

Diastereoselective Synthesis of Optically Active C2-Substituted Spiro[4.5]decanes: Two Key Intermediates for Spirovetivane Sesquiterpenes

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We investigated the stereoselective construction of the C2 stereogenic center of the spiro[4.5]decane skeleton present in the spirovetivanes, spiroaurane, and spiroaxanes, and succeeded in synthesizing 2 α - and 2 β -substituted 6-spiro[4.5]decanones with diastereoselectivity by employing *n*-Bu₃SnH-mediated spiroannulation of the alkylmercury chloride, and Pd(II)-mediated spiroannulation followed by catalytic hydrogenation of the resulting unsaturated ester, respectively.

Key words spirovetivane; spiro[4.5]decane; radical cyclization; spiroannulation; palladium chloride; alkylmercury chloride

The spiro[4.5]decane ring system is a key structural feature in a number of sesquiterpenes including the spirovetivanes, spiroaurane, and spiroaxanes (Chart 1).¹⁾ A number of these substances possess unique biological activities, along with the sterically congested quaternary carbon center, and these features have attracted the attention of synthetic chemists.²⁾ The spirovetivanes can be structurally classified into *trans*- and *cis*-spirovetivane sesquiterpenes based on the configuration between the C1–C5 bond and the methyl group at C10 in the spiro[4.5]decane skeleton. Although the *cis*-spirovetivanes such as agarospirol (**1**), known as fragrant principles, have no biological activity, the *trans*-compounds, represented by solavetivone (**2**), possess inhibitory activity against several bacteria.^{1c,d)} From the viewpoint of evaluating the structure–activity relationship of the phytoalexins and identifying the defense mechanisms of plants, stereoselective construction of all the stereogenic centers in **1** and **2** (C2, C5, and C10) is considered very important. Various cyclization techniques have been developed for the construction of the spiro skeleton of these natural products, but most are limited to racemic preparation, and stereocontrol at the C2 and C10 chiral centers still remains to be resolved.³⁾ In the course of our studies directed toward the asymmetric synthesis of all stereoisomers such as **1** and **2** by stereoselective chemical reactions, we have reported an asymmetric synthesis of a quaternary carbon center (C5) by using Michael addition of an allylmagnesium chloride to a chiral vinylic sulfoxide,⁴⁾ and regioselective ring-opening of cyclopropyl sulfides with mercury(II) salt.⁵⁾ We have recently succeeded in stereoselective introduction of both α - and β -substituents at the C2 chiral center *via* an alkylmercury chloride (**6**). These results were published in a preliminary communication,⁶⁾

and the details are described in this paper.

Our synthetic plan relied on the intramolecular cyclization of the alkylmercury chloride (**6**) which would be a versatile intermediate for further transformation into natural products by radical-mediated and transmetallation reactions (Chart 2). From the perspective view of **6**, the vinylic sulfide at C6 (*vs.* the methylene at C10) is recognized as the only stereo-differentiating feature. Therefore, intramolecular radical-initiated cyclization of **6** would give rise to the 2 β -substituted product (**3**), if the cyclization proceeds *via* the less sterically hindered transition state, where the C2 substituent is located *anti* to the vinylic sulfide at C6. On the other hand, intermolecular catalytic hydrogenation of the unsaturated ester (**5**) would provide the 2 α -substituted product (**4**), if metal hydrides of the reagent attack the C–C double bond of **5** from the opposite site of the C6-substituent due to steric hindrance or conformational rigidity. This strategy inherently permits control of the diastereoselectivity at the C-2 stereogenic center.

