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SYNTHESIS OF THE ENANTIOMERS OF 1,7-DIOXASPIRO[5.5]UNDECANE, 4-HYDROXY-1,7-DIOXASPIRO[5.5]UNDECANE AND 3-HYDROXY-1,7-DIOXASPIRO[5.5]UNDECANE, THE COMPONENTS OF THE OLIVE FRUIT FLY PHEROMONE†

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Abstract--All of the enantiomers of the title compounds, the components of the pheromone of the olive fruit fly (Dacus oleae Gmelin), were synthesized from (S)-malic acid.

In 1980 Baker et al. isolated 1,7-dioxaspiro[5.5]undecane **1** as the major component of the sex pheromone of the olive fruit fly, Dacus oleae Gmelin.[1] The minor components of the pheromone were also isolated later by Baker et al. and identified as 4-hydroxy-1,7-dioxaspiro[5.5]undecane **2a** and 3-hydroxy-1,7-dioxaspiro[5.5]undecane **3a**.[2] Although several syntheses of (±)-**1**,[2,3] (±)-**2a**,[2,4,5] and (±)-**3a**[2] were recorded, the enantiomers of **1** were synthesized by only three groups[6~8] due to

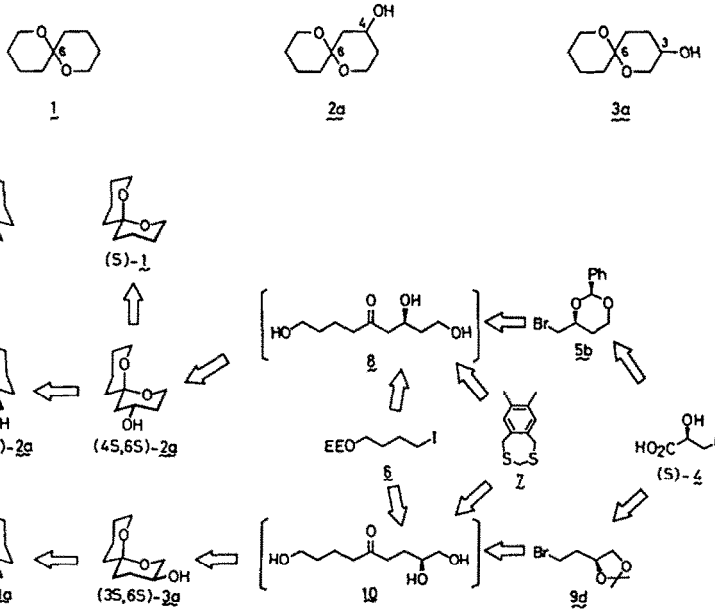

Fig.1. Synthetic plan.

†Pheromone Synthesis--79. Part 78, K. Mori, H. Soga and M. Ikunaka, Liebigs Ann. Chem. in the press. This work was presented by K. M. as a part of his lecture at the International Symposium on Recent Advances in the Chemistry of Insect Control, Cambridge, U. K. (September, 1984). The chemical experimental part of this work was taken from the M. Sc. thesis of H. W. (March, 1985). The X-ray crystallographic work was done by K. Y. and M. M.

the difficulty encountered in controlling the stereochemistry at the spirocenter. Our previous synthesis of **1** started from (S)-malic acid **4** and yielded only small amounts of enantiomers of **1**.[6] Herein we describe another synthesis of (R)- and (S)-**1**, one that enabled us to prepare the pheromone enantiomers in amounts sufficient for field tests. We also record here the synthesis of the enantiomers of **2a** and **3a**. The outline of the present work appeared elsewhere as preliminary communications.[6a,9]

Our synthetic plan as shown in Fig. 1 was to synthesize all of the pheromone enantiomers starting from a single chiral source, (S)-malic acid **4**. We envisaged the use of the OH group of **4** as the substituent on a tetrahydropyranyl ring of **2a** or **3a**. The OH group will adopt the thermodynamically more stable eq position and hence, in combination with the oxygen anomeric effect[10] due to the two O atoms of the spiroacetal, will fix the absolute configuration of the spiro C atom. Conversion of (4S,6S)-**2a** or (3S,6S)-**3a** to their respective antipodes has been shown to be feasible in our previous work.[6b] Removal of the OH group of **2a** is also possible to give **1**. The immediate precursor of (4S,6S)-**2a** must be a keto triol **8**, which can be constructed by connecting **5b** and **6** with **7**, an acyl carbanion equivalent.[11] Similarly for the synthesis of (3S,6S)-**3a**, the key intermediate **10** can be prepared by combining **6**, **7** and **9d**. Both **5b** and **9d** are derivable from (S)-malic acid **4**. The realization of the above plan will be detailed below.

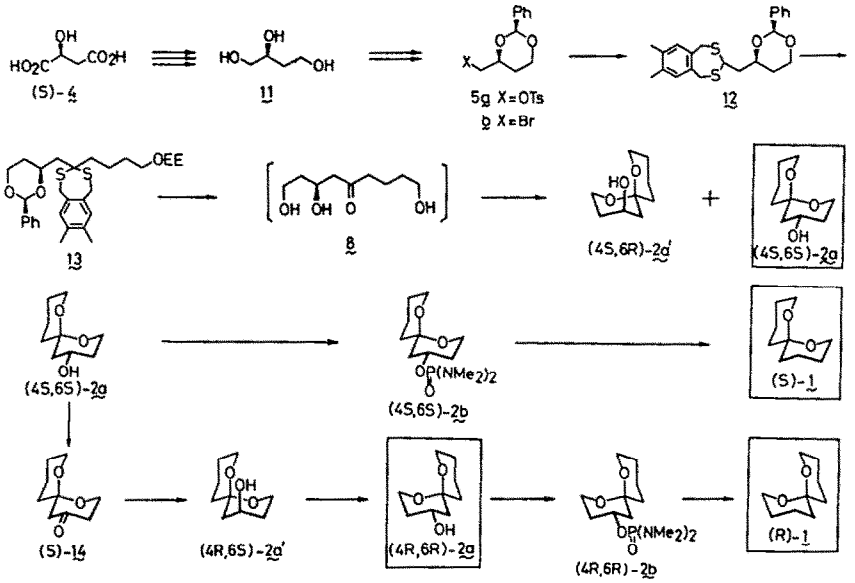

Fig.2. Synthesis of the enantiomers of 1 and 2a.

The synthesis of the enantiomers of **1** and **2a** is shown in Fig. 2. (S)-Malic acid **4** was converted to a triol **11** by an established procedure.[12] A crystalline tosylate **5a**, m.p. 64~64.5°, was prepared from **11** according to Seebach *et al.*[13] This was treated with LiBr in DMF in the presence of $NaHCO_3$ to give **5b** in 97 % yield. Alkylation of 7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin **7**[11] with **5b** employing n-BuLi as a base yielded **12** in 83 % yield as a crystalline solid, m.p. 146~147°. Further alkylation of **12** with tetramethylene iodohydrin 1-ethoxyethyl (EE) ether **6** gave **13** in 83 % yield. Treatment of **13** with $CuCl_2 \cdot 2H_2O$ and CuO in Me_2CO-H_2O (10:1) gave a mixture of (4S,6S)-**2a** and (4S,6R)-**2a'** in a ratio of ca. 11:1. As expected, (4S,6S)-**2a** with an eq OH group was the predominant isomer. By changing the water content of the solvent for this deprotection-acetalization reaction from 1 % as in original Mukaiyama procedure[14] to the present ratio, we were able to avoid the partial racemization that results from a retro-Michael-Michael process. Presumably the larger amount of water made the hydrolytic removal of the EE group more facile than the removal of the other protective groups. The liberated prim OH group would mask the CO group by forming a hemiacetal immediately after the removal of the dithioacetal group, and this would prevent the retro-Michael-Michael racemization. Complete separation of the spiroacetal mixture

was effected by SiO_2 chromatography to give (4S,6S)-**2a** (79.3 % yield), $[\alpha]_D^{20}$ +120° (n-pentane), and (4S,6R)-**2a'** (7.1 % yield), $[\alpha]_D^{20}$ -120° (n-pentane). The spectral properties of (4S,6S)-**2a** were in good accord with those reported previously for (±)-**2a**.[2,4,5] The optical purity of (4S,6S)-**2a** was proved to be 100 % by the HPLC analysis of the corresponding (S)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester).[15]

Deoxygenation of (4S,6S)-**2a** to (S)-**1** was possible by the reduction of its N,N,N',N'-tetramethylphosphorodiamidate **2b** with Li/$EtNH_2$ according to the method of Ireland et al.[16] Thus, phosphorylation of (4S,6S)-**2a** with n-BuLi and $(Me_2N)_2POCl$ in DME-TMEDA gave (4S,6S)-**2b** in 88 % yield. This product was reduced with Li in $EtNH_2$-t-BuOH-THF to give (S)-**1** (392 mg, 64 % yield), $[\alpha]_D^{21}$ +119° (n-pentane). The spectral properties of (S)-**1** coincided with those reported in the literature.[2,3,6b,7] The optical purity of our (S)-**1** was kindly estimated by Prof. V. Schurig employing his complexation GLC technique[17] and shown to be 92 %.

