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INTRAMOLECULAR MICHAEL ADDITION REACTION TO CHIRAL VINYLIC SULFOXIDES. AN ENANTIOSELECTIVE SYNTHESIS OF (R)- AND (S)-1,7-DIOXASPIRO[5.5]UNDECANE

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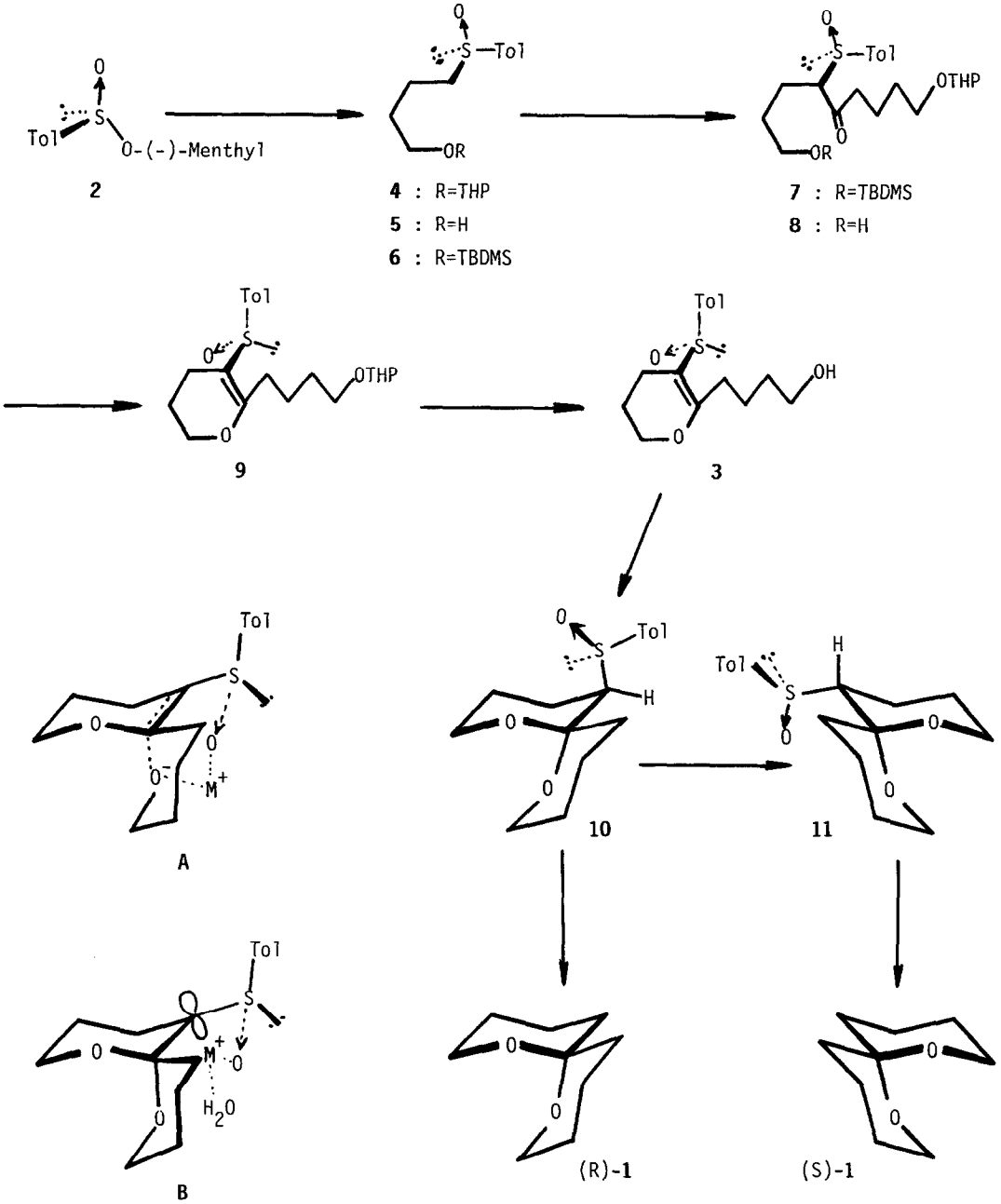
Summary: (R)- and (S)-1,7-Dioxaspiro[5.5]undecane ((R)-**1** and (S)-**1**), sex pheromone of an olive fly, was each stereoselectively synthesized using an intramolecular Michael addition of hydroxyl group to a chiral vinylic sulfoxide moiety as an asymmetric induction step.