Results

Synthesis Before constructing the spiro[4.5]decane skeleton, our initial efforts were focused on synthesis of the optically active alkylmercury chloride (**6**) from the cyclopropyl sulfide (**7**)^{5c)} (Chart 3). Swern oxidation of **7** afforded the aldehyde (**8**) (87%), Horner–Emmons reaction of **8** with diethyl (ethoxycarbonyl)methylphosphonate provided the α,β -unsaturated ester (**9**) effectively in 82% yield. Treatment of **9** with mercury(II) trifluoroacetate and sodium acetate in methylene chloride resulted in the anticipated chemo- and regio-selective ring-opening to give rise to the alkylmercury chloride (**6**) as a single isomer in 89% yield.⁵⁾

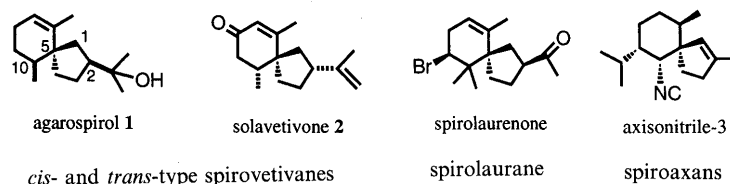


Chart 1

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Radical-Mediated Cyclization We first examined the radical-mediated cyclization of **6**. According to the literature,⁷ **6** was treated with *n*-Bu₃SnH at -40 °C and the mixture was allowed to warm slowly to room temperature, giving the desired spiro[4.5]decane derivatives (**10**) as a diastereoisomeric mixture in 86% yield. In order to determine the C2 diastereomeric ratio of **10**, we further transformed **10** into the corresponding ketones (**3** and **4**) by hydrolysis with 10% hydrochloric acid in refluxing acetonitrile. By HPLC analysis of the mixture, the stereoselectivity was determined to be 3/4=89/11. The stereo-

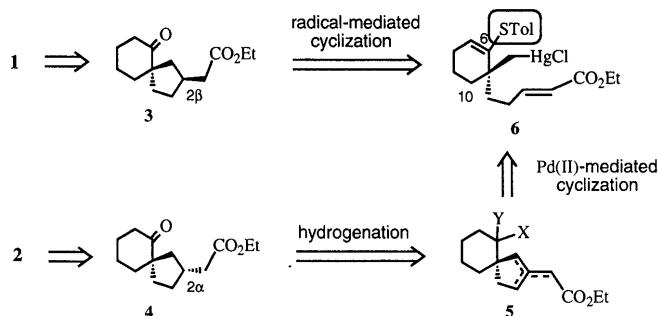


Chart 2. Retrosynthetic Analysis of C2 α - and C2 β -Substituted Spirovetivanes

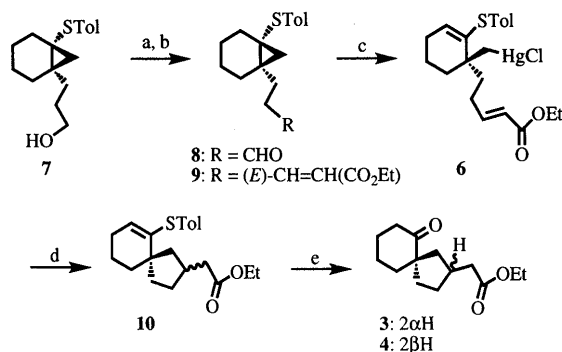


Chart 3

a: (COCl)₂, DMSO, CH₂Cl₂, -50 °C; Et₃N, r.t. (87%); b: (EtO)₂POCH₂CO₂Et, NaH, THF, r.t. (82%); c: Hg(OCOCH₃)₂, NaOAc, CH₂Cl₂, r.t.; aq. saturated NaCl (89%); d: *n*-Bu₃SnH, CH₂Cl₂, -40 °C→r.t. (86%); e: 10% HCl, CH₃CN, 60 °C (84%).

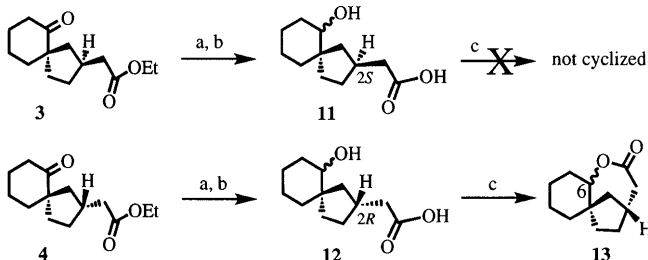


Chart 4

a: NaBH₄, EtOH, 0 °C (87% from **3** and **4**); b: 3 N KOH, MeOH, r.t. (85% for **11**, 88% for **12**); c: 2,2'-dipyridyl disulfide, Ph₃P, xylene, r.t.→reflux (75%).

