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STEREOSELECTIVE SYNTHESIS OF ALL ISOMERS OF 2-METHYL-1,6-DIOXASPIRO[4.5]DECANE (INSECT PHEROMONE) USING A CHIRAL SULFOXIDE AUXILIARY

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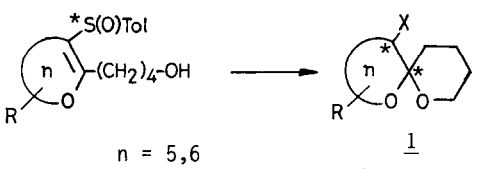
Summary: All four isomers of 2-methyl-1,6-dioxaspiro[4.5]decane were synthesized stereoselectively by means of successful asymmetric induction using only a chiral sulfoxide auxiliary.

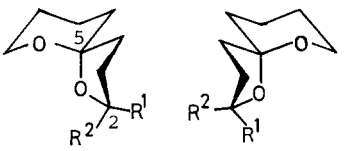
Simple spiro-ketal compounds attract much attention of organic chemists because of their potential role as whole or partial structures for many biologically active natural products.[1] In previous communications we reported the novel construction method for spiro-ketal framework (**1**) with extremely high stereocontrol around the spirocenter in the course of six-membered ring cyclization, as shown below.[2] We wish to report here the first stereoselective preparation of all four isomers [(2S,5R)-, (2R,5R)-, (2R,5S)-, and (2S,5S)-**2**] of 2-methyl-1,6-dioxaspiro[4.5]decane[3-5] by means of asymmetric induction not only at the spiro center (C-5) but also at the C-2 one using only a chiral sulfoxide auxiliary, via five-membered ring cyclization as a crucial step.