Numerous addition reactions, such as conjugate addition of nitrogen nucleophiles,[1] organometallic reagents[2] or stabilized carbanions,[3] cycloaddition[4] of dienes or 1,3-dipoles, and others,[5] toward chiral vinylic sulfoxides, have been shown to be very useful for asymmetric synthesis.[6] Most of these examples, however, involved intermolecular bond formation reactions[7] and therefore optical activities of the products were often found to be relatively low. In the previous paper we have reported that (±)-(E)- and -(Z)-2-methyl-1,6-dioxaspiro[4.5]decane was each stereoselectively synthesized using a novel method for spiroketal construction, an intramolecular Michael addition of hydroxyl group to the vinylic sulfoxide in diastereomers of 4,5-dihydro-2-(4-hydroxybutyl)-5-methyl-3-phenylsulfinylfuran, and stereochemistry of the newly created dioxaspiro center was severely controlled only by configuration of the sulfinyl group.[8] This high performance on diastereoselectivity have prompted us its further application to chiral syntheis of natural spiro-ketal compounds.

In this communication we wish to describe a highly stereocontrolled synthesis of both enantiomers of 1,7-dioxaspiro[5.5]undecane ((R)-**1** and (S)-**1**) *via* the intramolecular Michael addition reaction in the hydroxybutylated chiral vinylic sulfoxide (**3**) derived from easily available (-)-menthyl (S)-*p*-toluenesulfinate (**2**).[9] 1,7-Dioxaspiro[5.5]undecane (**1**), one of C_2 chiral compounds,[10] was reported to be identical with the major component of sex pheromones produced by the olive fly (*Dacus oleae*) but no information on its

chirality was obtained.[11] There have been many reports concerning synthesis of racemic **1** to date.[12] Just recently, Mori et al.[13a] have achieved the first enantioselective synthesis of (R)- and (S)-**1** utilizing (-)-malic acid as a chiral source, and Redlich and his co-worker[13b] have also reported the enantioselective preparation starting from D-glucose.



The key intermediate (**3**) was prepared as follows. (-)-Menthyl (S)-p-toluenesulfinate (**2**), $[\alpha]_D^{19}$ -200° (c=0.30, acetone), obtained according to the known method,[9] was treated with 3 equiv. of 4-(tetrahydro-2H-pyran-2-yl)oxybutylmagnesium chloride in THF at -10°C to afford the sulfoxide (**4**), $[\alpha]_D^{22}$ +111° (c=1.02, $CHCl_3$), which was subjected to a mild acidic hydrolysis to give the alcohol (**5**), $[\alpha]_D^{20}$ +189° (c=0.95, $CHCl_3$), in 93% yield from **2**. After silylation with tert-butyldimethylsilyl chloride, the produced **6** (92% yield) was treated with lithium diethylamide in THF followed by reaction with 3 equiv. of methyl 5-(tetrahydro-2H-pyran-2-yl)oxyvalerate[14] in the presence of HMPA at -70°C to afford the keto sulfoxide (**7**), $[\alpha]_D^{28}$ +37.4° (c=1.00, $CHCl_3$), in 56% yield with 39% recovery of **6**. Desilylation of **7** with tetra-n-butylammonium fluoride in THF at r.t. followed by treatment with a small amount of p-TsOH in dichloromethane at r.t. in the presence of anhyd. magnesium sulfate (2 equiv.) gave the dihydropyran derivative (**9**), $[\alpha]_D^{20}$ -29.1° (c=1.56, $CHCl_3$), via **8** in 68% yield. Finally, a mild acidic hydrolysis of **9** afforded the expected hydroxy sulfoxide (**3**) [79% yield; an oil; $[\alpha]_D^{19}$ -37.2° ($CHCl_3$, c=0.87); m/z 294 (M); ν 3380, 1628, 1597, 1022; δ 2.36 (3H, s), 2.65 (2H, t, J=6), 2.96 (1H, br s), 3.63 (2H, t, J=6), 3.7-4.2 (2H, m), 7.18 (2H, d, J=9), 7.34 (2H, d, J=9)].