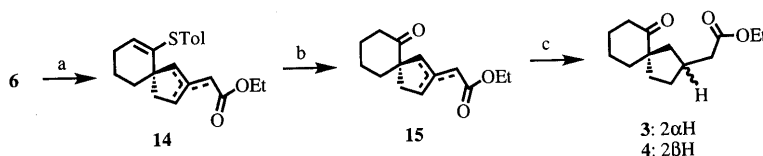


Chart 5

a: Li₂PdCl₄, DMF, THF, reflux (91%); b: 10% HCl, CH₃CN, 60 °C (82%); c: H₂, 10% Pd-C, EtOH, r.t. (93%).

chemistries of **3** and **4** were determined by chemical transformation into a seven-membered lactone (**13**) (Chart 4). That is, NaBH₄ reduction of both isomers **3** and **4** in EtOH was followed by hydrolysis with aqueous 3 N KOH solution in MeOH to afford the carboxylic acids (**11** and **12**) in 74% and 77% yields, respectively. Finally, the lactonization of the minor isomer **12** proceeded smoothly by refluxing the corresponding 2-pyridyl thioester,⁸ prepared from **12**, di-2-pyridyl disulfide, and triphenylphosphine at room temperature, in dry xylene to give rise to the lactone (**13**) as a 1 : 1 diastereoisomeric mixture at the C6 position in 75% yield. In contrast, the same treatment of the major isomer **11** afforded no cyclized product. These results confirmed that the major isomers (**3** and **11**) possess 2 β (2*S*)-configuration and the minor ones (**4** and **12**) possess 2 α (2*R*)-configuration. As mentioned above, the stereoselectivity of the radical-mediated spirocyclization of **6** can be explained by comparing the stability of the transition state models A and B (Fig. 1). Namely, **3** would be predominantly produced *via* the more accessible transition state A, because B suffers from severe steric hindrance between the vinylic proton (H_a) and two methylene protons at the C10 position (H_b).

Palladium(II)-Mediated Cyclization With the aim of diastereoselective synthesis of the 2 α -substituted spiro[4.5]decane (**4**), we next investigated catalytic hydrogenation of the unsaturated esters (**15**), which would be prepared from **6** by the following sequence (Chart 5). The spiroannulation reaction of **6** with Li₂PdCl₄ in a mixture of tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) proceeded smoothly and gave the spiro[4.5]decane products (**14**) as a regioisomeric mixture in 91% yield.⁹ Subsequent hydrolysis of **14** with 10% hydrochloric acid in acetonitrile afforded the corresponding ketones (**15**) in 82% yield. Fortunately, the catalytic hydrogenation of **15** with 10% palladium/carbon in EtOH under a hydrogen atmosphere gave the desired product (**4**) as a major product along with a small amount of **3** (93% total yield, 4/3=83/17 from HPLC analysis). The reason why the hydrogenation proceeded from the opposite side to the ketone group at the C6 position is not clear, but solvation around the C6-ketone group¹⁰ or the axially oriented C6-ketone group in the preferred conformation might interfere with the upper-side approach of the catalyst (Fig. 2).

