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A NEW AND FACILE ROUTE TO SPIRO-KETAL SKELETON VIA HIGHLY STEREOSELECTIVE C-O BOND FORMATION BY INTRAMOLECULAR MICHAEL ADDITION TO α,β-UNSATURATED SULFOXIDES

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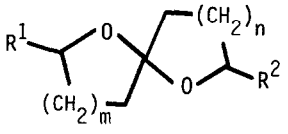
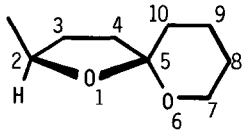
Summary: Diastereoisomerically pure (*E*)- and (*Z*)-2-methyl-1,6-dioxaspiro[4.5]-decane (insect pheromone) was efficiently prepared *via* a highly stereo-controlled intramolecular Michael addition of hydroxyl group to an unsaturated sulfoxide moiety during the crucial cyclization step.

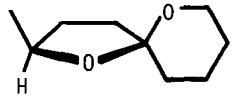
Spiro-ketal moiety plays a very important role as structural elements of many biologically active natural products, *e.g.* insect pheromones,[1] talaromycins,[2] monensin,[3] phyllantoside,[4] milbemycins,[5] and avermectins.[6] Simple alkyl-1,7-dioxaspiro[5.5]undecanes, alkyl-1,6-dioxaspiro[4.5]decanes, and alkyl-1,6-dioxaspiro[4.4]nonanes (1) are of particular interest because of their identification as insect pheromones and their existence in a *E*:*Z* mixture.[7] Continuous efforts are being paid to develop new construction methods for spiro-ketal skeleton and many interesting methods have been reported. They involve as the key step a hetero-Diels-Alder reaction,[8] a NOC approach,[9] an organoselenium mediated cyclization,[10] a cation-olefin cyclization,[11] and others.[12] However, little is known concerning successful stereocontrol around the spiro carbon center.[13] In this communication we wish to report a new and facile route to spiro-ketal system with extreme stereoselectivity at the spiro carbon center, illustrated by selective preparation of diastereomerically pure (*E*)- and (*Z*)-2-methyl-1,6-dioxaspiro[4.5]decane (2-E and 2-Z) which was isolated as insect pheromone from the common wasp *Paravespula vulgaris*.[14]



1 m,n = 1,2
R^1,R^2 = H, alkyl



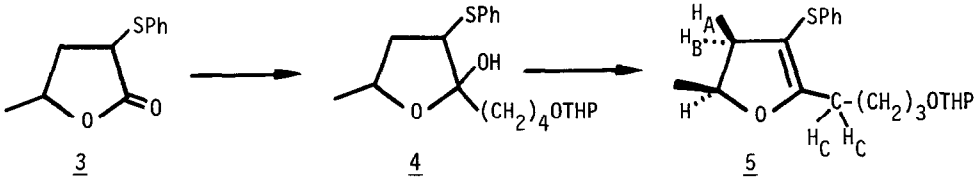
2-E



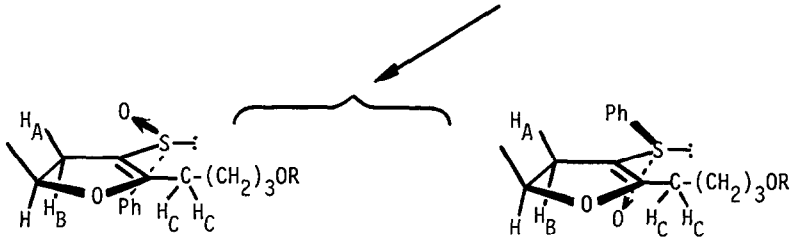
2-Z

5-Methyl-3-phenylthiotetrahydrofuran-2-one[15] (3) was treated with 5 equivalents of the Grignard reagent prepared from 4-(tetrahydropyranyloxy)butyl chloride[16] in boiling tetrahydrofuran (THF) to afford the hemi-acetal (4) as a diastereoisomeric mixture in 68% yield. Dehydration of 4 was fairly accom-

plished by the reaction with a catalytic amount of *p*-toluenesulfonic acid in ether at 0°C to give the *endo*-olefin (5)[quantitative yield; ν^{17} 1640; δ^{17} 1.35(3H,d,*J*=6), 2.27(1H,dd,*J*=8,14,H_A), 2.33(2H,m,H_C), 2.83(1H,dd,*J*=10,14,H_B)], which was oxidized in the usual manner (MCPBA or $NaIO_4$ oxidation) to the isomeric sulfoxides [6: ν 1640; δ 1.33(3H,d,*J*=6), 2.14(1H,dd,*J*=10,14,H_B), 2.47 (1H,dd,*J*=8,14,H_A), 2.69(2H,m,H_C) and 7: ν 1640; δ 1.17(3H,d,*J*=6), 1.58(1H,dd, *J*=8,14,H_A), 2.58(2H,m,H_C), 2.98(1H,dd,*J*=10,14,H_B)] in *ca.* 1:1 ratio in 93% yield. Each component was easily separable by means of silica gel chromatography and the stereochemistry was confirmed by ^{1}H-NMR spectroscopic consideration.[18] On treatment of each isomer with a catalytic amount of *p*-toluenesulfonic acid in methanol at 0°C, a chemoselective deprotection of the pyranyl ether part took place to provide the corresponding alcohols (8 and 9) in each *ca.* 90% yield.



