (s, 9 H), 1.41–1.44 (m, 7 H), 1.70 (m, 1 H), 2.32 (s, 3 H), 2.85 (qt, *J* = 7.5, 1 H), 3.66 (d, *J* = 2.1, 1 H), 3.80 (dd, *J* = 8.7 and 3.0, 1 H), 7.14 (s, 2 H); ^{13}C NMR δ 12.05, 13.02, 14.35, 20.62, 21.55, 31.57, 31.62, 34.04, 35.30, 35.42, 36.69, 44.29, 74.86, 127.50, 127.73, 135.28, 142.31, 142.51, 146.42, 177.86; IR 3530, 1735, and 1600 cm^{-1}; MS *m*/*z* 249 (5), 220 (71), 204 (32), 111 (15), 83 (22), 71 (32), 57 (100). Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.84; H, 10.36.

(2*RS*,3*SR*,4*RS*)-2,4-Dimethyl-1,3-heptanediol (5). A solution of aldol **4a** (1.69 g, 4,5 mmol) in 10 mL of THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.34 g, 9.0 mmol) in 10 mL of THF at 0 °C. The mixture was stirred at room temperature for 20 h when it was diluted with 10 mL of ether. The mixture was cooled to 0 °C and treated with water (0.34 mL), 15% aqueous NaOH (0.34 mL), and water (1.0 mL), successively. The organic phase was separated by filtration, and the inorganic residue was washed with ether (3 × 10 mL). Normal workup gave 1.65 g of a colorless oil which was chromatographed on silica gel (1:1 CH_2Cl_2–ether) to afford diol **5**[11] (0.56 g, 3.5 mmol) in 78% yield as a colorless oil: ^{1}H NMR ($CDCl_3/D_2O$) δ 0.81 (d, *J* = 6.9, 3 H), 0.87 (d, *J* = 6.9, 3 H), 0.91 (t, *J* = 6.9, 3 H), 1.21–1.44 (m, 4 H), 1.66 (m, 1 H), 1.85 (m, 1 H), 3.47 (dd, *J* = 8.9. and 2.7, 1 H), 3.63 (dd, *J* = 10.8 and 7.8, 1 H), 3.72 (dd, *J* = 10.8 and 3.9, 1 H); ^{13}C NMR ($CDCl_3/D_2O$) δ 12.26, 13.59, 14.29, 20.43, 34.82, 36.31, 37.27, 68.52, 80.04; MS *m*/*z* 101 (58), 89 (100), 71 (75), 59 (48), 58 (47), 57 (17), 55 (29), 43 (93).

(2*RS*,3*SR*,4*SR*)-2,4-Dimethyl-3-*O*-propionyl-1-*O*-(*p*-toluenesulfonyl)-1,3-heptanediol (6). To a stirred solution of diol **5** (0.48 g, 3.0 mmol) in 5.0 mL of CH_2Cl_2 at −15 °C was added *p*-toluenesulfonyl chloride (0.57 g, 3.0 mmol) and triethylamine (0.32 g, 3.2 mmol). The reaction mixture was kept at −15 °C for 3 h when it was diluted with 10 mL of CH_2Cl_2 and washed with 1% aqueous HCl (2 × 5.0 mL), and after the normal workup the crude tosylate (0.90 g) was taken up in 6.0 mL of CH_2Cl_2 and treated with propionic anhydride (0.37 g, 2.85 mmol), triethylamine (0.28 g, 2.85 mmol), and a catalytic amount of 4-(dimethylamino)pyridine (0.005 g, 0.04 mmol). The reaction mixture was allowed to stirr for 30 min at room temperature when it was diluted with 20 mL of CH_2Cl_2 and washed with 1% aqueous HCl (2 × 10 mL). After normal workup and column chromatography (5% ether–hexanes), **6** (1.02 g, 2.76 mmol) was obtained in 92% yield: IR 1736, 1598, 1362, and 1178 cm^{-1}; ^{1}H NMR δ 0.81 (d, *J* = 6.6, 3 H), 0.84 (t, *J* = 6.9, 3 H), 0.92 (d, *J* = 6.9, 3 H), 1.09 (t, *J* = 7.5, 3 H), 1.27 (m, 4 H), 1.67 (m, 1 H), 2.12 (m, 1 H), 2.25 (q, *J* = 7.5, 2 H), 2.45 (s, 3 H), 3.76 (dd, *J* = 9.6 and 7.2, 1 H), 3.99 (dd, *J* = 9.6 and 4.2, 1 H), 4.75 (dd, *J* = 8.1 and 4.2, 1 H), 7.34 (d, *J* = 8.4, 2 H), 7.77 (d, *J* = 8.4, 2 H); ^{13}C NMR δ 9.30, 13.34, 14.14, 20.08, 21.63, 27.57, 33.81, 34.81, 35.76, 71.99, 76.66, 127.98, 129.77, 132.88, 144.72, 173.96. Anal. Calcd for $C_{19}H_{30}O_5S$: C, 61.60; H, 8.16. Found: C, 61.75; H, 8.43.