n = 5,6
R = Me,H

1

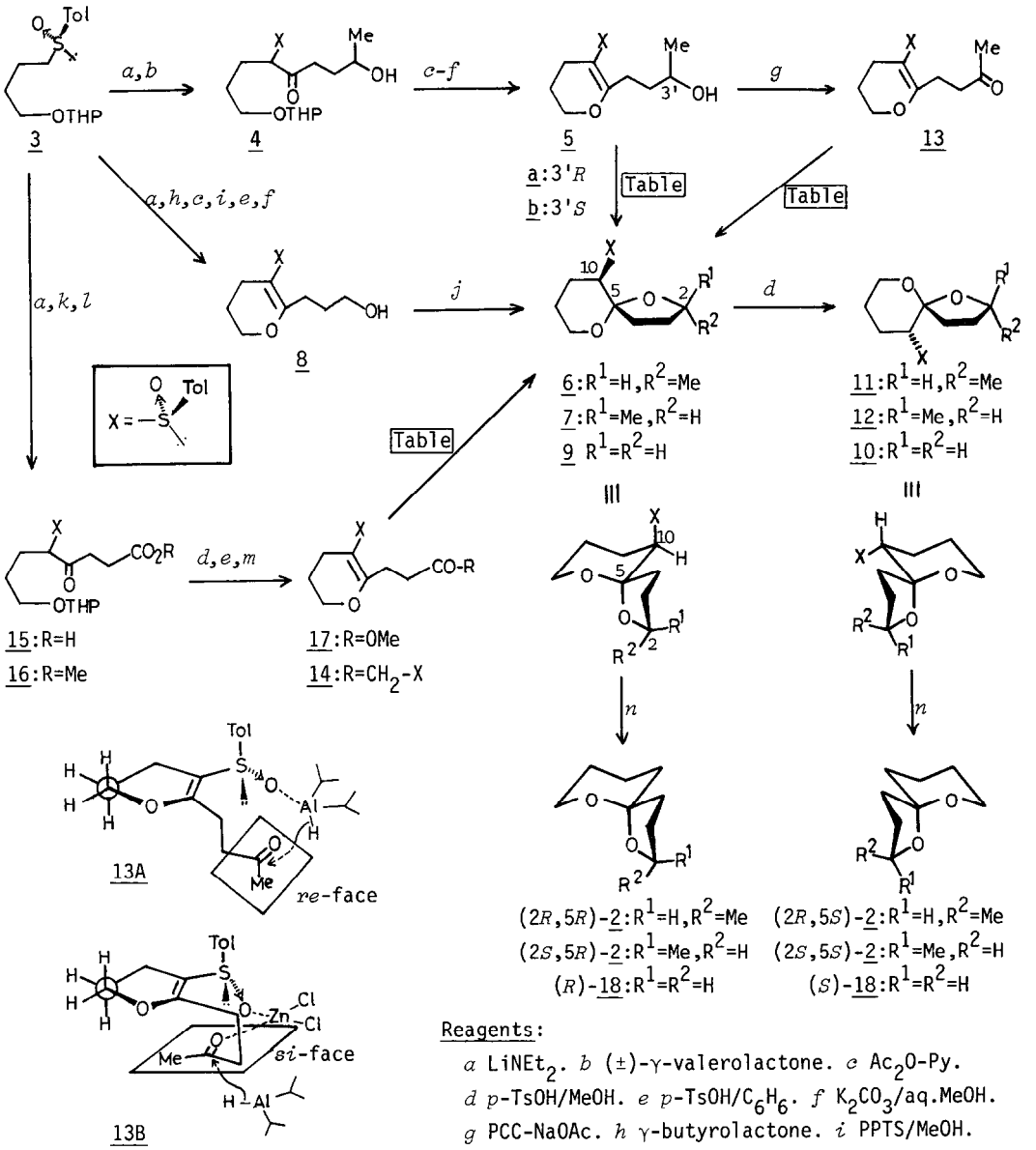
X = *S(O)Tol,H



(2*R*,5*R*)-**2**:R^1=H,R^2=Me (2*R*,5*S*)-**2**:R^1=H,R^2=Me
(2*S*,5*R*)-**2**:R^1=Me,R^2=H (2*S*,5*S*)-**2**:R^1=Me,R^2=H

The anion of the easily available chiral sulfoxide[2b] (**3**) was condensed with (±)-γ-valerolactone to give the ketol (**4**; 91.4%), which was transformed into a 1:1 diastereomeric mixture of the dihydropyran derivative (**5**) in 66.5% yield by a four-step sequence [acetylation, depyranylation, dihydropyran ring formation, and then deacetylation]. On treatment of **5** with a large excess of potassium hydride in tetrahydrofuran at room temperature followed by chromatographic separation, two diastereomers of the expected dioxaspiro compounds were obtained in 83.5% combined yield. The structural assignment of the products to **6**[6] (38.5%) and **7** (45.3%) was based on the following evidences. Namely, the demethyl analogue (**8**) of **5** was prepared from **3** and γ-

butyrolactone according to the Scheme and subjected to cyclization under the condition mentioned above to afford the kinetically controlled product (**9**) [δ 2.75 (1H, t-like, J = ca. 3 Hz, C_{10}-H)] as a single isomer in 84.2% yield, which was found to isomerize easily to the more stable isomer (**10**) [δ 2.98 (1H, dd, J = 5, 12 Hz, C_{10}-H)] in 74.9% yield[7] on an acidic treatment. The both isomers (**6** and **7**) exhibited C_{10}-axial hydrogen signals in their ^{1}H-NMR spectra and readily isomerized to the alternative isomers (**11** and **12**,



Reagents:

a $LiNEt_2$. *b* (±)-γ-valerolactone. *c* Ac_2O-Py.
d *p*-TsOH/MeOH. *e* *p*-TsOH/C_6H_6. *f* K_2CO_3/aq.MeOH.
g PCC-NaOAc. *h* γ-butyrolactone. *i* PPTS/MeOH.
j KH/THF. *k* succinic anhydride. *l* CH_2N_2.
m $LiCH_2$-X. *n* Raney Ni/MeOH.

respectively) by an acid. These features show that the initially formed products (**6** and **7**) are the kinetically controlled products and possess the same (5S,10R)-configuration. Stereochemistry at C_2 of each isomer was determined by chemical shift of the secondary methyl protons.