In conclusion, we have established a stereoselective

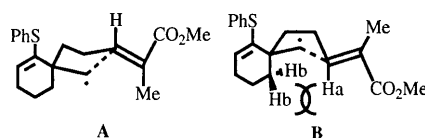


Fig. 1. Plausible Transition States in the Radical-Mediated Cyclization of **6**

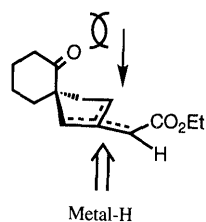


Fig. 2. Presumed Reaction Process in the Hydrogenation of **15**

method for constructing both 2*R* and 2*S* chiral centers involved in spirovetivanes, spiroaurane, and spiroaxanes. Our synthetic approach should provide a useful tool for the total asymmetric syntheses of all types of spirovetivane sesquiterpenes, which would be very helpful in evaluating the structure-activity relationship of the phytoalexins and studying the defense mechanisms of plants.

Experimental

Optical rotations were measured using a JASCO DIP-360 digital polarimeter. IR spectra were measured with a Hitachi 260-10 IR spectrometer using a CHCl₃ solution of the sample, or with a Horiba FT-210 IR spectrometer using a neat sample on KBr powder by the diffuse reflection measurement method. ¹H-NMR spectra were measured with a Varian VXR-200 spectrometer (200 MHz), a Hitachi 250RT spectrometer (250 MHz), a JNM-EX270 spectrometer (270 MHz) or a JEOL JNM-GX500 spectrometer (500 MHz). ¹³C-NMR spectra were measured with a JEOL JNM-EX270 spectrometer (67.8 MHz). All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Mass spectra were taken with a Shimadzu QP-1000 mass spectrometer and a JEOL JMS-D300 mass spectrometer. High-resolution mass spectra (HI-MS) were measured with a JEOL JMS-D300 spectrometer. Unless otherwise noted, all reactions were performed in anhydrous solvents. Merck Kieselgel 60 was used as an adsorbent for column chromatography. All extracts were dried over anhydrous MgSO₄.

3-[(1*S*,6*R*)-6-(*p*-Tolylthio)bicyclo[4.1.0]heptan-1-yl]propanal (8**)** A solution of DMSO (0.062 ml, 0.87 mmol) in CH₂Cl₂ (0.2 ml) was added to a solution of oxalyl chloride (0.035 ml, 0.40 mmol) in CH₂Cl₂ (1.0 ml) at -60°C and the mixture was stirred for 2 min, then a solution of **7**^(c) (100 mg, 0.36 mmol) in CH₂Cl₂ (0.4 ml) was added at -60°C . Stirring was continued for 15 min at -60°C , then triethylamine (0.253 ml, 1.82 mmol) was added and the whole was allowed to warm to room temperature. Water was added and the resulting mixture was extracted with ether. The extract was washed with 1% HCl solution, water, and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt = 10/1 to give the aldehyde (**8**) (86.5 mg, 87%) as a colorless oil, $[\alpha]_D^{25} + 75.7^\circ$ ($c = 0.995$, CHCl₃). ¹H-NMR (CDCl₃) δ : 0.68 (1H, d, $J = 5.2$, C7'-H_a), 0.85 (1H, dd, $J = 5.2$, 1.2 Hz, C7'-H_b), 1.15–2.75 (12H, m), 2.31 (3H, s, Ar-CH₃), 7.09 (2H, d, $J = 8.2$ Hz, Ar-H), 7.17 (2H, d, $J = 8.2$ Hz, Ar-H), 9.77 (1H, t, $J = 2.0$ Hz, CHO). IR (CHCl₃): 2955, 2880, 1734 (CO), 1509 (aromatic), 1464 (aromatic), 1100, 1074, 1026, 810 cm⁻¹. MS m/z (%): 274 (M^+ , 25), 230 (100), 217 (30), 123 (52). High MS Calcd for C₁₇H₂₂OS: 274.1390. Found: 274.1385.