Conversion of (4S,6S)-**2a** to its antipode was executed as follows. Oxidation of (4S,6S)-**2a** with pyridinium chlorochromate (PCC) and NaOAc in CH_2Cl_2[18] gave **14**, m.p. 69~70°, in 82 % yield. This was reduced with LiB(sec-Bu)$_3$H in THF to give (4R,6S)-**2a'**, $[\alpha]_D^{20}$ +121° (n-pentane), in 71 % yield. The reduction was highly stereoselective, furnishing only (4R,6S)-**2a'** with an ax OH group, since the hydride reagent attacked the CO group only from the less hindered α-side. The presence of the ax OH group in (4R,6S)-**2a'** rendered the molecule thermodynamically unstable. Indeed, equilibration between (4R,6S)-**2a'** and the more stable (4R,6R)-**2a** was brought about by treating (4R,6S)-**2a'** with a trace amount of p-TsOH in MeOH. After the equilibration, the desired (4R,6R)-**2a**, $[\alpha]_D^{20}$ -116° (n-pentane), was obtained in 88 % yield in addition to 7.3 % of the recovered (4R,6S)-**2a'**. The spectral properties of (4R,6R)-**2a** were in agreement with those of the starting (4S,6S)-**2a**. The optical purity of (4R,6R)-**2a** was estimated to be 99.6 % by the HPLC analysis of the corresponding (S)-MTPA ester. Quite independently at the same time Redlich and Francke synthesized (4R,6R)-**2a** from D-glucose.[7] Reductive removal of the OH group of (4R,6R)-**2a** was again carried out via (4R,6R)-**2b** by Ireland's method[16] to give (R)-**1** [401 mg, 61.5 % yield from (4R,6R)-**2a**], $[\alpha]_D^{21}$ -121° (n-pentane). Its optical purity as determined by Prof. Schurig was > 99.5 %.

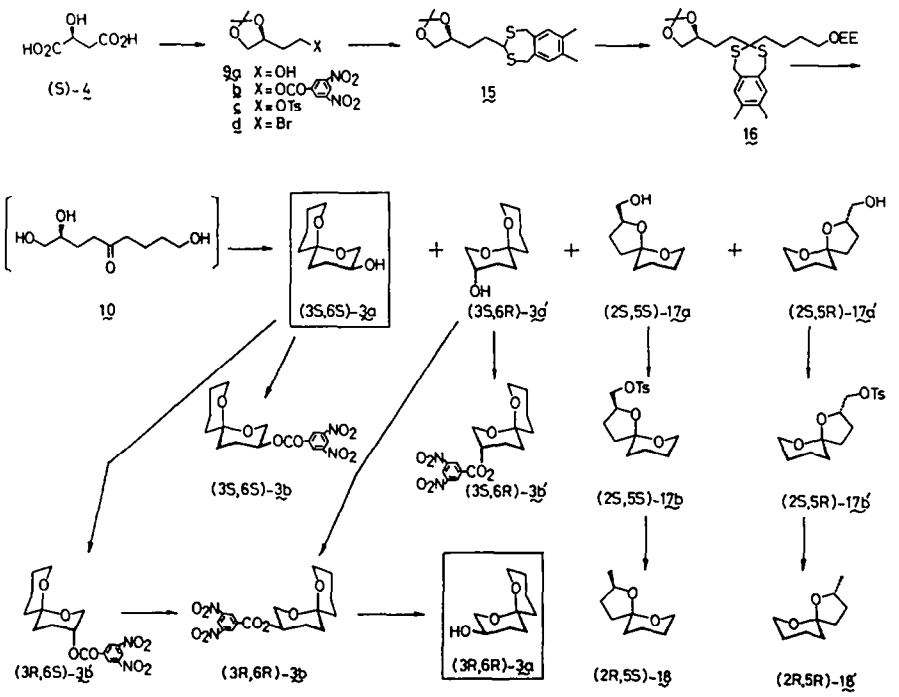

Fig.3. Synthesis of the enantiomers of 3a.

We then turned our attention to the synthesis of both the enantiomers of **3a** (Fig. 3). This synthesis proved to be more difficult than that of the enantiomers of **2a**. (S)-Malic acid **4** was converted to pure **9a** via its crystalline derivative **9b** as described by Meyers et al.[19] The corresponding tosylate **9c** was treated with LiBr in DMF in the presence of $NaHCO_3$ to give a bromide **9d**. Alkylation of **7** with **9d** employing n-BuLi as a base furnished a crystalline product **15**, m.p. 108.5~109° , in 88 % yield. Further alkylation of a carbanion derived from **15** with tetramethylene iodohydrin EE ether **6** gave **16** in 83 % yield.

Treatment of **16** with $CuCl_2 \cdot 2H_2O$ and CuO in Me_2CO-H_2O (99:1) under reflux[14] yielded a complex mixture of products. Removal of the protective groups of **16** generated a keto triol **10**, which cyclized to give all of the four possible isomers. Fortunately, separation of the mixture into four pure components was possible by medium pressure LC employing a Merck Lobar column. The isomers were eluted in the following order: (2S,5R)-**17a'** (9 % yield), $[\alpha]_D^{22}$ -80.8° (ether); (2S,5S)-**17a** (15 %), $[\alpha]_D^{22}$ +91.3° (ether); (3S,6R)-**3a'** (18 %), $[\alpha]_D^{21.5}$ -129° (ether); and the desired product (3S,6S)-**3a** as crystals (33 %), m.p. 98.5~99°, $[\alpha]_D^{22.5}$ +115° (ether). The structures of these isomers were assigned on the basis of the NMR spectral comparison with the published NMR data of (±)-**3a** and (±)-**3a'** by Baker et al.[2] and those of a mixture of (±)-**17a** and (±)-**17a'** by Ireland et al.[20] In particular our data from the lanthanide shift experiments on (3S,6S)-**3a** and (3S,6R)-**3a'** were in complete accord with Baker's data.[2] The two isomers, **17a** and **17a'**, of 2-hydroxymethyl-1,6-dioxaspiro[4.5]decane were converted to the corresponding tosylates **17b** and **17b'**, whose LAH reduction gave (2R,5S)-**18** and (2R,5R)-**18'**, respectively. The spiroacetals **18** and **18'** with unknown absolute stereochemistries were reported to be pheromone components of Paravespula vulgaris L,[21] and their detailed NMR studies were carried out by Francke et al.[21,22] The IR, ^{1}H-NMR, ^{13}C-NMR and MS data of (2R,5S)-**18** and those of (2R,5R)-**18'** were in agreement with those reported for (±)-**18** and (±)-**18'** by Francke et al.[21,22] The structure assignments of the four isomeric products were thus completed.

The formation of (3S,6R)-**3a'** with an ax OH group in a considerable proportion to (3S,6S)-**3a** with an eq OH group deserves comment. In the case of the cyclization of **8** to a mixture of **2a** and **2a'**, the ax OH group of **2a'** interacts with an ax H atom and an ax O atom. This destabilizes the isomer **2a'** severely and results in a ratio for **2a** to **2a'** of 92:8. However, in the case of the formation of **3a'**, its ax OH group possesses only one 1,3-diaxial interaction with an axial H atom. This must make **3a'** only slightly less stable than **3a**, as indicated by the ratio for **3a** to **3a'** of 65:35. The optical purity of (3S,6S)-**3a** was 100 % as checked by the HPLC analysis of its (S)-MTPA ester.