On the other hand, each isomer of **6** and **7** was stereoselectively obtainable as follows. DIBAL reduction of the ketone (**13**), prepared in 66.9% yield by PCC oxidation of **5**, was followed by cyclization to give the (2S)-isomer (**7**) predominantly, while the (2R)-isomer (**6**) was mainly produced in the case of DIBAL-$ZnCl_2$. Although asymmetric reduction of α-sulfinyl ketones is well known,[8] the present successful 1,6-asymmetric induction (**13** → **5**) is novel. The observed stereoselectivity may be attributable to chelate intermediates (**13A** and **13B**) for DIBAL and DIBAL-$ZnCl_2$ reductions, respectively.[9] On the contrary, such stereoselectivity was not observed on reductions of the α-sulfinyl ketone (**14**), which was obtained via a several-step sequence initiated by condensation of **3** with succinic anhydride [**3** → **15** → **16** → **17** → **14**]. Either reduction of **14** with DIBAL or DIBAL-$ZnCl_2$, followed by a limited desulfurization and subsequent cyclization, afforded only an almost 1:1 mixture of **6** and **7** (see Table).[10]

Table. Preparation of the Dioxaspiro[4.5]decanes (6 and 7) *via* 5.

Run	Starting Material	Conditions[b]	Isolated Yields of 5	Ratios of 5a:5b[c]	Isolated Yields of Cyclization[e]	Ratios of 6:7[f]
1	5[a]			47:53	76%	48:52
2	13	A	94%	15:85	85%	18:82
3	13	B	98%	76:24	74%	73:27
4	13	C	99%	58:42	86%	55:45
5	14	A+D	50%	—[d]	95%	47:53
6	14	B+D	43%	—[d]	93%	47:53

[a] Obtained from 4. [b] A: DIBAL/THF, -78°C, B: DIBAL-$ZnCl_2$/THF, -78°C, C: LAH/THF, -78°C, D: Raney Ni/MeOH, reflux. [c] Determined by HPLC analysis. [d] Not determined. [e] Cyclization conditions: KH/THF, r.t. [f] Determined by HPLC analysis and good agreement with values obtained from the isolated yields of 6 and 7.

Thus stereoselectively prepared dioxaspiro compounds (**6**, **7**, **11**, and **12**) were desulfurized to the corresponding parent compounds [(2R,5R)-, (2S,5R)-, (2R,5S)-, and (2S,5S)-**2**] in good yields. Furthermore, the first preparation of (R)- and (S)-1,6-dioxaspiro[4.5]decane[11] (**18**) was also accomplished by the catalytic reduction of the corresponding sulfoxides (**9** and **10**). In conclusion, all four isomers of **2** have been first synthesized with stereocontrol by means of 1,3-asymmetric induction (C-5 chirality) and 1,6-asymmetric one (C-2 chirality) using a single chiral sulfoxide auxiliary. The present investigations are of great value from the viewpoint of structure-activity relationship of insect pheromones.