(2*SR*,3*SR*,4*RS*)-1-Iodo-2,4-dimethyl-3-*O*-propionyl-3-heptanol (7). To a solution of sodium iodide (0.23 g, 1.54 mmol) in 1.0 mL of acetone was added tosylate **6** (0.28 g, 0.75 mmol)

(19) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 360.

dissolved in 1.0 mL of acetone. The mixture was refluxed for 3 h, cooled to room temperature, and worked up as usual. Column chromatography of the crude product (5% ether–hexanes) afforded iodide **7** (0.18 g, 0.55 mmol) in 73% yield: IR 1740, 1465, 1190 cm^{-1}; ^1H NMR (CCl_4, 80 MHz) δ 0.80 (d, J = 7.0, 3 H), 0.85 (t, J = 7.0, 3 H), 1.00 (d, J = 6.0, 3 H), 1.15 (t, J = 7.0, 3 H), 1.2–1.7 (m, 5 H), 1.8–2.0 (m, 1 H), 2.25 (q, J = 7.0, 2 H), 2.9 (dd, J = 7.0 and 10.0, 1 H), 3.20 (dd, J = 4.0 and 10.0, 1 H), 4.7 (q, J = 6.0, 1 H). Anal. Calcd for $C_{12}H_{23}O_2I$: C, 44.18; H, 7.11. Found: C, 44.54; H, 7.35.

(3*RS*,5*RS*,6*SR*,1′*RS*)- and (3*SR*,5*RS*,6*SR*,1′*RS*)-Tetrahydro-6-(1′-methylbutyl)-3,5-dimethyl-2*H*-pyran-2-one (1 and 1′). To a stirred solution of *t*-BuOK (0.25 g, 2.24 mmol) dissolved in 4.5 mL of THF at 0 °C was added dropwise a solution of **6** (0.20 g, 0.55 mmol) dissolved in 1.0 mL of THF. After the mixture was stirred for 30 min, 1.0 mL of ethanol was added followed by the addition of saturated aqueous NH_4Cl (3.0 mL), and the mixture was allowed to stir for 30 min at room temperature. Normal workup gave 0.110 g of the crude product which was chromatographed on Florisil (5% ether–hexanes) to afford a mixture of δ-lactones 1/1′ (0.085 g, 0.43 mmol), in 78% yield, as a 40:60 mixture by capillary GC.

(±)-Invictolide (1):[8j] IR 1730 and 1185 cm^{-1}; ^1H NMR δ 0.90 (d, J = 6.9, 3 H), 0.91 (d, J = 6.9, 3 H), 0.97 (d, J = 6.7, 3 H), 1.22 (d, J = 6.9, 3 H), 1.31–1.48 (m, 4 H), 1.68 (t, J = 8.1, 2 H), 1.72 (m, 1 H), 1.72–2.04 (m, 1 H), 2.74 (m, 1 H), 3.91 (dd, J = 10.1 and 2.0, 1 H); ^{13}C NMR δ 12.31, 14.15, 16.59, 17.68, 20.46, 28.44, 32.58, 33.67, 35.46, 36.14, 85.85, 176.50; MS m/z 198 (M, 3), 156 (19), 127 (87), 99 (48), 69 (26), 56 (100).

