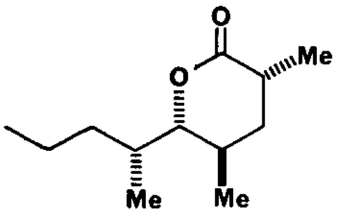
# DIALKYL ANHYDRO SUGARS IN ORGANIC SYNTHESIS.
# SYNTHESIS OF (-)-INVICTOLIDE

Takeshi Wakamatsu,* Yuji Nishikimi, Hiromi Kikuiri, and Hideo Nakamura
Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo 060, Japan
Yoshio Ban
School of Pharmaceutical Science, Toho University, Miyama 2-2-1,
Funabashi, Chiba 274, Japan

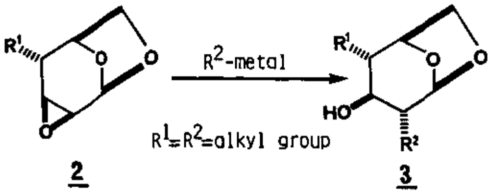
Abstract—— The levorotatory invictolide 1a has been synthesized via the stereocontrolled oxirane ring opening of dianhydro sugars, which are conveniently prepared from levoglucosan(1,6-anhydro-β-D-glucopyranose).

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]

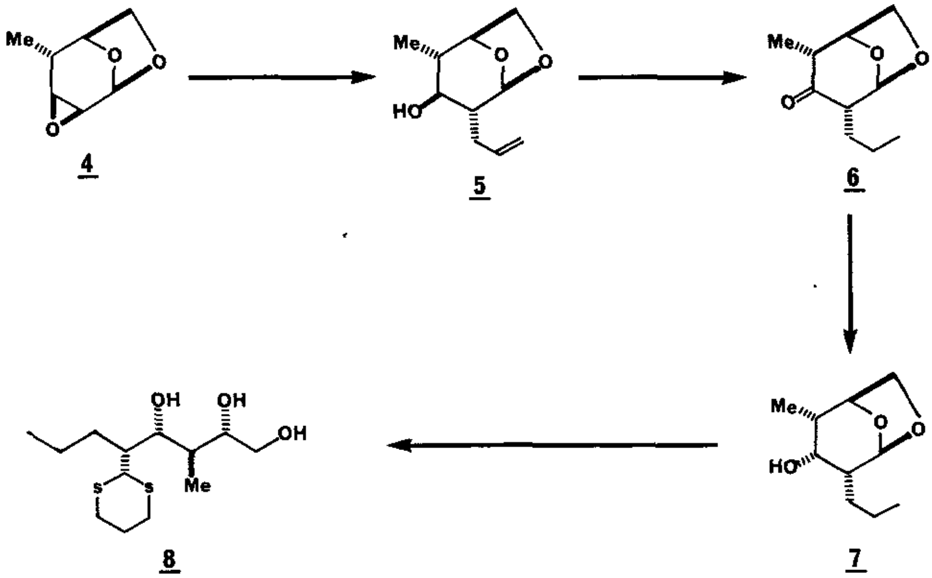
We herein describe the stereocontrolled synthesis of (-)-invictolide 1a through a strategy of the oxirane ring openings of the anhydro sugar 2 to dialkyl anhydro sugar 3.[7c]