REFERENCES AND NOTES

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5. Some optically active isomers of **2** have been synthesized in ref. 4a,d,h.
6. Physical and spectral data of representative compounds are given below. Optical rotations, IR, and ^{1}H-NMR spectra were measured in $CHCl_3$, $CHCl_3$, and $CDCl_3$, respectively, unless otherwise noted: **6**, mp 102-103°C, $[\alpha]_D^{13}$ +34.1° (c=1.08), δ 1.31 (3H,d,J=6Hz), 2.40 (3H,s), 2.74 (1H,t-like, J=3Hz), 3.68 (1H,ddd,J= 2,7,11Hz), 4.02 (1H,dd,J=3,11Hz), 4.13-4.37 (1H,m), 7.25 (2H,d,J=8Hz), 7.57 (2H,d,J=8Hz). **7**, mp 132-133°C, $[\alpha]_D^{13}$ +47.5° (c=1.04), δ 1.18 (3H,d,J=6Hz), 2.40 (3H,s), 2.76 (1H,t-like,J=3Hz), 3.64 (1H,ddd,J=2,7,11Hz), 3.90 (1H,dd,J=3,11Hz), 4.05-4.40 (1H,m), 7.26 (2H,d,J=8Hz), 7.56 (2H,d,J=8Hz). **9**, mp 126-128°C, $[\alpha]_D^{17}$ +62.6° (c=1.87), δ 2.39 (3H,s), 2.75 (1H,t-like,J=3Hz), 7.24 (2H, d,J=9Hz), 7.54 (2H,d, J=9Hz). **10**, mp 84-86°C, $[\alpha]_D^{19}$ +95.9° (c=0.73), δ 2.40 (3H,s), 2.98 (1H,dd,J=5,12Hz), 7.22 (2H,d,J=9Hz), 7.51 (2H,d,J=9Hz). **11**, mp 91-92.5°C, $[\alpha]_D^{15}$ +87.9° (c=1.11), δ 1.38 (3H,d,J=6Hz), 2.41 (3H,s), 2.93 (1H,dd, J=5,12Hz), 3.50 (1H,ddd,J=2,5,10Hz), 4.29 (1H,sex,J=6Hz), 7.24 (2H,d, J=8Hz), 7.54 (2H,d,J=8Hz). **12**, mp 111-113°C, $[\alpha]_D^{15}$ +90.1° (c=1.07), δ 1.35 (3H,d,J=7Hz), 2.41 (3H,s), 2.98 (1H,dd,J=7,11Hz), 3.50 (1H,ddd, J=2,4,10Hz), 3.66-3.99 (1H,m), 4.30-4.69 (1H,m), 7.24 (2H,d,J=8Hz), 7.53 (2H,d,J=8Hz). (2R,5R)-**2**, bp 100-110°C (20 mmHg), $[\alpha]_D^{20}$ +83.4° (c=0.728), n-pentane), δ 1.23 (3H,d,J=6Hz), 1.35-2.32 (10H,m), 3.30-4.28 (3H,m), High-MS m/z 156.1149 (Calcd for $C_9H_{16}O_2$ m/z 156.1149). (2S,5R)-**2**, bp 100-110°C (20 mmHg), $[\alpha]_D^{20}$ -79.1° (c=0.392, n-pentane), δ 1.17 (3H,d,J=6Hz), 1.35-2.31 (10H,m), 3.33-3.95 (2H,m), 4.09 (1H,sex,J=6Hz), High-MS m/z 156.1167. (2R,5S)-**2**, bp 100-110°C (20 mmHg), $[\alpha]_D^{20}$ +79.2° (c=0.725, n-pentane), High-MS m/z 156.1161. (2S,5S)-**2**, bp 100-110°C (20 mmHg), $[\alpha]_D^{20}$ +84.2° (c=0.101, n-pentane), High-MS m/z 156.1128. (R)-**18**, bp 110-120°C (30 mmHg), $[\alpha]_D^{25}$ -44.4° (c=0.635, n-pentane), δ 1.33-2.20 (10H,m), 3.41-4.10 (4H,m). High-MS m/z 142.0984 (Calcd for $C_8H_{14}O_2$ m/z 142.0991). (S)-**18**, bp 110-120°C (30 mmHg), $[\alpha]_D^{25}$ +43.9° (c=0.760, n-pentane), High-MS m/z 142.0990.
7. The crude product (94.1% recovered) was found to contain 91.3% of **8** calculated by a HPLC analysis.
8. G. Solladié, C. Greck, G. Demailly, and A. Solladié-Cavallo, Tetrahedron Lett., **23**, 5047 (1982).
9. Although Solladie et al. posturated a dipolar intermediate for DIBAL reduction of α-sulfinyl ketones,[10] the same arguement would be hardly applicable to the present DIBAL reduction of **13**. A similar transition state to **13B** was assumed by D.A. Evans and K.T. Chapman [Tetrahedron Lett., **27**, 5939 (1986)]. Non-selectivity in the case of LAH reduction supports a large contribution of **13B** toward the DIBAL reduction.
10. cf. S. Masamune and W. Choy, Aldrichimica Acta, **15**, 47 (1982).
11. Synthesis of (±)1 are found in several literatures. For example, S.V. Ley, B. Lygo, H.M. Organ, and A. Wonnacott, Tetrahedron, **41**, 3825 (1985).

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