DIALKYL ANHYDRO SUGARS IN ORGANIC SYNTHESIS. SYNTHESIS OF (-)-INVICTOLIDE

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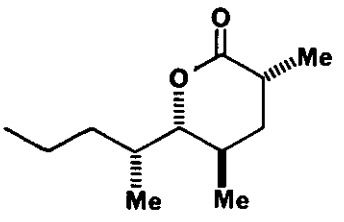
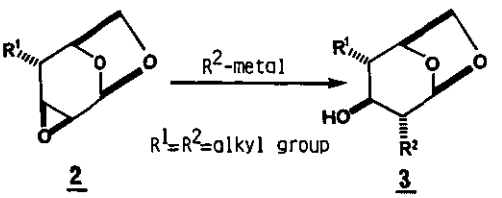
Abstract— The levorotatory invictolide 1a has been synthesized via the stereocontrolled oxirane ring opening of dianhydro sugars, which are conveniently prepared from levoglucosan(1,6-anhydro-β-D-glucopyranose).

Invictolide 1a, isolated from the red imported fire ant queens (Solenopsis invicta(Buren)),is responsible, in part, for queen recognition pheromone by workers of the species and was demonstrated to have the δ-lactone involving four chiral centers on the basis of spectral analyses and its synthesis.[1a,b] The syntheses of racemic invictolide initially reported by Rocca[1b] and co-workers were followed by three other laboratories.[2,3,4] Although there has been no informations as to whether or not dextrorotatory and/or levorotatory invictolide is biologically active, quite recently, both enantiomers of invictolide were synthesized by two groups[5] and the dextrorotatory enantiomer[6] of the pheromone invictolide which eventually, in admixture with its related pheromones, proved to be inactive in surrogate queen field tests. On the other hand, the racemic invictolide displayed activity.[1b]
We herein describe the stereocontrolled synthesis of (-)-invictolide 1a through a strategy of the oxirane ring openings of the anhydro sugar 2 to dialkyl anhydro sugar 3.[7c]

