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R-3-Methyl-γ-butyrolactone as a Template for the Synthesis of (+)-Invictolide

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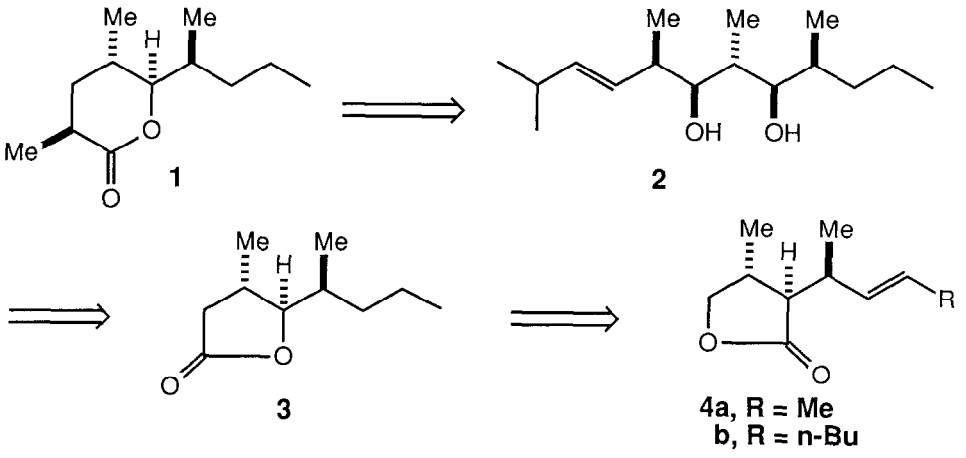
Abstract: The dextrorotatory antipode of the pheromone invictolide has been synthesized from R-3-methyl-γ-butyrolactone, which is employed as a stereochemical template for the addition of propionate units via a Claisen rearrangement and a palladium-catalyzed alkylation. (+)-Invictolide is inactive.

Invictolide, one of three lactonic substances that serve as the queen recognition pheromone of the red imported fire ant, Solenopsis invicta (Buren)[1a], was demonstrated by Tumlinson and co-workers[1b] to have stereostructure **1** through a combination of spectroscopic analysis and synthesis. The Tumlinson synthesis, in addition to those of Hoye[2] and Schreiber,[3] produced racemic material. While no evidence exists as to whether or not invictolide is a single enantiomer, we chose to apply the homochiral 3-methyl-γ-butyrolactone strategy to the synthesis of the antipode of invictolide represented by structure **1**. The strategy (Scheme) clearly requires a right-to-left construction as dictated by the presence of functionality at the left terminus of **1** (or **2**). Lactone **3** serves as the progenitor of diol **2** by way of an S-phosphate alkylation.[4] Transposition of the "CO_2" moiety of lactone **3**[4] mandates lactone **4a** as the logical starting material. While lactone **4a** is readily prepared by the Claisen rearrangement of the diethyl ortholactone of (R)-3-methyl-γ-butyrolactone[5] (**5**) and R-pent-3(E)-en-2-ol (**6**) followed by equilibration, the difficulty associated with the isolation of water-soluble alcohol **6** and the variable enantiomeric excess obtained in the Sharpless kinetic resolution[6] of rac-**6** led to R-oct-2(E)-en-4-ol (**7**) as an alcohol of choice.[7]

Rearrangement of the ortholactone of **5** and R-alcohol **7** (toluene, reflux, pivalic acid, 2 days) followed by epimerization (t-BuOK, t-BuOH, Et_2O, 3h, 25°C) led to an 87% yield of lactone **4b** (%ds=95, %ee>99).[8] Lactone **4b** was transformed into the acetonide **8a** (%ds=96) via the Criegee sequence[9] (MeLi, Et_2O; H_2O_2, HOAc/THF; Ac_2O, DMAP, Et_3N, CH_2Cl_2; KOH/MeOH; $Me_2C(OMe)_2$, p-TsOH) in 68% yield. Ozonolysis of the acetonide (O_3, MeOH, −78°C; DMS; 93%)

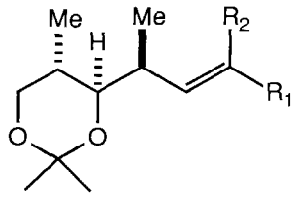
Scheme



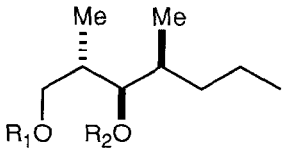
afforded an aldehyde which was subjected to Wittig olefination ($Ph_3P{=}CHCH_3$, Et_2O, $-78^oC \rightarrow 25^oC$; 60%), producing a mixture (2:1) of olefins **8b**. Hydrogenation (Ni(R), H_2, 25^oC) of the olefins provided acetonide **9a** in 83% yield (%ds=96.5, capill. gc). Lactone **10a** was readily prepared (1N aq. HCl, THF; TsCl, pyr., -6^oC, 18h; NaCN, DMSO, 80^oC, 24h; 0.4 N aq. methanolic HCl, reflux, 24h) from the acetonide in 78% yield. The transposed lactone **10a** set the stage for the introduction of the final propionate unit.