Ethyl (*E*)-5-[(1*S*,6*R*)-6-(*p*-Tolylthio)bicyclo[4.1.0]heptan-1-yl]-2-pentenoate (9**)** Diethylphosphonoacetic acid ethyl ester (0.146 ml, 0.730 mmol) was added to a suspension of NaH (29.2 mg, 0.730 mmol) in THF (4.0 ml) at 0°C under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, then a solution of **8** (100 mg, 0.365 mmol) in THF (0.4 ml) was added and the whole was stirred for another 1 h. To this, a saturated NaHCO₃ solution was added and the resulting mixture was extracted with ether. The extract was washed with water and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/ether = 10/1 to give the (*E*)-ester (**9**) (109 mg, 87%) and (*Z*)-ester (4.9 mg, 4%) as colorless oils. **9**: $[\alpha]_D^{24} + 5.37^\circ$ ($c = 0.515$, CHCl₃). ¹H-NMR (CDCl₃) δ : 0.69 (1H, d, $J = 5.4$ Hz, C7'-H_a), 0.84 (1H, d, $J = 5.4$, C7'-H_b), 1.10–2.54 (12H, m), 1.27 (3H, t, $J = 7.2$ Hz, CH₃CH₂O), 2.31 (3H, s, Ar-CH₃), 4.16 (2H, q, $J = 7.2$ Hz, CH₃CH₂O), 5.80 (1H, d, $J = 15.6$ Hz, C2-H), 6.97 (1H, ddd,

$J = 15.6$, 7.0, 7.0 Hz, C3-H), 7.09 (2H, d, $J = 8.0$ Hz, Ar-H), 7.16 (2H, d, $J = 8.0$ Hz, Ar-H). IR (CHCl₃): 2940, 1714 (CO), 1660 (C=C), 1500 (aromatic), 1326, 1284, 1192, 1048 cm⁻¹. MS m/z (%): 345 ($M^+ + 1$, 1), 222 (100), 147 (96), 133 (72). High MS Calcd for C₂₁H₂₈O₂S: 344.1810. Found: 344.1822. (*Z*)-ester: ¹H-NMR (CDCl₃) δ : 0.72 (1H, d, $J = 5.2$ Hz, C7'-H_a), 0.84 (1H, d, $J = 5.2$ Hz, C7'-H_b), 1.20–3.00 (12H, m), 1.29 (3H, t, $J = 7.2$ Hz, CH₃CH₂O), 2.31 (3H, s, Ar-CH₃), 4.17 (2H, q, $J = 7.2$ Hz, CH₃CH₂O), 5.73 (1H, d, $J = 11.4$ Hz, C2-H), 6.22 (1H, ddd, $J = 11.4$, 7.8, 7.8 Hz, C3-H), 7.09 (2H, d, $J = 8.0$ Hz, Ar-H), 7.17 (2H, d, $J = 8.0$ Hz, Ar-H). IR (CHCl₃): 2940, 2870, 1720 (CO), 1650 (C=C), 1500 (aromatic), 1460 (aromatic), 1192, 1164, 1040 cm⁻¹. MS m/z (%): 345 ($M^+ + 1$, 1), 222 (100), 147 (97), 133 (66). High MS Calcd for C₂₁H₂₈O₂S: 344.1810. Found: 344.1826.