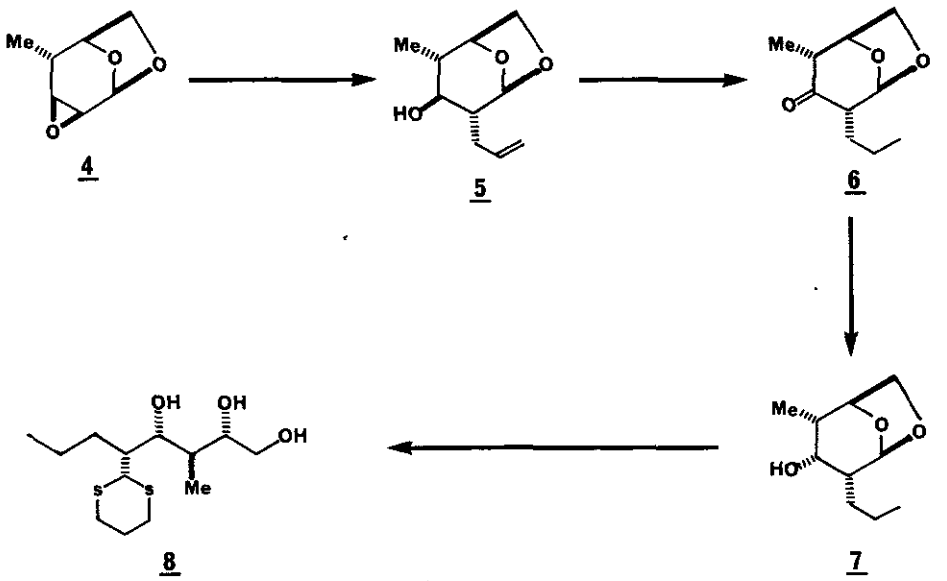


1a



2 3

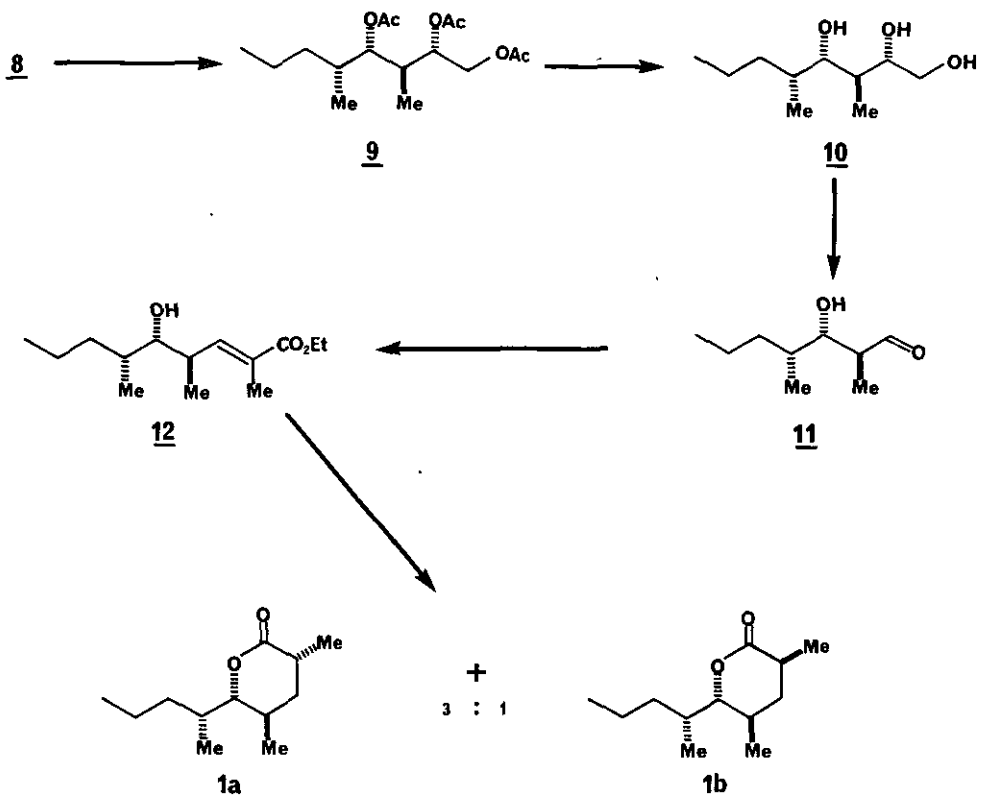
Levoglucosan(1,6-anhydro-β-D-glucose)[8] readily accessible from corn starch by pyrolysis was converted into the known 3,4-epoxytosylate[9], which was then subjected to copper(I) induced reaction[10] with methylmagnesium chloride in tetrahydrofuran, followed by treatment with sodium hydride to lead epoxide 4 in good yield. Transformation of the 2,3-epoxide 4 into the dialkylated *anhydro* sugar 5 was achieved with allylmagnesium bromide in the presence of cuprous iodide in 78% yield. This reaction proceeded with a high regioselectivity in a preferential trans-diaxial opening of oxirane ring.[7]



4 5 6 7 8

Hydrogenation of alcohol 5 with Pearlman's catalyst[11] (H_2/$Pd(OH)_2$/AcOEt) afforded the corresponding alcohol which in turn was oxidized with pyridinium chlorochromate in the presence of molecular sieves 4A in dichloromethane[12] to produce smoothly ketone 6 in 85% overall yield. Subsequent reduction of 6 with lithium aluminum hydride in ether at 0°C for 10 min gave cleanly the desired alcohol 7 as the sole product in 91% yield.[7a] No stereoisomer was detected by either nmr or chromatographic means.

Anhydro ring opening of 7 obtained in this way was carried out with propanedithiol($CF_3COOH/BF_3 \cdot Et_2O/CH_2Cl_2$) at -30°C for 30min and concomitant treatment with 10 % NaOH to cleave its borane complex furnished thioacetal 8 in 95% yield.



Acetylation of 8 ($Ac_2O/Et_3N/DMAP/CH_2Cl_2/rt$, 92%) followed by desulfurization (Raney Ni(W-2)/EtOH/reflux, 84%) gave triacetate 9 in good yield, which was converted to 10 with $LiAlH_4$(ether/0°C, 81%).[13] Oxidation of 10 with lead tetraacetate in benzene for 20 min gave aldehyde 11 in 80% yield, of which nmr spectrum showed no occurrance of epimerization under these conditions. Wittig reaction of 11 ($Ph_3P=C(Me)CO_2Et$/benzene/reflux,75%) afforded (E)-α, β-unsaturated ester 12. Finally, a wide variety of solvent and catalyst were attempted to find a suitable condition for the stereoselective reduction of double bond in compound 12. When 12 was subjected to the reduction with heterogeneous catalyst ($H_2/Pd(OH)_2/ClCH_2CH_2Cl/rt$, 70%), levorotatory invictolide 1a $[\alpha]_D^{22}$ -76° (c 0.12,$CHCl_3$) was obtained in a 74:26 ratio of 1a and epi-invictolide 1b in the desired sence.[14] The spectral properties of synthetic invictolide were identical with those of an authentic specimen in all appropriate respects.

ACKNOWLEDGMENTS

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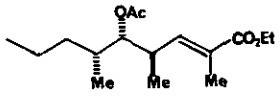
13. Direct desulfurization of 8 to 10 was performed in 53% overall yield.
14. Hydrogenation in dichloromethane gave 1a and 1b in a ratio of 69:31 in 86% yield. Acetyl compound (i)(H_2/Pd(OH)$_2$/CH_2Cl_2) resulted in inferior diastereoselection(1a:1b=41:59).



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