The remaining task was the synthesis of (3R,6R)-**3a**. Since we already possessed (3S,6R)-**3a'**, a Walden inversion was executed at the C-3 position employing the Mitsunobu reaction.[23] (3S,6R)-**3a'** was thus treated with 3,5-dinitrobenzoic acid, Ph_3P and $EtO_2CN{=}NCO_2Et$ in THF to afford (3R,6R)-**3b**, m.p. 155~156°, in 78 % yield. This product was hydrolyzed with KOH to give (3R,6R)-**3a**, m.p. 98.5~99°, $[\alpha]_D^{22}$ -112° (ether), in 99 % yield. Its spectral properties were identical with those of (3S,6S)-**3a**. The optical purity of (3R,6R)-**3a** was proved to be 100 % by the HPLC analysis of the corresponding (S)-MTPA ester.

Finally transformation of (3S,6S)-**3a** to (3R,6R)-**3a** was also investigated. A strategy similar to that employed for the conversion of (4S,6S)-**2a** to (4R,6R)-**2a** could not be adopted for the present case. First of all, low stereoselectivity was anticipated in the course of the hydride reduction of (S)-1,7-dioxaspiro[5.5]undecan-3-one. The reduction would yield a mixture of (3R,6S)-**3a'** and (3S,6S)-**3a**, because the approach of the hydride reagent [LiB(sec-Bu)$_3$H] to the CO group would be possible from both the α- and β-sides. Secondly, even after securing pure (3R,6S)-**3a'**, its acid-catalyzed equilibration would give a mixture of four isomers, (3R,6R)-**3a**, (3R,6S)-**3a'**, (2R,5R)-**17a** and (2R,5S)-**17a'**. Therefore the OH group at C-3 must be protected prior to the equilibration to avoid the formation of the undesired **17a** and **17a'**. A reaction that was particularly appropriate for our purpose was the Mitsunobu reaction[23] by which we could achieve both the inversion of configuration at C-3 and the protection of the OH group as an ester.

Treatment of (3S,6S)-**3a** with 3,5-dinitrobenzoic acid, Ph_3P and $EtO_2CN{=}NCO_2Et$ in THF furnished a crystalline ester (3R,6S)-**3b'**, m.p. 173~173.5°, in 87 % yield. This was dissolved in CH_2Cl_2 and treated with $Zn(OTf)_2$ to effect equilibration, and the resulting mixture was separated by prep TLC to give (3R,6S)-**3b'** (70 % yield) and (3R,6R)-**3b** (29 %). The latter was identical in every respect with that prepared previously by the Mitsunobu inversion of (3S,6R)-**3a'**. To confirm our results of the Mitsunobu reaction, the alcohols (3S,6S)-**3a** and (3S,6R)-**3a'** were esterified as usual with 3,5-dinitrobenzoic acid, DCC and DMAP to give the esters (3S,6S)-**3b** and (3S,6R)-**3b'**, respectively. The m.p., IR and NMR spectra of (3S,6S)-(+)-**3b** were identical with those of (3R,6R)-(-)-**3b**. Similarly (3S,6R)-(-)-**3b'** showed the m.p., IR and NMR spectra identical with those of (3R,6S)-(+)-**3b'**.

A remarkable feature of the equilibration between (3R,6S)-**3b'** and (3R,6R)-**3b** was the fact that the (3R,6S)-**3b'** with an ax substituent was the predominant isomer: The ratio of (3R,6S)-**3b'** to (3R,6R)-**3b** was 7:3. Even in different solvents (CCl_4, C_6H_6, ether or MeOH) or with TsOH as a catalyst, (3R,6S)-**3b'** was predominant. What makes the seemingly unstable ax isomer (3R,6S)-**3b'** more stable than the eq isomer (3R,6R)-**3b**? To solve this enigma, we carried out an X-ray crystallographic analysis of (3R,6S)-**3b'**. The structure was determined by MULTAN 11/82 with the final agreement values of R=0.039 and R_w=0.060.[24] The ORTEP computer drawing of (3R,6S)-**3b'** is shown in Fig. 4a. Its crystal structure is also shown in Fig. 4b. The axial C(3)-O(12) bond is clearly observable. However, we were unable to obtain any structural information which might explain the unusual stability of (3R,6S)-**3b'**. The enigma therefore remains unsolved.

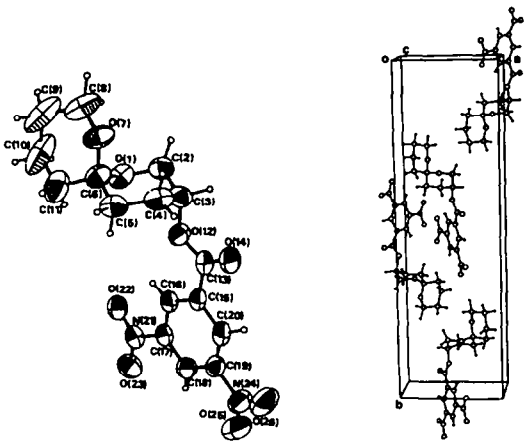

Fig. 4 a.(left) The molecular and b.(right) crystal structure of (3R,6S)-3b'

In summary, we synthesized the enantiomers of the components of the olive fruit fly pheromone (**1**, **2a**, and **3a**) in amounts sufficient for biological study. Bioassay of our samples is now under way by Dr. G. Haniotakis of Greek Atomic Energy Commission. The results so far obtained indicate that male olive fruit flies respond only to (R)-(-)-**1**, while females respond only to (S)-(+)-**1**.[25]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as film for oils and as Nujol mull for solids on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter.

(2S,4S)-(+)-4-Bromomethyl-2-phenyl-1,3-dioxane **5b**. To a soln of **5a** [m.p. 64~64.5°, $[\alpha]_D^{21}$ -2.3° (c=1.06, $CHCl_3$); 85.0 g, 244 mmol] in dry DMF (900 ml) were added $NaHCO_3$ (205 g, 2.44 mol) and LiBr (212 g, 2.44 mol). The suspension was stirred for 2 h at 90° under Ar. After cooling, the mixture was filtered and the filter cake was washed three times with ether. The combined filtrate and washings were diluted with water (2500 ml) and extracted with ether. The ether soln was washed with water, $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 60.8 g (97 %) of **5b**, b.p. 111~114°/ 0.4 Torr; n_D^{19} 1.5581; $[\alpha]_D^{19}$ +35.3° (c=2.55, $CHCl_3$); ν max 1130 (s), 1020 (s), 750 (s), 700 (s) cm^{-1}; δ (CCl_4) 1.35~1.90 (2H, m), 3.15 (1H, dd, J=7 and 10 Hz), 3.18 (1H, dd, J=5 and 10 Hz), 3.45~4.35 (3H, m), 5.33 (1H, s), 6.80~7.75 (5H, m). (Found: C, 51.37; H, 5.01. Calc for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.10 %).

(+)-3-[(S)-2',4'-[(S)-Benzylidenedioxy]butyl]-7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin **12**. A soln of n-BuLi in n-hexane (1.65 M, 155 ml, 256 mmol) was added dropwise to a stirred and cooled soln of **7** (53.8 g, 256 mmol) at -13~-4° under Ar. The mixture was stirred for 30 min at -13~-10° to complete the carbanion formation. To the carbanion soln was added a

soln of **5b** (59.8 g, 233 mmol) in dry THF (50 ml) with stirring and cooling at -50°. The stirring was continued for 30 min at -50~-30° and for 8 h at -30°. The mixture was then poured into water and extracted with $CHCl_3$. The org soln was separated, washed with $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 120 g of a crude oil. This was dissolved in EtOAc (250 ml). The soln was diluted with n-hexane (500 ml) and left to stand at 0° for 4 h. The separated crystals were collected on a filter to give 74.9 g (83 %) of **12**. A small portion of it was recrystallized with EtOAc-n-hexane (1:2) to give an analytical sample as colorless needles, m.p. 146~147°; $[\alpha]_D^{20}$+69.2°(c=0.64, $CHCl_3$); ν max 1510 (w), 1120 (s), 995 (s), 895 (m), 750 (m), 700 (s) cm^{-1}; δ ($CDCl_3$) 1.10~2.80 (4H, m), 1.18 (6H, s), 3.40~4.70 (8H, m), 5.48 (1H, s), 6.90 (2H, s), 7.10~7.70 (5H, m). (Found: C, 68.08; H, 6.73. Calc for $C_{22}H_{26}O_2S_2$: C, 68.36; H, 6.78 %).