Cyclization of **3** was accomplished under the conditions similar to that previously employed for preparation of 1,6-dioxaspiro[4.5]decane ring system.[8] Namely, the vinylic sulfoxide (**3**) was treated with 5 equiv. of sodium hydride[15] in THF at r.t. for 1 hr to afford the kinetically controlled product (**10**) [77% yield; mp. 108-109°C; $[\alpha]_D^{16}$ +7.0° ($CHCl_3$, c=0.80); δ 2.40 (3H, s), 2.51 (1H, dd, J=2, 5); m/z(CI) 295 (M+1)] as a sole stereoisomer via intermediates **A** and **B**.[8] The sulfinyl group in **10** situates axially on the tetrahydropyran ring and its exclusive isomerization to the more stable isomer (**11**) [mp. 113-114°C; $[\alpha]_D^{16}$ +92.6° ($CHCl_3$, c=0.83); δ 2.35 (3H, s), 2.49 (1H, dd, J=9.5, 4.5)] was found to proceed with inversion of configuration at the spiro center upon treatment with 1 equiv. of p-TsOH in MeOH at r.t.[16] Thus selectively prepared diastereomers (**10** and **11**) furnished the corresponding enantiomers of 1,7-dioxaspiro[5.5]undecane ((R)-**1** and (S)-**1**),[17] respectively, on desulfurization under the usual conditions.[8]

As above mentioned, starting from one enantiomer of the suitable vinylic sulfoxide, both enantiomers of 1,7-dioxaspiro[5.5]undecane (**1**) were selectively synthesized by means of kinetically controlled asymmetic induction at the spiro center, acidic isomerization, and removal of the chiral source. And it has been proved that this novel method for spiro-ketal construction is applicable to the synthesis of not only dioxaspiro[4.5]decane system but also dioxaspiro[5.5]undecane one with extremely high stereoselectivity. Further applications of this methodlogy to other kinds of target compounds are currently under way.

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14. Prepared from methyl 5-hydroxyvalerate [Y. Muramoto, I. Ichimoto, and H. Ueda, Nippon Nogei Kagaku Kaishi, **48**, 525 (1974) [Chem. Abs., **82**, 124673j (1975)]] by the usual tetrahydropyranylation.
15. Potassium hydride was found to lower the yield of **10** (66% yield).
16. The isomerization process afforded quantitatively a 4:96 mixture of **10** and **11**, a recrystalization of which gave pure **11** in 69% yield.
17. (R)-**1**: 78% yield from **10**; bp. 68-70°C (bath temp.)/25 mmHg; $[\alpha]_D^{25}$ -128° (c=0.39, n-pentane); m/z 156 (M, 17), 128 (13), 101 (100); $\nu(CCl_4)$ 1042, 1067, 1099, 1193; ^{1}H-NMR (C_6D_6) 1.0-2.2 (12H, m), 3.2-3.8 (4H, m); ^{13}C-NMR (C_6D_6) 19.03, 25.79, 36.19, 60.16, 94.87. (S)-**1**: 83% from **11**; bp. 73°C (bath temp.)/39 mmHg; $[\alpha]_D^{24}$ +123° (c=0.23, n-pentane). Mass, IR, ^{1}H-, and ^{13}C-NMR spectra between both enantiomers were well coincident.

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