(±)-3-Epiinvictolide (1′): ^1H NMR δ 0.86 (d, J = 6.8, 3 H), 0.88 (t, J = 6.9, 3 H), 0.94 (d, J = 6.4, 3 H), 1.26 (d, J = 7.1, 3 H), 1.31–1.52 (m, 4 H), 1.63–1.74 (m, 2 H), 1.83–1.99 (m, 2 H), 2.46 (m, 1 H), 3.93 (dd, J = 10.1 and 1.6, 1 H); ^{13}C NMR δ 12.35, 14.12, 17.23, 17.33, 20.45, 30.97, 34.06, 35.95, 36.33, 37.79, 89.36, 174.92.

(2*RS*,3*SR*,4*RS*)-1-*O*-Benzyl-2,4-dimethyl-1,3,5-pentanetriol (11). To a stirred suspension of $LiAlH_4$ (0.14 g, 3.7 mmol) in 3.0 mL of THF at 0 °C was added dropwise a solution of thioester **10**[15] (0.60 g, 1.85 mmol) dissolved in 3.0 mL of THF. After 20 h at room temperature the reaction was quenched by the addition of water (0.15 mL), aqueous 15% NaOH (0.15 mL), and water (0.45 mL), successively. Extraction with ether (3 × 20 mL) followed by normal workup gave **11**[16] (0.43 g, 1.80 mmol) in 97% yield: IR 3410, 1460, 735, and 700 cm^{-1}; ^1H NMR (C_6D_6) δ 0.59 (d, J = 6.9, 3 H), 0.97 (d, J = 6.9, 3 H), 1.58 (m, 1 H), 1.86 (m, 1 H), 3.32 (m, 2 H), 3.58 (s, br, 2 H), 3.69 (m, 3 H), 4.21 (s, 2 H), 7.16 (m, 5 H); ^{13}C NMR (C_6D_6) δ 9.13, 13.43, 36.60, 37.08, 67.71, 73.75, 76.29, 78.22, 128.16, 128.30, 128.36, 138.49.

(2*RS*,3*RS*,4*RS*)-5-*O*-Benzyl-2,4-dimethyl-1-*O*-(*p*-toluenesulfonyl)-1,3,5-pentanetriol (12). The same procedure described for **6** afforded crude tosylate **12** in 85% yield: ^1H NMR δ 0.74 (d, J = 7.0, 3 H), 0.84 (d, J = 6.9, 3 H), 1.92 (m, 1 H), 2.00 (dq, J = 7.0 and 2.3, 1 H), 2.43 (s, 3 H), 2.96 (s, br, 1 H), 3.45 (t, J = 8.9, 1 H), 3.55–3.61 (m, 2 H), 3.89 (dd, J = 9.4 and 6.7, 1 H), 4.09 (dd, J = 9.4 and 7.5, 1 H), 4.50 (s, 2 H), 7.26–7.40 (m, 7 H), 7.79 (d, J = 8.4, 2 H); ^{13}C NMR δ 8.66, 12.98, 21.62, 35.34, 35.61, 73.37, 73.58, 75.12, 76.52, 127.69, 127.93, 128.51, 129.77, 133.14, 137.41, 144.58. A sample was purified by column chromatography (10% ether–hexanes) for elemental analysis. Anal. Calcd for $C_{21}H_{28}O_5S$: C, 64.26; H, 7.19. Found: C, 64.41; H, 7.41.