4-(1'-Ethoxyethyl)butyl iodide **6**. conc H_2SO_4 (95 %, 38.0 g, 368 mmol) was added dropwise to a stirred and ice-cooled suspension of NaI (55.1 g, 368 mmol) in dry THF (300 ml) under Ar. After the addition, the mixture was stirred for 1 h at 0°. It was then poured into ice-water and extracted with ether. The ether soln was washed with water, 10 % $Na_2S_2O_3$ soln and water, dried ($MgSO_4$) and concentrated in vacuo to give 55 g of a pale yellow oil. To this were added $EtOCH{=}CH_2$ (300 ml) and p-TsOH (0.5 g) with stirring and ice-cooling. The mixture was stirred for 1 h at 0°, poured into sat $NaHCO_3$ soln and extracted with ether. The ether soln was washed with water and sat $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 54.3 g (54 %) of **6**, b.p. 59~64°/ 0.34 Torr; n_D^{20}1.4787; ν max 1125 (s), 1080 (s), 1055 (s) cm^{-1}; δ (CCl_4) 1.12 (3H, t, J=7 Hz), 1.18 (3H, d, J=6 Hz), 1.20~2.30 (4H, m), 3.14 (2H, t, J=7 Hz), 3.10~3.80 (4H, m), 4.54 (1H, q, J=6 Hz). (Found: C, 35.40; H, 6.38. Calc for $C_8H_{17}O_2I$: C, 35.31; H, 6.30 %).

3-[(S)-2',4'-[(S)-Benzylidenedioxy]butyl]-3-[4"-(1"-ethoxyethoxy)butyl]-7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin **13**. A soln of n-BuLi in n-hexane (1.65 M, 38.0 ml, 62.7 mmol) was added dropwise to a stirred and cooled soln of **12** (20.0 g, 51.8 mmol) in dry THF (200 ml) at -15~-10° under Ar. After the addition, the inner temp was lowered to -30° over 5 min. To the stirred and cooled soln of the carbanion, a soln of **6** (18.6 g, 68.4 mmol) in dry THF (20 ml) was added dropwise at -30~-20°. The stirring was continued for 3 h at -30°. The mixture was then poured into water and extracted with EtOAc. The org soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 20.3 g (74 %) of **13**. Since 2.1 g (10.5 %) of crystalline **12** was recovered, the yield of **13** based on the consumed **12** was 83 %. The oily **13** was used in the next step without further purification and showed the following physical properties: ν max 1505 (m), 1130 (s), 1095 (s), 750 (m), 695 (m) cm^{-1}; δ (CCl_4) 1.12 (3H, t, J=7 Hz), 1.17 (3H, d, J=6 Hz), 1.00~2.70 (8H, m), 2.63 (6H, s), 3.00~4.40 (11H, m), 4.52 (1H, q, J=6 Hz), 5.40 (1H, s), 6.77 (2H, s), 7.10~7.60 (5H, m).

(4S,6S)-(+)-4-Hydroxy-1,7-dioxaspiro[5.5]undecane **2a** and its (4S,6R)-(-)-isomer **2a'**. To a soln of **13** (20.0 g, 37.7 mmol) in acetone (400 ml) and water (40 ml) were added $CuCl_2 \cdot 2H_2O$ (12.9 g, 75.7 mmol) and CuO(12.1 g, 152 mmol). The suspension was stirred and heated under reflux for 40 min under Ar. It was then filtered through Celite while it was still hot. The Celite layer was washed with hot acetone. The combined filtrate and washings were concentrated in vacuo. The residual oil was chromatographed over SiO_2 (Merck Kieselgel 60, 500 g). Gradient elution with n-hexane-EtOAc (10:1→2:1) gave 7.9 g of a mixture of **2a** and **2a'**. This was shown to be separable upon rechromatography over SiO_2 (Merck Kieselgel 60, 250 g). Gradient elution with n-hexane-EtOAc (10:1→1:1) yielded (4S,6S)-**2a** and (4S,6R)-**2a'**. Further purification of the product by distillation gave 5.15 g (79.3 %) of (4S,6S)-**2a**, b.p. 82~84°/0.35 Torr; n_D^{20}1.4830; $[\alpha]_D^{20}$+120° (c=2.61, n-pentane); ν max 3400 (m), 2950 (s), 2880 (m), 1450 (m), 1370 (m), 1330 (w), 1300 (w), 1270 (w), 1250 (w), 1235 (m), 1215 (m), 1195 (m), 1180 (m), 1155 (m), 1125 (m), 1110 (m), 1090 (m), 1060 (s), 1045 (s), 980 (s), 950 (w), 930 (m), 905 (m), 870 (m), 850 (w), 795 (m), 745 (w), 660 (w) cm^{-1}; δ (100 MHz, C_6D_6) 1.00~2.10 (9H, m), 2.18 (1H, ddd, J=1.7, 4.7 and 12.5 Hz), 3.46 (1H, br.s), 3.30~3.80 (4H, m), 4.20 (1H, tt, J=5.5 and 11.0 Hz); ^{13}C-NMR (25 MHz, C_6D_6) δ 18.96, 25.51, 35.65, 35.89, 45.86, 58.95, 60.26, 64.19, 97.45; MS: m/z 172 (M^+, 20 %), 155 (8 %), 127 (19 %), 117 (100 %, base peak), 114 (47 %), 101 (94 %), 98 (58 %), 83 (14 %), 55 (29 %); TLC (Merck Kieselgel 60 F-254; Developed with n-hexane-EtOAc=3:2) Rf 0.16; GLC (Column, PEG 20 M, 2 m x 4 mm at 160°+5°/min; Carrier gas, N_2, 1.1 kg/cm^2) Rt 13.0 min. (Found: C, 62.32; H, 9.37. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %). The optical purity of (4S,6S)-**2a** was shown to be 100 % by the HPLC analysis of its (S)-MTPA ester: HPLC (Column, Partisil 5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH=6000:100:1, 1.0 ml/min; Press, 30 kg/cm^2; Detection at 254 nm) Rt 24.7 min (single peak). Distillation of crude (4S,6R)-**2a'** gave 460 mg (7.1 %) of pure (4S,6R)-**2a'**, b.p. 73~78°(bath temp)/1.5 Torr; n_D^{20}1.4729; $[\alpha]_D^{20}$-120°(c=4.26, n-pentane); ν max 3530 (m), 2950 (s), 2880 (m), 1460 (m), 1435 (m), 1415 (m), 1380 (m), 1370 (m), 1350 (m), 1320 (w), 1280 (w,sh), 1250 (m), 1200 (s), 1175 (m), 1155 (m), 1135 (s), 1100 (s), 1070 (s), 1055 (s), 1045 (s), 1030 (s), 1000 (s), 975 (s), 935 (m), 915 (m), 895 (m), 860 (m), 830 (m), 790 (s), 730 (w), 695 (w) cm^{-1}; δ (100 MHz,C_6D_6) 0.85~1.05 (10H, m), 3.20~4.15 (5H, m), 4.07 (1H, s, OH); ^{13}C-NMR (25 MHz, C_6D_6) δ 18.37, 25.20, 32.68, 35.68, 41.16, 55.17, 60.58, 64.28, 97.20; TLC (Merck Kieselgel 60 F-254; Developed with n-hexane-EtOAc=3:2) Rf 0.33; GLC (Column, PEG 20 M, 2 m x 4 mm at 160°+5°/min; Carrier gas, N_2, 1.1 kg/cm^2) Rt 6.8 min. (Found: C, 62.30; H, 9.34. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %).