3 4 5



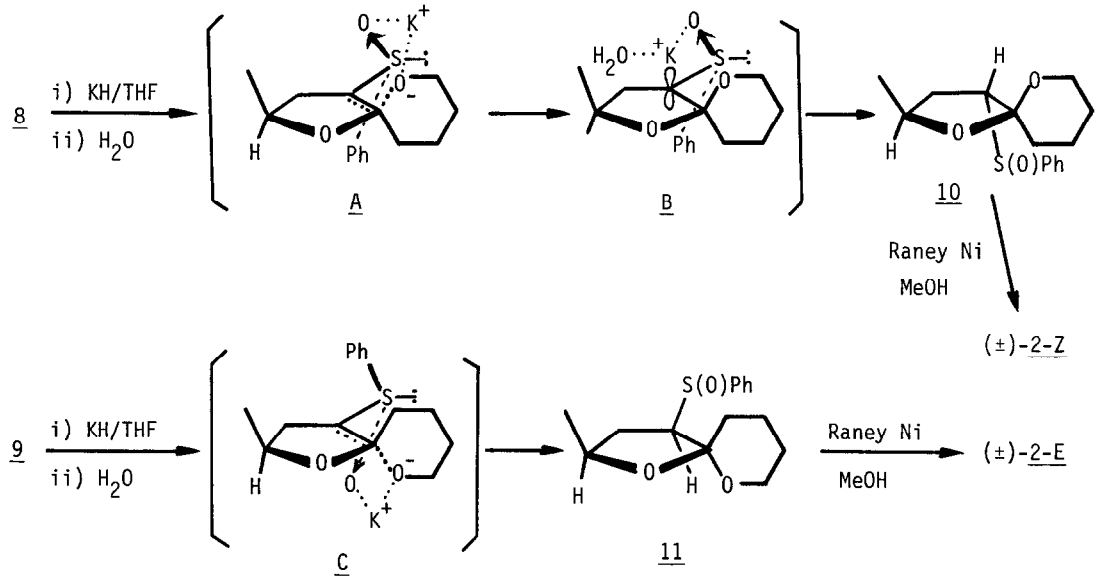
6: R = THP
8: R = H

7: R = THP
9: R = H

After several conditions were examined for a spiro-ketal cyclization of 8 and 9, it was found that the reaction with potassium hydride[19] in THF at room temperature gave a satisfactory result in view of stereoselectivity. Namely, exposure of 8 under the above mentioned condition resulted in exclusive formation of the single dioxaspiro compound (10)[90% yield; δ($CDCl_3$) 1.22(3H,d,*J*=6), 3.34(1H,dd,*J*=3,7,C_4-H)]. The excellent stereoselectivity in this Michael addition step could be well interpreted in terms of a stable chelation mediated by the potassium cation.[20] As shown in the possible transition state A, the chelation between the side-chain oxido anion and the sulfoxide oxygen should severely control the direction of newly formed C-O bond. In the second step, it is assumed that protonation to the α-sulfinyl carbanion undergo kinetically from the same side of the sulfoxide oxygen *via* intermediate B.[21] On the other hand, the isomer (9) similarly afforded the sole cyclized product (11)[90% yield; δ($CDCl_3$) 1.20(3H,d,*J*=6), 3.31(1H,dd,*J*=7.5,8.5,C_4-H)], which seems to be afforded *via* intermediate C under the same steric control as that for 8. Thus, the crucial spiro-ketal formation reaction was found to proceed under a severe

control of the configuration of pyramidal sulfoxide moiety rather than the C-2 stereochemistry.[22]

Finally, catalytic hydrogenolysis of 10 and 11 over Raney Ni furnished (±)-(Z)-2-methyl-1,6-dioxaspiro[4.5]decane (2-Z)[88% yield; δ($CDCl_3$) 1.28(3H, d,J=6), 3.4-4.1(2H,m,C_7-H), 4.20(1H,q,J=6,C_2-H)] and the E-isomer (2-E)[79% yield; δ($CDCl_3$) 1.22(3H,d,J=6), 3.4-4.1(2H,m,C_7-H), 4.24(1H,q,J=6,C_2-H)], respectively.[23]



The present work has shown the first example that successfully stereocontrolled C-O bond formation was performed by an intramolecular Michael addition of a hydroxy group to the α,β-unsaturated sulfoxide moiety.[24] This novel construction method for spiro-ketal system seems to be of great value from the viewpoint that stereochemistry of the crucial step is controlled by only the removable sulfinyl chirality and therefore not only the stable isomer (such as 2-E) but also the labile one (such as 2-Z) is obtainable with high stereoselectivity.

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13. *cf.* J.Y.C. Chan, L. Hough, and A.C. Richardson, *J.C.S., Chem. Commun.*, 1151 (1982).
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17. IR and ^{1}H-NMR spectra were measured in CCl_4 solution unless otherwise stated.
18. In the ^{1}H-NMR spectrum of 6, H_A which is *trans* to the C_2-H appeared in lower field (δ 2.47) and H_B in higher field (δ 2.14) than those of the parent compound (5), attributable to anisotropy of the sulfinyl oxygen and the phenyl group, respectively.
19. When sodium hydride or *n*-butyllithium was used instead of potassium hydride, the stereoselectivity somewhat decreased.
20. A similar chelation was also assumed in the case of the Grignard reaction. *cf.* N. Kunieda, J. Nokami, and M. Kinoshita, *Chem. Lett.*, 369 (1974).
21. Stereochemical consideration about protonation to the anion adjacent to the sulfoxide appeared in T. Durst, R. Viau, and M.R. McClory, *J. Am. Chem. Soc.*, 93, 3077 (1971) and references cited therein.
22. The relative configuration between C-2 and C-5 in 10 and 11 was finally confirmed after their desulfurization, while the relationship between C-4 and C-5 were easily determined from the chemical shifts of C_4-H in ^{1}H-NMR spectra.
23. E. Hungerbühler, R. Naef, D. Wasmuth, and D. Seebach, *Helv. Chim. Acta*, 63, 1960 (1980).
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