1a

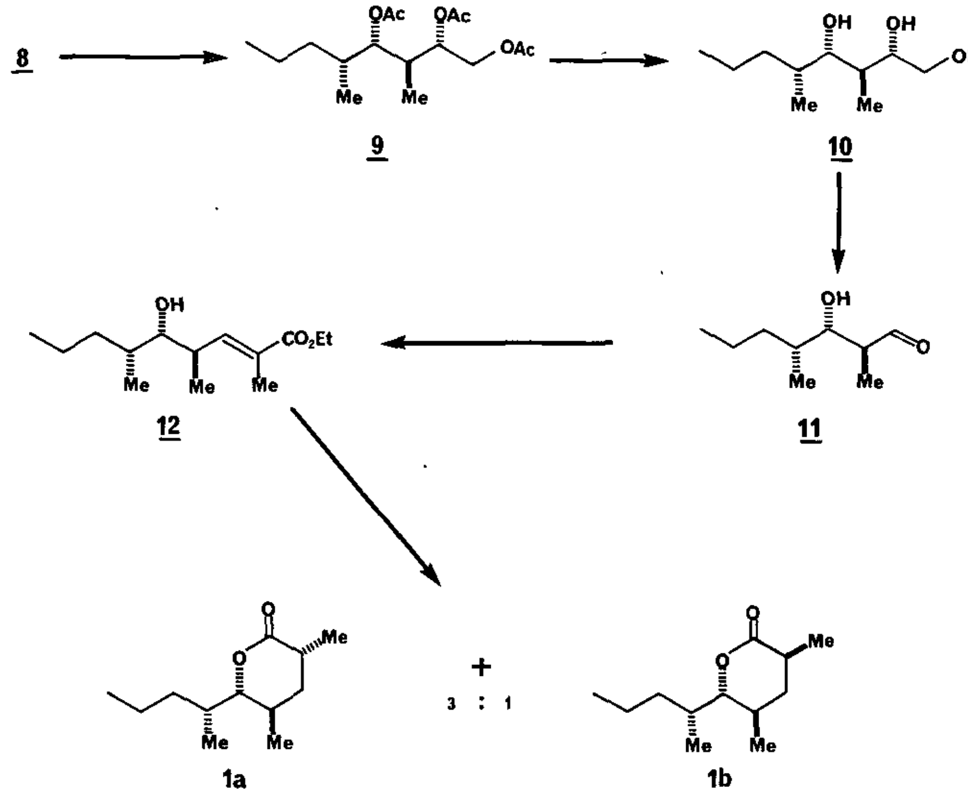


Levoglucosan(1,6-anhydro-β-D-glucose)[8] readily accessible from corn starch by pyrolysis was converted into the known 3,4-epoxytosylate[9], which was then subjected to copper(I) induced reaction[10] with methylmagnesium chloride in tetrahydrofuran, followed by treatment with sodium hydride to lead epoxide 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]



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.



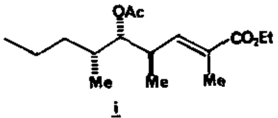
Acetylation of 8 ($Ac_2O/Et_3N/DMAP/CH_2Cl_2$/rt, 92%) followed by desulfurization (Raney Ni(W-2)/EtOH/reflux, 84%) gave triacetate 9 in good yield, which was converted to 10 with $LiAlH_4$(ether/0°C, 81%).[13] Oxidation of 10 with lead tetraacetate in benzene for 20 min gave aldehyde 11 in 80% yield, 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

This work was supported by Grant-in-Aid for the Special Project Research "Chemical Syntheses for Elucidation of Biological Functions" (No. 61224001) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowleged. We express our thanks to Dr. J. H. Tumlinson, Insect Attractants, Behavior, and Basic Biology Research Lab., Agric. Res. Ser., USDA for supplying spectra of invictolide.

## REFERENCES AND NOTES

1. a) J. R. Rocca, J. H. Tumlinson, B. M. Glancey, and C. S. Lofgren, Tetrahedron Lett., 1889 (1983). b) J. R. Rocca, J. H. Tumlinson, B. M. Glancey, and C. S. Lofgren, Tetrahedron Lett., 1893 (1983).
2. T. R. Hoye, D. R. Peck, and T. A. Swanson, J. Am. Chem. Soc., 106 2738 (1984).
3. S. L. Schreiber and Z. Wang, J. Am. Chem. Soc., 107, 5303 (1985).
4. Y. Yamamoto, K. Taniguchi, and K. Maruyama, J. Chem. Soc., Chem. Commun., 1429 (1985).
5. a)F. E. Ziegler, E. P. Stirchak, and R. T. Wester, Tetrahedron Lett., 1229 (1986); b) K. Mori and Y. Nakazono, Tetrahedron, 42, 6459 (1986).
6. Bioassay of Mori's synthetic enantiomers is currently under way in the laboratories of Dr. J. H. Tumlinson, see ref. 5b).
7. a) P. J. Hodges and G. Procter, Tetrahedron Lett., 4111 (1985); b) S. Challenger and G. Procter, Tetrahedron Lett., 391 (1986); c) T. Wakamatsu, H. Nakamura, Y. Nishikimi, K. Yoshida, T. Noda, M. Taniguchi, and Y. Ban, Tetrahedron Lett., 6071 (1986).
8. R. B. Ward, Methods in Carbohydrate Chemistry, 2, 394 (1963).
9. L. J. Carlson, J. Org. Chem., 30, 3953 (1965).
10. a) A. G. Kelly and J. S. Roberts, J. Chem. Soc., Chem. Commun., 228 (1980); b) N. K. Kochetkov, A. F. Sviridof, M. S. Ermolenko, Tetrahedron Lett., 4315 (1981); c) L. Magdzinski, B. Cweiber, and B. Fraser-Reid, Tetrahedron Lett., 5823 (1983); d) M. P. Edwards, S. V. Ley, S. G. Lister, and B. D. Palmer, J. Chem. Soc., Chem. Commun., 630 (1983).
11. W. M. Pearlman, Tetrahedron Lett., 1663 (1967).
12. J. Herscovici and K. Antonakis, J. Chem. Soc., Chem. Commun., 561 (1980).
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).



i

Received, 20th March, 1987