(S)-(+)-1,7-Dioxaspiro[5.5]undecan-4-one **14**. To a stirred and ice-cooled soln of (4S,6S)-**2a** (3.2 g, 18.6 mmol) in CH_2Cl_2 (64 ml) were added NaOAc (610 mg, 7.4 mmol) and PCC ($CrO_3 \cdot C_5H_5N \cdot HCl$; 8.0 g, 37.1 mmol). The mixture was stirred for 3.5 h at room temp. Florisil (30 g) was then added to the mixture and the stirring was continued vigorously for 5 min. Ether (120 ml) was added and the mixture was vigorously stirred for 15 min. It was filtered through Florisil (150 g). The filter cake was washed with ether. The combined filtrate and washings were concentrated in vacuo (<20°) to give a pale yellow oil. This was dissolved in n-pentane and left to stand to afford 2.6 g (82 %) of **14** as crystals. Further recrystallization from n-pentane yielded an analytical sample as needles, m.p. 69~70°; $[\alpha]_D^{18}$+140°(c=1.24, MeOH); ν max 1720 (s), 1380 (s), 1320 (s), 1060 (s), 1045 (s), 990 (s) cm^{-1}; δ (CCl_4) 1.00~2.00 (6H, m), 2.10~2.50 (4H, m), 3.40~3.70 (2H, m), 3.86 (2H, dd, J=5 and 8 Hz). (Found: C, 63.61; H, 8.26. Calc for $C_9H_{14}O_3$: C, 63.51; H, 8.29 %).

(4R,6S)-(+)-4-Hydroxy-1,7-dioxaspiro[5.5]undecane **2a'**. A soln of LiB(sec-Bu)$_3$H in THF (Aldrich, 1 M; 17.6 ml, 17.6 mmol) was added dropwise to a stirred and cooled soln of **14** (2.0 g, 11.8 mmol) in dry THF (28 ml) at -78° under Ar. The inner temp was allowed to rise to -20° over 5 h. Then the reaction was quenched at 0° by the dropwise addition of sat $NaHCO_3$ soln (3 ml). After stirring for 1 h at room temp, the mixture was concentrated in vacuo. The residue was put directly onto a column of SiO_2 (Merck Kieselgel 60) and purified by chromatography and distillation to give 1.44 g (71 %) of (4R,6S)-**2a'**, b.p. 95~97°/8 Torr; n_D^{20}1.4727; $[\alpha]_D^{20}$+121° (c=4.44, n-pentane); GLC (Column, PEG 20 M, 2 m x 4 mm at 160°+5°/min; Carrier gas, N_2, 1.1 kg/cm^2) Rt 6.8 min (single peak). Its IR, ^{1}H- and ^{13}C-NMR spectra were identical with those of (4S,6R)-**2a'**. (Found: C, 62.95; H, 9.26. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %).

(4R,6R)-(-)-4-Hydroxy-1,7-dioxaspiro[5.5]undecane **2a.** p-TsOH·$2H_2O$ (ca 1 mg) was added to a soln of (4R,6S)-**2a'** (1.20 g, 6.98 mmol) in MeOH (30 ml). The soln was stirred for 3.5 h at room temp. Subsequently $NaHCO_3$ powder (0.12 g) was added to the stirred soln. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over SiO_2 (Merck Kieselgel 60) to give 88 mg (7.3 %) of the recovered (4R,6S)-**2a'** and 1.12 g of (4R,6R)-**2a.** The latter was distilled to give 1.05 g (88 %) of pure (4R,6R)-**2a,** b.p. 79-81°/0.25 Torr; n_D^{20} 1.4822; $[\alpha]_D^{20}$ -116°(c=2.41, n-pentane); GLC (Column, PEG 20 M, 2 m x 4 mm at 160°+5°/min; Carrier gas, N_2, 1.1 kg/cm^2) Rt 12.8 min (single peak). Its IR, ^1H- and ^{13}C-NMR, and mass spectral data were identical with those of (4S,6S)-**2a.** (Found: C, 62.49; H, 9.24. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %). The optical purity of (4R,6R)-**2a** was shown to be 99.6 % by the HPLC analysis of its (S)-MTPA ester: HPLC (Column, Partisil 5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH=6000:100:1, 1.0 ml/min; Press, 30 kg/cm^2; Detection at 254 nm) Rt 25.4 min (0.21 %), 27.5 min (99.79 %).

(4S,6S)-1,7-Dioxaspiro[5.5]undec-4-yl N,N,N',N'-tetramethylphosphorodiamidate **2b.** A soln of n-BuLi in n-hexane (1.65 M, 5.7 ml, 9.4 mmol) was added dropwise to a stirred and ice-cooled soln of (4S,6S)-**2a** (1.0 g, 5.8 mmol) in dry DME (16 ml) and TMEDA (4 ml) at 0-5° under Ar. The mixture was stirred for 15 min at room temp and ice-cooled. To the stirred mixture was added dropwise $(Me_2N)_2POCl$ (4.3 ml, 5.0 g, 29 mmol) at 0-5°. The stirring was continued for 30 min at room temp. Then the reaction was quenched by the addition of water (20 ml). After stirring for 30 min at room temp, the mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 1.56 g (88 %) of (4S,6S)-**2b,** ν max 1300 (m), 1225 (s), 1195 (m), 1175 (m), 1060 (m), 1040 (s), 1020 (s), 990 (s), 910 (m), 880 (m), 750 (m) cm^{-1}; δ ($CDCl_3$) 0.80-2.40 (10H, m), 2.51 (6H, s), 2.68 (6H, s), 3.10-4.10 (4H, m), 4.20-5.10 (1H, m). This was employed in the next step without further purification.

(4R,6R)-1,7-Dioxaspiro[5.5]undec-4-yl N,N,N',N'-tetramethylphosphorodiamidate **2b.** In the same manner as described above (4R,6R)-**2a** (770 mg) yielded (4R,6R)-**2b** (1.17 g, 85.4 %). Its spectral data were identical with those of (4S,6S)-**2b.**

(S)-(+)-1,7-Dioxaspiro[5.5]undecane **1.** To a stirred and cooled soln of Li (408 mg, 58.8 mg atom, 15 eq) in dry $EtNH_2$ (62 ml) was added dropwise a soln of (4S,6S)-**2b** (1.20 g, 3.92 mmol) in t-BuOH (1.48 ml, 15.7 mmol) and dry THF (3.7 ml) at -78~-55° under Ar. After stirring for 30 min at -78°, the reaction was quenched by the addition of water (5 ml) at -78°, which destroyed the excess Li. The mixture was poured into water and extracted with n-pentane. The pentane soln was washed with water, sat $NaHCO_3$ soln and brine, dried (Na_2SO_4), and concentrated in vacuo at 0°. The residue was filtered through SiO_2 (0.3 g) and K_2CO_3 (0.5 g). The column was washed with a small amount of n-pentane-ether (1:1). The combined filtrate and washings were concentrated and the residue was distilled to give 392 mg (64 %) of (S)-**1,** b.p. 76-80°/30 Torr; n_D^{21} 1.4592; $[\alpha]_D^{21}$ +119°(c=1.41, n-pentane); ν max 2950 (s), 2880 (s), 2740 (w), 1470 (w), 1455 (m), 1440 (m), 1385 (m), 1370 (m), 1350 (w), 1340 (w), 1290 (m), 1280 (m), 1255 (m), 1230 (m), 1205 (m), 1180 (m), 1155 (w), 1110 (m), 1095 (s), 1065 (s), 1040 (s), 990 (s), 930 (m), 910 (m), 875 (s), 820 (w), 795 (m) cm^{-1}; δ (100 MHz, C_6D_6) 1.00-2.30 (12H, m), 3.30-3.85 (4H, m); ^{13}C-NMR (25 MHz, C_6D_6) δ 19.08, 25.85, 36.26, 60.21, 94.91; MS: m/z 156 (M^+, 20 %, $C_9H_{16}O_2$=156), 128 (15 %), 111 (19 %), 101 (99 %), 100 (57 %), 98 (100 %, base peak), 83 (33%), 56 (28 %), 55 (46 %), 43 (23 %); GLC (Column, PEG 20 M, 2 m x 4 mm at 70°+5°/min; Carrier gas, N_2, 1.0 kg/cm^2) Rt 16.0 min (99.0 %). The optical purity of (S)-**1** was 92 % as determined by Prof. Schurig. (Found: C, 69.16; H, 10.43. Calc for $C_9H_{16}O_2$: C, 69.19; H, 10.32 %).