(2*SR*,3*RS*,4*RS*)-5-*O*-Benzyl-1-iodo-2,4-dimethyl-3,5-pentanediol (13). The same procedure as described for **7** afforded iodide **13** in 73% yield: ^1H NMR δ 0.79 (d, J = 7.0, 3 H), 1.01 (d, J = 6.7, 3 H), 1.88 (dq, J = 7.0 and 2.4, 1 H), 1.95 (m, 1 H), 3.19 (dd, J = 9.5 and 6.6, 1 H), 3.36 (dd, J = 9.5 and 7.7, 1 H), 3.50 (t, J = 9.0, 1 H), 3.61 (dd, J = 9.1 and 3.9, 1 H), 3.66 (dd, J = 8.0 and 2.4, 2 H), 4.51 (d, J = 12.0, 1 H), 4.54 (d, J = 12.0, 1 H), 7.32 (m, 5 H); ^{13}C NMR δ 12.89, 13.19, 13.31, 36.14, 38.72, 73.58, 76.37, 77.97, 127.70, 127.88, 128.50, 137.39; MS m/z 172 (24), 155 (40), 107 (49), 91 (100).

(2*RS*,3*SR*,4*RS*)-1-*O*-Benzyl-2,4-dimethyl-1,3-heptanediol (14). To a stirred suspension of CuBr·Me_2S (1.0 g, 5.0 mmol) in 3.5 mL of ether at −78 °C was added a 1.5 M solution of EtLi in ether[17] (7.0 mL, 10.5 mmol). The reaction temperature was raised to −30 °C when a brown color develops, and after 30 min the reaction was cooled back to −78 °C and a solution of **13** (0.35 g, 1.0 mmol) in 4.0 mL of ether was added dropwise. The reaction mixture was warmed up to room temperature, and after 30 min it was quenched with 10% NH_4OH saturated with NH_4Cl (20 mL). Normal workup followed by PTLC (5% ether–hexanes) afforded **14** (0.138 g, 0.55 mmol) as a colorless oil in 55% yield and oxetane **iii** (0.070 g, 0.32 mmol) as a colorless oil in 32% yield.

14: ^1H NMR δ 0.83 (d, J = 7.0, 3 H), 0.86 (d, J = 6.7, 3 H), 0.87 (t, J = 7.0, 3 H), 1.22–1.43 (m, 5 H), 1.98 (m, 1 H), 3.38 (s, br, 1 H), 3.41 (dd, J = 8.4 and 2.8, 1 H), 3.50 (t, J = 8.6, 1 H), 3.60 (dd, J = 8.6 and 4.2, 1 H), 4.52 (s, 2 H), 7.32 (m, 5 H); ^{13}C NMR δ 12.39, 13.72, 14.34, 20.50, 34.86, 35.98, 36.45, 73.56, 76.32, 79.03, 127.71, 127.77, 128.45, 137.73; MS m/z 120 (3), 108 (31), 91 (100), 87 (25). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.89; H, 10.13.

Oxetane iii: ^1H NMR δ 0.86 (d, J = 6.7, 3 H), 1.24 (d, J = 7.1, 3 H), 2.31 (m, 1 H), 2.95 (m, 1 H), 3.30 (dd, J = 9.0 and 7.1, 1 H), 3.55 (dd, J = 9.0 and 3.3, 1 H), 3.95 (t, J = 10.3, 1 H), 4.50 (s, 2 H), 4.60 (dd, J = 10.7 and 7.3, 1 H), 4.76 (dd, J = 7.2 and 5.8, 1 H), 7.32 (s, 5 H); ^{13}C NMR δ 12.54, 13.68, 31.84, 35.20, 71.27, 73.24, 75.04, 85.41, 127.37, 127.54, 128.27, 138.75; MS m/z 113 (3), 107 (31), 91 (100), 71 (29).

(2*RS*,3*SR*,4*RS*)-2,4-Dimethyl-1,3-heptanediol (5). To a stirred solution of lithium (0.060 g, 10 mmol) in 50 mL of liquid ammonia at −78 °C was added alcohol **14** (0.087 g, 0.35 mmol) dissolved in 2.0 mL of THF. After 2 h at −78 °C the reaction was quenched with solid NH_4Cl (2.0 g), and it was let to warm up to room temperature. Normal workup and column chromatography (1:1 CH_2Cl_2–hexanes) afforded diol **5** (0.053 g, 0.33 mmol) as a colorless oil in 94% yield.