[(1*R*)-1-[(*E*)-4-(Ethoxycarbonyl)-3-butenyl]-2-(*p*-tolylthio)-2-cyclohexenyl]methylmercury Chloride (6**)** Hg(OCOCF₃)₂ (40.4 mg, 0.947 mmol) was added to a mixture of **9** (27.2 mg, 0.0791 mmol), NaOAc (6.5 mg, 0.079 mmol), and CH₂Cl₂ (1.0 ml), and the resulting mixture was stirred at room temperature for 12 h under a nitrogen atmosphere. The reaction was quenched with brine and water, and the mixture was extracted with CH₂Cl₂. The extract was washed with brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt = 10/1 to give **6** (37.5 mg, 82%) as a colorless oil, $[\alpha]_D^{28} - 0.26^\circ$ ($c = 1.100$, CHCl₃). ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, $J = 7.3$ Hz, CH₃CH₂O), 1.43–1.82 (6H, m, C5'-H, C6'-H, C4''-H), 1.95–2.25 (4H, m, C3'-H, C4'-H), 1.98 (1H, d, $J = 11.6$ Hz, C1-H_a), 2.09 (1H, d, $J = 11.6$ Hz, C1-H_b), 2.33 (3H, s, Ar-CH₃), 4.17 (2H, q, $J = 7.3$ Hz, CH₃CH₂O), 5.68 (1H, t, $J = 4.0$ Hz, C3'-H), 5.73 (1H, d, $J = 15.5$ Hz, C1''-H), 6.86 (1H, ddd, $J = 15.5$, 6.6, 6.6 Hz, C2''-H), 7.14 (2H, d, $J = 7.9$ Hz, Ar-H), 7.31 (2H, d, $J = 7.9$ Hz, Ar-H). ¹³C-NMR (CDCl₃) δ : 14.2 (CH₃CH₂O), 18.8 (C5'), 21.0 (Ar-CH₃), 27.0 (C4' and C3''), 36.8 (C6' or C4''), 40.7 (C6' or C4''), 43.6 (C1), 43.7 (C1'), 60.0 (CH₃CH₂O), 121.3 (C1''), 130.0 (quaternary carbon), 130.1 (Ar-CH), 132.0 (Ar-CH), 133.3 (C3'), 137.8 (quaternary carbon), 139.8 (quaternary carbon), 148.28 (C2''), 166.22 (CO). IR (CHCl₃): 2940, 1712 (CO), 1656 (C=C), 1498 (aromatic), 1280, 1186, 1046 cm⁻¹. MS m/z (%): 581 (M^+ , 2), 343 (51), 216 (100). Anal. Calcd for C₂₁H₂₇ClHgO₂S: C, 43.52; H, 4.70. Found: C, 43.80; H, 4.82.

Ethyl [(*S*)-6-(*p*-Tolylthio)spiro[4.5]dec-6-en-2-yl]acetate (10**)** A solution of *n*-Bu₃SnH (36.1 mg, 0.124 mmol) in CH₂Cl₂ (0.5 ml) was added to a solution of **6** (59.1 mg, 0.102 mmol) in CH₂Cl₂ (9 ml) at -40°C under a nitrogen atmosphere and the mixture was allowed to warm slowly to room temperature over a 5 min period. The reaction was quenched with water, and the reaction mixture was extracted with ether. The extract was washed with brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt = 15/1 to give **10** (30.2 mg, 86%) as a colorless oil, $[\alpha]_D^{25} - 0.07^\circ$ ($c = 1.015$, CHCl₃). ¹H-NMR (CDCl₃) δ : 1.00–2.62 (15H, m), 1.23 (3H, t, $J = 7.3$ Hz, CH₃CH₂O), 2.31 (3H, s, Ar-CH₃), 4.10 (2H, q, $J = 7.3$ Hz, CH₃CH₂O), 5.62 (89/100 $\times$ 1H, t, $J = 4.0$ Hz, C7'-H), 5.70 (11/100 $\times$ 1H, t, $J = 4.0$ Hz, C7'-H), 7.09 (2H, d, $J = 8.0$ Hz, Ar-H), 7.16 (2H, d, $J = 8.0$ Hz, Ar-H). IR (CHCl₃): 2940, 1726 (CO), 1496 (aromatic), 1270, 1190, 1148, 1034 cm⁻¹. MS m/z (%): 344 (M^+ , 59), 133 (100), 91 (91). High MS Calcd for C₂₁H₂₈O₂S: 344.1811. Found: 344.1817.

Ethyl [(2*S*,5*S*)-6-Oxospiro[4.5]decan-2-yl]acetate (3**) and Ethyl [(2*R*,5*S*)-6-Oxospiro[4.5]decan-2-yl]acetate (**4**)** From **10**: A mixture of **10** (8.8 mg, 0.026 mmol), 10% HCl solution (0.1 ml), and CH₃CN (0.3 ml) was heated at 60°C for 40 min. The reaction was quenched with a saturated NaHCO₃ solution. After removal of the solvent *in vacuo*, the resulting mixture was extracted with ether. The extract was washed with water and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt = 5/1 to give a mixture of **3** and **4** (5.1 mg, 84%, **3/4** = 89/11).