(R)-(-)-1,7-Dioxaspiro[5.5]undecane **1.**
In the same manner as above (4R,6R)-**2b** (1.10 g) gave (R)-**1** (401 mg, 72 %), b.p. 74-83°/33 Torr; n_D^{21} 1.4589; $[\alpha]_D^{21}$ -121° (c=1.84, n-pentane); GLC (Column, PEG 20 M, 2 m x 4 mm at 70°+5°/min; Carrier gas, N_2, 1.0 kg/cm^2) Rt 16.1 min (99.2 %). The optical purity of (R)-1 was >99.5 % as determined by Prof. Schurig. (Found: C, 69.31; H, 10.30. Calc for $C_9H_{16}O_2$: C, 69.19; H, 10.32 %). Its IR, ^1H- and ^{13}C-NMR, and mass spectral data were identical with those of (S)-1.

(S)-3,4-Isopropylidenedioxybutyl tosylate **9c.**
p-TsCl (6.50 g, 34.1 mmol) was added to a stirred and ice-cooled soln of **9a** [n_D^{21} 1.4296; $[\alpha]_D^{21}$ -2.4°(c=3.91, MeOH); 4.15 g, 28.4 mmol] in dry C_5H_5N (20 ml). The mixture was stirred for 1.5 h under ice-cooling. It was then poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 8.35 g (98 %) of **9c,** ν max 1600 (m), 1495 (w), 1360 (s), 1185 (s), 1175 (s), 1055 (s), 950 (s) cm^{-1}; δ ($CDCl_3$) 1.26 (3H, s), 1.30 (3H, s), 1.87 (2H, dt, J=6 and 6 Hz), 2.41 (3H, s), 3.20-3.60 (1H, m), 3.70-4.40 (4H, m), 7.30 (2H, d, J=8 Hz), 7.75 (2H, d, J=8 Hz). This was employed in the next step without further purification.

(S)-(-)-3,4-Isopropylidenedioxybutyl bromide **9d.** To a stirred and ice-cooled soln of **9c** (4.96 g, 16.5 mmol) in dry DMF (60 ml) were added $NaHCO_3$ (13.9 g, 165 mmol) and LiBr (14.4 g, 166 mmol). An exothermic reaction took place. Subsequently the mixture was stirred for 30 min at room temp. It was then poured into water and extracted with ether. the ether soln was washed with water and sat $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated in vacuo in an ice-water bath. The residue was distilled to give 3.12 g (80 %) of **9d,** b.p. 89-90°/19 Torr; n_D^{21} 1.4571; $[\alpha]_D^{21}$ -27.2°(c=1.25, $CHCl_3$); ν max 1370 (s), 1250 (s), 1210 (s), 1150 (m), 1060 (s), 840 (m) cm^{-1}; δ (CCl_4) 1.26 (3H, s), 1.31 (3H, s), 2.01 (2H, dt, J=6 and 6 Hz), 3.20-3.60 (2H, m), 3.80-4.30 (2H, m). (Found: C, 40.55; H, 6.19. Calc for $C_7H_{13}O_2Br$: C, 40.21; H, 6.27 %).

(S)-(+)-3-(3',4'-Isopropylidenedioxybutyl)-7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin **15.** A soln of n-BuLi in n-hexane (1.54 M, 8.4 ml, 12.9 mmol) was added dropwise to a stirred and cooled suspension of **7** (2.70 g, 12.9 mmol) in dry THF (33 ml) at -20~-15° under Ar. The mixture was stirred for 45 min at -20° to complete the carbanion formation. To the stirred and cooled red soln of the carbanion was added dropwise a soln of **9d** (2.90 g, 12.2 mmol) in dry THF (3 ml) at -40°. The mixture was stirred for 2 h at -40~-30°. It was then poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from n-hexane-ether (1:1) to give 3.64 g (88 %) of **15,** m.p. 108.5~109°; $[\alpha]_D^{23}$ +1.6°(c=2.76, $CHCl_3$); ν max 1500 (w), 1155 (m), 1070 (s), 1045 (m), 855 (m), 790 (w) cm^{-1}; δ (CCl_4) 1.21 (3H, s), 1.28 (3H, s), 1.40-2.00 (4H, m), 2.16 (6H, s), 3.10-3.50 (1H, m), 3.60-4.30 (3H, m), 3.76 (4H, s), 6.79 (2H, s). (Found: C, 64.00; H, 7.75. Calc for $C_{18}H_{26}O_2S_2$: C, 63.87; H, 7.74 %).

(3'S)-3-[4'''-(1''-Ethoxyethoxy)butyl]-3-(3',4'-isopropylidenedioxybutyl)-7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin **16.** A soln of n-BuLi in n-hexane (1.54 M, 7.4 ml, 11.4 mmol) was added dropwise to a stirred and cooled soln of **15** (3.50 g, 10.3

mmol) in dry THF (40 ml) at -25~-20° under Ar. The resulting red soln was gradually cooled over 4 min to -30°. A soln of **6** (3.40 g, 12.5 mmol) in dry THF (4 ml) was added dropwise to the stirred and cooled soln at -30~-20°. The mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 4.12 g (83 %) of **16** as an oil, ν max 1500 (w), 1130 (s), 1055 (s) cm^{-1}; δ (CCl_4) 1.11 (3H, t, J=7 Hz), 1.19 (3H, d, J=5 Hz), 1.23 (3H, s), 1.30 (3H, s), 1.20~2.00 (10H, m), 2.14 (6H, s), 3.00~4.20 (11H, m), 4.52 (1H, q, J=5 Hz), 6.69 (2H, s). This was employed in the next step without further purification.