(2*RS*,3*RS*,4*RS*)-5-*O*-Benzyl-2,4-dimethyl-1,3-*O*-isopropylidene-1,3,5-pentanetriol (15). To a stirred solution of diol **11** (0.10 g, 0.42 mmol) in 20 mL of benzene were added acetate (0.5 mL) and a catalytic amount of pyridinium *p*-toluenesulfonate (0.01 g, 0.04 mmol). The reaction was refluxed with removal of water (Dean–Stark) for 2 h. Normal workup afforded acetonide **15** (0.11 g, 0.41 mmol) as a colorless oil in 97% yield: ^1H NMR δ 0.94 (d, J = 6.9, 3 H), 1.06 (d, J = 6.9, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.53 (m, 1 H), 1.80 (m, 1 H), 3.45 (dd, J = 14.7 and 6.1, 1 H), 3.49 (dd, J = 14.7 and 3.0, 1 H), 3.59 (dd, J = 13.2 and 1.5, 1 H), 3.76 (dd, J = 13.2 and 2.1, 1 H), 4.09 (dd, J = 5.7 and 2.7, 1 H), 4.45 (d, J = 12.0, 1 H), 4.51 (d, J = 12.0, 1 H), 7.33 (s, 5 H); ^{13}C NMR δ 10.24, 12.65, 19.11, 29.69, 29.87, 35.57, 67.47, 72.24, 72.40, 73.42, 98.92, 127.80, 127.94, 128.71, 139.44; MS m/z 278 (M, 3), 263 (35), 220 (20), 148 (33), 107 (83), 91 (100).

(2*SR*,3*RS*,4*RS*)-Methyl 5-*O*-Benzyl-2,4-dimethyl-3,5-dihydroxypentanoate. To a stirred solution of mercuric acetate (0.20 g, 0.62 mmol) in 2.0 mL of methanol was added aldol **10** (0.10 g, 0.31 mmol), and the reaction mixture was kept at room temperature for 1 h. The reaction mixture was diluted with ligroin (20 mL), the inorganic solids were filtered off, and the organic phase was worked up as usual to afford the crude product (0.070 g) which was used without further purification: ^1H NMR δ 0.92 (d, J = 7.2, 3 H), 1.19 (d, J = 7.2, 3 H), 1.89 (m, 1 H), 2.62 (dq, J = 7.2 and 4.2, 1 H), 3.55 (dd, J = 9.0 and 6.6, 1 H), 3.59 (d, J = 3.5, 1 H), 3.63 (dd, J = 4.5 and 9.0, 1 H), 3.69 (s, 3 H), 3.90 (m, 1 H), 4.51 (s, 2 H), 7.32 (s, 5 H); ^{13}C NMR δ 9.80, 13.93, 35.89, 42.54, 51.87, 73.70, 74.80, 76.02, 128.04, 128.13, 128.82, 138.21, 176.64; MS m/z 266 (M, 2), 235 (8), 179 (23), 160 (16), 142 (61), 108 (58), 107 (46), 92 (42), 91 (100), 57 (46).

(2*SR*,3*RS*,4*RS*)-Methyl 3,5-*O*-isopropylidene-2,4-dimethyl-3,5-hydroxypentanoate (16). To a solution of the foregoing ester (0.067 g, 0.25 mmol) in 5 mL of ethanol containing 0.5 mL of formic acid was added 10% Pd/C (0.03 g), and the mixture was shaken under 4 atm of H_2 (Parr apparatus) for 5 h. The catalyst was removed by filtration on Celite, the organic phase was neutralized with saturated $NaHCO_3$, and after normal workup the colorless oil (0.45 g) was dissolved in benzene (4 mL), acetone (0.10 mL) and pyridinium *p*-toluenesulfonate (0.001 g) were added, and the solution was refluxed with removal of water (Dean–Stark) for 2 h. The reaction was cooled to room temperature, and after normal workup the residue was chromatographed (5% ether–hexanes) to afford **16** (0.028 g, 0.13 mmol) in 52% yield as a colorless oil: ^1H NMR δ 0.75 (d, J = 6.9, 3 H), 1.16 (d, J = 7.2, 3 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.82 (m, 1 H), 2.65 (dq, J = 7.2 and 3.6, 1 H), 3.52 (t, J = 10.8, 1 H), 3.64 (s, 3 H), 3.65 (m, 1 H),

4.02 (dd, J = 10.2 and 3.6, 1 H); ^{13}C NMR δ 9.08, 12.23, 18.96, 31.18, 41.10, 51.69, 66.07, 75.32, 98.37, 174.90.