From **15**: A mixture of **15** (232 mg, 0.983 mmol), 10% palladium/carbon (23 mg), and EtOH (2.5 ml) was stirred at room temperature for 3 h under a hydrogen atmosphere. After filtration of the reaction mixture through a pad of Celite and concentration of the filtrate *in vacuo*, the residue was purified by column chromatography with hexane/AcOEt = 5/1 to give a mixture of **3** and **4** (217 mg, 93%, **3/4** = 13/87). Further purification by HPLC (Waters 6000A pump, Sumipax OA2000A, hexane/AcOEt = 10/1; flow rate; 1.0 ml/min) gave pure **3** ($t_R = 5.5$ min) and **4** ($t_R = 5.0$ min), each as a colorless oil. **3**: $[\alpha]_D^{28} + 2.82^\circ$ ($c = 1.05$, CHCl₃). ¹H-NMR (CDCl₃) δ : 0.99 (1H, dd, $J = 12.8$, 10.3 Hz, C1'-H_a), 1.25 (3H, t, $J = 6.8$ Hz, CH₃CH₂O), 1.21–1.31 (1H, m, C3'-H_a), 1.55 (1H, ddd, $J = 12.8$, 7.6, 3.4 Hz, C4'-H_a), 1.67–1.91 (7H, m, C3'-H_b,

C8'-H, C9'-H, C10'-H), 2.04 (1H, ddd, $J=12.8, 8.6, 8.6$ Hz, C4'-H_b), 2.16—2.37 (3H, m, C2-H, C2'-H), 2.37—2.46 (3H, C1'-H_b, C7'-H), 4.11 (2H, q, $J=6.8$ Hz, CH₃CH₂O). ¹³C-NMR (CDCl₃) δ : 14.1 (CH₃CH₂O), 22.8 (C9'), 27.2 (C8'), 31.4 (C3'), 34.3, (C4'), 35.9 (C2'), 38.9 (C7'), 40.1 (C2), 40.8 (C10'), 42.3 (C1'), 56.6 (C5'), 60.0 (CH₃CH₂O), 172.7 (ester CO), 213.8 (CO). IR (KBr): 2939, 2861, 1732 (ester CO), 1705 (CO), 1444, 1371, 1338, 1263, 1187, 1153, 1132, 1030 cm⁻¹. MS m/z (%): 238 (M⁺, 17), 151 (95), 111 (100). Anal. Calcd for C₁₄H₂₂O₃: C, 70.56; H, 9.30. Found: C, 70.51; H, 9.26. 4: $[\alpha]_D^{25} +2.02^\circ$ ($c=1.00$, CHCl₃). ¹H-NMR (CDCl₃) δ : 1.14—1.24 (1H, m, C3'-H_a), 1.25 (3H, t, $J=6.8$ Hz, CH₃CH₂O), 1.40 (1H, ddd, $J=12.8, 10.3, 6.8$ Hz, C4'-H_a), 1.66—1.89 (9H, m, C1'-H, C3'-H_b, C8'-H, C9'-H, C10'-H), 2.19 (1H, ddd, $J=12.8, 8.5, 3.4$ Hz, C4'-H_b), 2.30—2.45 (5H, m, C2-H, C2'-H, C7'-H), 4.12 (2H, q, $J=6.8$ Hz, CH₃CH₂O). ¹³C-NMR (CDCl₃) δ : 14.2 (CH₃CH₂O), 22.5 (C9'), 27.1 (C8'), 31.9 (C3'), 35.2 (C4'), 35.6 (C2'), 39.3 (C7'), 39.6 (C2), 40.2 (C1' or C10'), 42.6 (C1' or C10'), 56.4 (C5'), 60.1 (CH₃CH₂O), 173.1 (ester CO), 213.9 (CO). IR (KBr): 2937, 2864, 1732 (ester CO), 1707 (CO), 1444, 1375, 1336, 1190, 1146, 1030 cm⁻¹. MS m/z (%): 238 (M⁺, 20), 150 (37), 111 (100). Anal. Calcd for C₁₄H₂₂O₃: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.33.