(3S,6S)-(+)-3-Hydroxy-1,7-dioxaspiro[5.5]undecane **3a**, its (3S,6R)-(-)-isomer **3a'**, (2S,5S)-(+)-2-hydroxymethyl-1,6-dioxaspiro[4.5]decane **17a** and (2S,5R)-(-)-**17a'**. To a soln of **16** (2.46 g, 5.09 mmol) in Me_2CO-H_2O (99:1; 60 ml) were added $CuCl_2 \cdot 2H_2O$ (1.73 g, 10.1 mmol) and CuO (1.62 g, 20.4 mmol). The mixture was stirred and heated under reflux for 30 min, and filtered through Celite while it was hot. The Celite layer was washed three times with hot Me_2CO. To the combined filtrate and washings was added SiO_2 (30 g), and the mixture was concentrated in vacuo. The residue was placed on the top of an SiO_2 column (Merck Kieselgel 60, 100 g). Elution with n-hexane-EtOAc (1:1) yielded 1.03 g of an acetal mixture. This was chromatographed repeatedly (seventeen times!) on a Merck Lobar® column (Grösse B). Elution with $CHCl_3$-MeOH (30:1) gave the following products. The least polar one was (2S,5R)-**17a'** (81 mg, 9 %), b.p. 65~70°(bath temp)/0.1 Torr; n_D^{22} 1.4708; $[\alpha]_D^{22}$-80.8°(c=1.63, ether); ν max 3450 (s), 1075 (s), 1035 (s), 1010 (s), 990 (s) cm^{-1}; δ(100 MHz, C_6D_6) 1.00~2.20 (10H, m), 3.00 (1H, br.s), 3.20~4.00 (4H, m), 4.18 (1H, m); ^{13}C-NMR (25 MHz, C_6D_6) δ 20.64, 25.39, 25.54, 34.33, 38.67, 61.92, 66.16, 81.83, 105.95; MS: m/z 172 (M^+, 4 %), 141 (100 %, base peak), 117 (28 %), 99 (31 %), 85 (48 %). (Found: m/z 172.1116. Calc for $C_9H_{16}O_3$: 172.1099). Secondly, (2S,5S)-**17a** (129 mg, 15 %) was eluted, b.p. 65~70°(bath temp)/0.28 Torr; n_D^{22} 1.4710; $[\alpha]_D^{22}$+91.3°(c=1.67, ether); ν max 3450 (s), 1220 (m), 1140 (m), 1080 (s), 1040 (s), 1020 (s,sh), 985 (m), 965 (m), 940 (m), 870 (m) cm^{-1}; δ (100 MHz, C_6D_6) 1.10~2.20 (10H, m), 3.40~4.10 (5H, m), 4.21 (1H, m); ^{13}C-NMR (25 MHz, C_6D_6) δ 20.62, 25.66, 25.98, 33.82, 37.89, 61.51, 65.04, 79.17, 106.32; MS: m/z 172 (M^+, 4 %), 141 (100 %, base peak), 117 (28 %), 99 (28 %), 85 (43 %). (Found: m/z 172.1126. Calc for $C_9H_{16}O_3$: 172.1099). The third compound was (3S,6R)-**3a'** (158 mg, 18 %), b.p. 72~76°/0.05 Torr; $n_D^{21.5}$ 1.4794; $[\alpha]_D^{21.5}$ -129°(c=0.93, ether); ν max 3450 (s), 1230 (m), 1160 (m), 1100 (s), 1080 (s), 1060 (s), 1050 (m), 985 (s), 960 (m), 935 (m), 870 (m), 800 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.00~2.20 (10H, m), 3.20~3.80 (5H, m); δ [100 MHz, 5 mg of (3S,6R)-**3a'** in 0.30 ml of C_6D_6 + 3 mg of $Eu(fod)_3$-d_{27}] 1.10~1.90 (4H, m), 2.00~2.50 (3H, m), 2.50~3.10 (2H, m), 3.30 (1H, dt, J=6 and 12 Hz), 3.80 (1H, dm, J=11 Hz), 4.00 (1H, dt, J=3 and 11 Hz), 4.48 (1H, dd, J=2 and 12 Hz), 5.20 (1H, dm, J=12 Hz), 5.73 (1H, br.m) [lit.[2] δ 3.7 (m), 3.9 (m), 4.2 (dd, J=2 and 12 Hz), 4.6 (dm, J=12 Hz), 5.0 (m)]; ^{13}C-NMR (25 MHz, C_6D_6) δ 18.91, 25.61, 25.71, 30.24, 35.58, 60.70, 64.50, 64.89, 95.18; MS: m/z 172 (M^+, 12 %), 142 (18 %), 117 (24 %), 98 (100 %, base peak). (Found: m/z 172.1081. Calc for $C_9H_{16}O_3$: 172.1099). The most polar compound was (3S,6S)-**3a** (289 mg, 33 %). It was recrystallized from n-hexane to give prisms, m.p. 98.5~99.0°; $[\alpha]_D^{22.5}$ +115°(c=0.92, ether); ν max 3470 (s), 1220 (m), 1160 (m), 1080 (s), 1050 (s), 1015 (s), 1005 (s), 970 (m), 880 (s), 865 (m), 785 (m) cm^{-1}; δ(100 MHz, C_6D_6) 0.97 (1H, br.s), 1.00~2.10 (10H, m), 3.20~3.90 (5H, m); δ [100 MHz, 5 mg of (3S,6S)-**3a** in 0.30 ml of C_6D_6 + 4.2 mg of $Eu(fod)_3$-d_{27}] 1.10~2.70 (8H, m), 2.98 (1H, m), 3.50 (1H, ddt, J=4, 10 and 12 Hz), 3.80~4.20 (2H, m), 4.90~5.40 (2H, m), 5.66 (1H, br. m) [lit.[2] δ 3.9 (m), 5.2 (m), 5.6 (br.m)]; ^{13}C-NMR (25 MHz, C_6D_6) δ 19.15, 25.56, 28.61, 35.04, 35.29, 60.38, 64.99, 66.35, 94.38; MS: m/z 172 (M^+, 6 %), 142 (17 %), 117 (24 %), 98 (100 %, base peak). (Found: C, 62.63; H, 9.26. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %). The optical purity of (3S,6S)-**3a** was shown to be 100 % by the HPLC analysis of its (S)-MTPA ester: HPLC (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detector, 217 nm) Rt 33.3 min (single peak).

(3R,6R)-(-)-1,7-Dioxaspiro[5.5]undec-3-yl 3,5-dinitrobenzoate **3b**. To a stirred soln of (3S,6R)-**3a'** (124 mg, 0.721 mmol) in dry THF (3 ml) were added Ph_3P (378 mg, 1.44 mmol), 3,5-dinitrobenzoic acid (305 mg, 1.44 mmol) and $EtO_2CN{=}NCO_2Et$ (251 mg, 1.44 mmol). The mixture was stirred overnight at room temp. Direct separation of the reaction mixture with prep TLC (Merck Kieselgel 60 F-254, Art 5717) was followed by the recrystallization of the product from n-hexane-ether (2:1) to give 206 mg (78 %) of (3R,6R)-**3b**, m.p. 155~156°; $[\alpha]_D^{22}$-69.9°(c=1.60, $CHCl_3$); ν max 3110 (w), 1715 (s), 1630 (w), 1545 (s), 1340 (s), 1280 (m), 1170 (m), 1065 (m), 1010 (m), 715 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.20~2.30 (10H, m), 3.40~3.90 (4H, m), 5.15 (1H, m), 8.90~9.30 (3H, m). (Found: C, 52.03; H, 4.83; N, 7.59. Calc for $C_{16}H_{18}O_8N_2$: C, 52.46; H, 4.95; N, 7.65 %).

(3R,6R)-(-)-3-Hydroxy-1,7-dioxaspiro[5.5]undecane **3a**. To a stirred soln of (3R,6R)-**3b** (205 mg, 0.56 mmol) in THF-MeOH (4:1, 2.5 ml) was added dropwise 2 N KOH soln (0.5 ml, 1 mmol). The mixture was stirred for 30 min at room temp. The product was isolated from the reaction mixture by prep TLC (Merck Kieselgel 60 F-254). Recrystallization of the product from n-hexane gave 95.7 mg (99 %) of (3R,6R)-**3a**, m.p. 98.5~99.8°; $[\alpha]_D^{22}$-112°(c=0.92, ether). (Found: C, 62.86; H, 9.16. Calc for $C_9H_{16}O_3$: C, 62.76; H, 9.36 %). The IR, ^{1}H- and ^{13}C-NMR, and mass spectral data of (3R,6R)-**3a** were identical with those of (3S,6S)-**3a**. The optical purity of (3R,6R)-**3a** was shown to be 100 % by the HPLC analysis of its (S)-MTPA ester: HPLC (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detector, 217 nm) Rt 34.8 min (single peak).

(3R,6S)-(+)-1,7-Dioxaspiro[5.5]undec-3-yl 3,5-dinitrobenzoate **3b'**. To a stirred soln of (3S,6S)-**3a** (100 mg, 0.581 mmol) in dry THF were added Ph_3P (305 mg, 1.16 mmol), 3,5-dinitrobenzoic acid (247 mg, 1.17 mmol) and $EtO_2CN{=}NCO_2Et$ (202 mg, 1.16 mmol). The mixture was stirred overnight at room temp. The product was isolated from the reaction mixture by prep TLC (Merck Kieselgel 60 F-254). Recrystallization of the product from n-hexane-ether (4:1) gave 185 mg (87 %) of (3R,6S)-**3b'** as pale yellow needles, m.p. 173~173.5°; $[\alpha]_D^{21.5}$ +71.7°(c=1.10, $CHCl_3$); ν max 3110 (w), 1720 (s), 1630 (w), 1540 (m), 1340 (s), 1290 (m), 1070 (m), 995 (m), 980 (m), 720 (m) cm^{-1}; δ(100 MHz, $CDCl_3$) 1.20~2.50 (10H, m), 3.40~4.00 (4H, m), 5.17 (1H, m), 9.10~9.30 (3H, m). (Found: C, 52.88; H, 4.95; N, 7.64. Calc for $C_{16}H_{18}O_8N_2$: C, 52.46; H, 4.95; N, 7.65 %).