Carbomethoxylation[9] of lactone **10a** afforded ester **10b** which was alkylated (2%$Pd(Ph_3P)_4$, 2% Ph_3P, THF, 25^oC, 3h) as its sodium salt (NaH/THF) with the diethylphosphate of S-2-methyl-hex-4(E)-en-2-ol (%ee = 96) to give a mixture of alkylation products (84%), which was subjected to decarbomethoxylation (LiCl, aq. DMSO, 150^oC, 19h). Flash chromatography afforded pure lactone **11b** (69%) in addition to a fraction containing a 2/1 mixture (15%) of **11b** and, ostensibly, **11c**. The Criegee sequence transformed lactone **11b** into diol **2** (51%), which was subjected to ozonolysis (O_3, MeOH, -78^oC; DMS; MeOH, $(MeO)_3CH$, p-TsOH) to give a mixture of the axial methoxyacetal **12a** (δ4.54; 1H, s, R_2-H; 44%) and the equatorial methoxyacetal **12b** (δ4.69, 1H, d, J=2.2 Hz; R_2-H; 32%). The latter acetal was deoxygenated (BuLi, PhOCSCl, THF; $n\text{-}Bu_3SnH$, AIBN, toluene, 90^oC, 2h) and oxidized (O_3, EtOAc, -78^oC; p-TsOH, CH_2Cl_2) to afford the volatile (+)-invictolide $[\alpha]^{25} = +77.4^o$ (c, 0.27, $CDCl_3$) in 33% yield from alcohol **12b**.[10] The 250 MHz-nmr spectra of the antipode and racemate were identical.

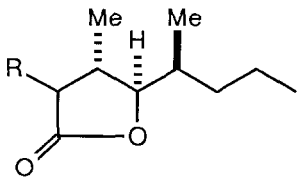
Dextrorotatory invictolide, in admixture with its related pheromones, was inactive in surrogate queen field tests, while the racemate displayed activity. [11,12]



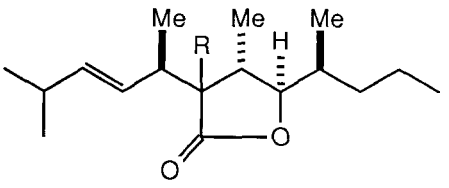
8a, R_1 = n-Bu, R_2 = H
b, R_1 = Me(H), R_2 = H(Me)



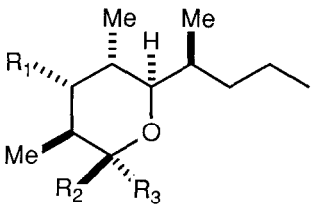
9a, R_1,R_2 = CMe_2
b, R_1 = R_2 = H



10a, R = H
b, R = CO_2Me



11a, R = CO_2Me
b, R = α-H
c, R = β-H



12a, R_1 = OH, R_2 = H, R_3 = OMe
b, R_1 = OH, R_2 = OMe, R_3 = H

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in the field tests conducted by the USDA (Gainesville). We thank Dr. J. H. Tumlinson (Gainesville) for his many valuable discussions and for his cooperation in obtaining the field tests.

References and Notes:

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3. Schreiber, S. L.; Wang, Z., J. Am. Chem. Soc., **1985**, 107, 5305.
4. See the preceding Letters in this issue.
5. The lactone was prepared by the method of Mori. Mori, K., Tetrahedron, **1983**, 39, 3107. The lactone had an enantiomeric excess $\geq$95%, using the assay method of Helmchen. Helmchen, G.; Nill, G., Angew. Chem., Int. Ed. Eng., **1979**, 18, 65. See preceding Letters.
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7. R-2-methylhex-4(E)-en-3-ol is equally suitable.
8. Capillary gc indicates a ratio of 95(B_t):2(C_c):3(C_t).[12] These values, in conjunction with the known %ee of the lactone and the known[12] transition states for $R_{lact}R_{alc}$ ($S_{lact}S_{alc}$) and $R_{lact}S_{alc}$ ($S_{lact}R_{alc}$) *rearrangements, requires* alcohol **7** to have an enantiomeric excess $\geq$99%. The %ee of lactone **4b** can be calculated to be in excess of 99%.[13] The %ds=% of major diastereomer in the mixture. Thaisrivongs, S; Seebach, D., J. Am. Chem. Soc., **1983**, 105, 7407.
9. See the preceding Letter.
10. The methoxy acetal **12a** can, in principle, be epimerized to methoxy acetal **12b** and subsequently oxidized.
11. All new compounds gave satisfactory spectroscopic and/or combustion data.
12. Ziegler, F. E.; Thottathil, J. K., Tetrahedron Lett., **1982**, 23, 3531.
13. a) Midland, M. M.; Gabriel, J., J. Org. Chem., **1985**, 50, 1143 (footnote 9); b) Hoye, T. R.; Suhadolnik, J. C., J. Am. Chem. Soc., **1985**, 107, 5312.

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