(5*SR*,6*SR*,1′*RS*)-5,6-Dihydro-6-(1′-methylbutyl)-3,5-dimethyl-2*H*-pyran-2-one (17). To a stirred solution of diisopropylamine (0.111 g, 1.1 mmol) in 1.0 mL of THF at 0 °C was added 1.5 M *n*-BuLi (0.67 mL, 1.0 mmol). After 15 min the solution was cooled to −78 °C, and 1/1′ (0.098 g, 0.5 mmol) dissolved in 0.5 mL of THF was added dropwise. After 30 min a solution of phenylselenenyl bromide (0.235 g, 1.0 mmol) in 1.0 mL of THF was added, and the reaction mixture was stirred at −78 °C for 2 h and then warmed up to 0 °C when a solution of 30% H_2O_2 (0.70 mL) and acetic acid (0.15 mL) in water (1.0 mL) was added. The reaction mixture was allowed to warm up to room temperature, and after stirring for 30 min it was poured into a mixture of saturated $NaHCO_3$ (20 mL) and 1:1 ether–hexanes (20 mL). The organic phase was washed with water (2 × 10 mL), 1% HCl (2 × 10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford 0.085 g of a pale yellow oil which was purified by PTLC (10% ether–hexanes): 17 (0.048 g, 0.25 mmol, 50% yield) and 18 (0.025 g, 0.13 mmol, 26% yield).

17: ^{1}H NMR δ 0.90 (t, J = 7.0, 3 H), 0.95 (d, J = 6.9, 3 H), 1.05 (d, J = 7.2, 3 H), 1.26–1.51 (m, 4 H), 1.73 (m, 1 H), 1.90 (d, J = 1.6, 3 H), 2.63 (m, 1 H), 3.97 (dd, J = 11.1 and 2.4, 1 H), 6.33 (d, J = 1.6, 1 H); ^{13}C NMR δ 13.18, 14.12, 16.22, 16.86, 20.39, 31.05, 33.49, 35.64, 86.10, 127.14, 146.39, 166.29; IR 1702, 1640, and 1150 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.75; H, 10.42.

18: ^{1}H NMR δ 0.90 (t, J = 6.9, 3 H), 0.91 (t, J = 6.9, 3 H), 0.97 (t, J = 7.2, 3 H), 1.28–1.57 (m, 4 H), 1.70 (m, 1 H), 1.95 (m, 1 H), 2.28 (m, 1 H), 2.66 (dd, J = 15.9 and 4.5, 1 H), 3.96 (dd, J = 9.6 and 2.1, 1 H), 5.52 (d, J = 1.2, 1 H), 6.39 (d, J = 1.2, 1 H).

(3*RS*,5*RS*,6*SR*,1′*RS*)-Tetrahydro-6-(1′-methylbutyl)-3,5-dimethyl-2*H*-pyran-2-one (1). To a solution of lactone 17 (0.025 g, 0.125 mmol) in 8 mL of ethanol was added a catalytic amount of 10% Pd/C (2 mg), and the mixture was shaken (Parr apparatus) under 4 atm of hydrogen for 17 h. The catalyst was removed by filtration on Celite, the solvent was removed under reduced pressure, and the residue was chromatographed on Florisil (10% ether–hexanes) to afford (±)-1 (0.020 g, 0.10 mmol, 80% yield). The ^{1}H- and ^{13}C-NMR spectra were fully consistent with those reported by Hoffman et al.[8j]

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