Equilibration of (3R,6S)-**3b'** to give (3R,6R)-**3b**. $Zn(OTf)_2$ (50 mg) was added to a soln of (3R,6S)-**3b'** (161 mg, 0.439 mmol) in dry CH_2Cl_2 (3 ml). The soln was stirred for 30 min at room temp. The dinitrobenzoates were isolated from the reaction mixture by prep TLC (Merck Kieselgel 60 F-254) to give (3R,6R)-**3b** (49 mg, 30 %) and (3R,6S)-**3b'** (112 mg, 70 %). The crude (3R,6R)-**3b** was recrystallized from n-hexane-ether (2:1) to give 46 mg (29 %) of pure (3R,6R)-**3b** as pale yellow needles, m.p. 155~156°; $[\alpha]_D^{21}$ -69.1° (c=1.02, $CHCl_3$). Its IR and NMR data were identical with those of (3R,6R)-**3b** prepared from (3S,6R)-**3a'** by the Mitsunobu reaction.

Preparation of (3S,6S)-**3b** from (3S,6S)-**3a**. To a soln of (3S,6S)-**3a** (10 mg, 0.06 mmol) in dry CH_2Cl_2 (0.5 ml) were added 3,5-dinitrobenzoic acid (18 mg), DCC (15 mg) and DMAP (trace amount). The mixture was stirred for 8 h at room temp. The product was isolated from the reaction mixture by prep TLC (Mereck Kieselgel 60 F-254). Recrystallization of the crude

product from n-hexane-ether (2:1) gave 17 mg (80 %) of (3S,6S)-**3b** as pale yellow needles, m.p. 154-155°; $[\alpha]_D^{22}$+69.5° (c=0.80, $CHCl_3$). Its IR and NMR data were identical with those described for (3R,6R)-**3b**. (Found: C, 52.68; H, 4.98; N, 7.48. Calc for $C_{16}H_{18}O_8N_2$: C, 52.46; H, 4.95; N, 7.65 %).

Preparation of (3S,6R)-**3b'** from (3S,6R)-**3a'**. In the same manner as described above, (3S,6R)-**3a'** (8 mg, 0.05 mmol) yielded 14 mg (82 %) of (3S,6R)-**3b'** as pale yellow needles from n-hexane-ether (4:1), m.p. 173-173.5°; $[\alpha]_D^{22.5}$ -68.8°(c=0.63, $CHCl_3$). Its IR and NMR data were identical with those described for (3R,6S)-**3b'**. (Found: C, 52.38; H, 4.98; N, 7.59. Calc for $C_{16}H_{18}O_8N_2$: C, 52.46; H, 4.95; N, 7.65 %).

(2R,5R)-(-)-2-Methyl-1,6-dioxaspiro[4.5]decane **18'**. p-TsCl (90 mg, 0.47 mmol) was added to a stirred and ice-cooled soln of (2S,5R)-**17a'** (52 mg, 0.23 mmol) in dry C_5H_5N (1 ml). The mixture was stirred for 2 h at 0-5°. It was then poured into ice-water, and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 100 mg (quantitative) of crude (2S,5R)-**17b'**, ν max 1595 (m), 1360 (s), 1175 (s), 975 (s), 955 (s) cm^{-1}. This was dissolved in dry ether (1 ml). To this was added under ice-cooling LAH (12 mg, 0.32 mmol). The mixture was stirred for 24 h at room temp. It was then cooled to 0° and the excess LAH was destroyed by the addition of water (12 μl), 15 % NaOH (12 μl) and water (36 μl). The mixture was stirred for 1 h at room temp. It was then filtered through Celite. The filter cake was washed three times with ether. The combined filtrate and washings were concentrated in vacuo at 0-5°. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 19.7 mg (42 %) of (2R,5R)-**18'**, n_D^{22}1.4451; $[\alpha]_D^{22}$-86°(c=0.32, n-pentane); ν max 2950 (s), 2880 (s), 1440 (m), 1360 (s), 1310 (w), 1260 (m), 1220 (s), 1150 (m), 1110 (m), 1060 (s), 1040 (s), 1030 (s,sh), 980 (s), 940 (m), 920 (m), 870 (s), 800 (m), 750 (w) cm^{-1}; δ (100 MHz, C_6D_6) 1.30 (3H, d, J=6 Hz), 1.00-2.20 (10H, m), 3.59 (1H, dm, J=11 Hz), 4.04 (1H, dt, J=4 and 11 Hz), 4.10 (1H, m); ^{13}C-NMR (25 MHz, C_6D_6) δ 20.79, 23.42, 25.93, 32.21, 34.60, 39.70, 61.21, 76.66, 105.56; MS: m/z 156 (M^+, 11 %), 141 (4 %), 128 (6 %), 112 (11 %), 111 (7 %), 101 (100 %, base peak), 100 (34 %), 98 (28 %), 85 (4 %), 83 (13 %). (Found: m/z 156.1178. Calc for $C_9H_{16}O_2$: 156.1149).

(2R,5S)-(+)-2-Methyl-1,6-dioxaspiro[4.5]decane **18**. In the same manner as described above, (2S,5S)-**17a** (91 mg) gave (2S,5S)-**17b** (178 mg, quantitative), ν max 1595 (m), 1360 (s), 1175 (s), 980 (s), 950 (s), 805 (m) cm^{-1}. This was reduced with LAH to give 10.5 mg (13 %) of (2R,5S)-**18**, n_D^{22}1.4458; $[\alpha]_D^{22}$+82°(c=0.31, n-pentane); ν max 2950 (s), 2880 (s), 1440 (m), 1375 (m), 1360 (m), 1305 (w), 1260 (m), 1210 (m), 1150 (m), 1070 (s), 1040 (s), 990 (s), 940 (m), 920 (m), 870 (s), 810 (m), 750 (w) cm^{-1}; δ (100 MHz, C_6D_6) 1.17 (3H, d, J=6 Hz), 1.00-2.20 (10H, m), 3.60 (1H, dm, J=11 Hz), 3.98 (1H, dt, J=3 and 11 Hz), 4.24 (1H, qm, J=6 Hz); ^{13}C-NMR (25 MHz, C_6D_6) δ 20.71, 21.47, 25.81, 31.90, 34.70, 38.38, 61.41, 74.03, 105.78; MS: m/z 156 (M^+, 8 %), 141 (4 %), 128 (5 %), 112 (10 %), 111 (7 %), 101 (100 %, base peak), 100 (40 %), 98 (24 %), 85 (4 %), 83 (12 %). (Found: m/z 156.1142. Calc for $C_9H_{17}O_2$: 156.1149).

X-ray analysis of (3R,6S)-**3b'**. The crystal was mounted in a glass capillary. Unit-cell dimensions and orientation matrices were obtained by least-squares methods from the setting angles of 25 reflections. Intensities were collected on an Enraf-Nonius CAD 4 diffractometer at room temp. Data were corrected for Lorentz-polarization effects. Absorption corrections were not applied. The crystal data and data collection parameters are summarized in Table 1.

The structure was solved by direct method using MULTAN 11/82.[24] All H atoms were located on a difference Fourier map. Full-matric least-squares refinement included anisotropic thermal parameters for non-H atoms as well as isotropic thermal parameters for H atoms. Convergence was reached at R=0.039 and R_w=0.060.

All calculations were performed on a PDP 11/34 computer using Enraf-Nonius SDP-PLUS programs.

Table 1. Summary of crystal data and data collection parameters

formula	$C_{16}H_{18}O_8N_2$
mol. wt.	366.33
crystal system	orthorhombic
space group	$P2_12_12_1$
crystal dimensions, mm^3	0.4 x 0.4 x 0.3
a, Å	9.778 (1)
b, Å	31.075 (3)
c, Å	5.768 (1)
V, $Å^3$	1752.6
Z	4
d(calcd), g cm^{-3}	1.388
diffractometer	Enraf-Nonius CAD 4
monochrometer	graphite
radiation	Cu Kα (1.5418 Å)
scan type	ω/2θ
$2\theta_{max}$, deg	130
no. of unique data	1765
no. of data used in refinement	1489
final R	0.039
final R_w	0.060

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