[(2S,5S)-6-Hydroxyspiro[4.5]decan-2-yl]acetic Acid (11) A stirred solution of **3** (100 mg, 0.420 mmol) in EtOH (1.0 ml) was treated with NaBH₄ (15.9 mg, 0.420 mmol) at 0 °C and the resulting mixture was stirred for 15 min at the same temperature. The reaction was quenched with water. After removal of the solvent *in vacuo*, the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt=4/1 to give the alcohols as a diastereoisomeric mixture (88.1 mg, 87%). Colorless oil. ¹H-NMR (CDCl₃) δ : 0.87 (1/2 $\times$ 1H, dd, $J=12.8, 8.6$ Hz), 1.00 (1/2 $\times$ 1H, dd, $J=12.8, 8.6$ Hz), 1.16—1.90 (16H, m), 1.94 (1/2 $\times$ 1H, dd, $J=13.7, 6.8$ Hz), 2.04 (1/2 $\times$ 1H, dd, $J=13.7, 6.8$ Hz), 2.20—2.36 (3H, m), 3.39 (1/2 $\times$ 1H, dd, $J=8.6, 3.4$ Hz, C6'-H), 3.43 (1/2 $\times$ 1H, dd, $J=8.6, 3.4$ Hz, C6'-H), 4.12 (2H, q, $J=6.8$ Hz, CH₃CH₂O). IR (KBr): 3460 (OH), 2931, 2856, 1735 (CO), 1448, 1268, 1207, 1151, 1043 cm⁻¹. MS m/z (%): 241 (M⁺ + 1, 0.6), 167 (34), 135 (100). High MS Calcd for C₁₄H₂₄O₃: 240.1726. Found: 240.1726. A solution of the alcohols obtained above (68.0 mg, 0.283 mmol) in MeOH (1 ml) was treated with a 3 N KOH solution (0.142 ml, 0.425 mmol) at room temperature and the mixture was stirred for 3 h. The resulting mixture was acidified with 10% HCl solution, then extracted with chloroform. The extract was washed with water and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt=1/2 to give the carboxylic acids (**11**) as a diastereoisomeric mixture (50.9 mg, 85%). Colorless oil. ¹H-NMR (CDCl₃) δ : 0.88 (1/2 $\times$ 1H, dd, $J=12.8, 9.4$ Hz), 1.01 (1/2 $\times$ 1H, dd, $J=12.8, 9.4$ Hz), 1.10—1.94 (13H, m), 1.97 (1/2 $\times$ 1H, dd, $J=12.8, 6.8$ Hz), 2.08 (1/2 $\times$ 1H, dd, $J=13.7, 7.7$ Hz), 2.22—2.43 (3H, m), 3.41 (1/2 $\times$ 1H, dd, $J=9.4, 3.4$ Hz, C6'-H), 3.45 (1/2 $\times$ 1H, dd, $J=9.4, 3.4$ Hz, C6'-H). IR (KBr): 3700—2300, 2933, 2858, 1709 (CO), 1448, 1273, 1041 cm⁻¹. MS m/z (%): 213 (M⁺ + 1, 0.4), 195 (21), 167 (47), 135 (100). High MS Calcd for C₁₂H₂₀O₃: 212.1413. Found: 212.1388.

[(2R,5S)-6-Hydroxyspiro[4.5]decan-2-yl]acetic Acid (12) By the same procedure as described for **11**, the carboxylic acids (**12**) (88.4 mg, 77%) were prepared as a colorless oil from **4** (130 mg, 0.546 mmol). ¹H-NMR (CDCl₃) δ : 1.14—1.50 (9H, m), 1.52—1.94 (6H, m), 2.25—2.45 (3H, m), 3.37—3.47 (1H, m, C6'-H). IR (KBr): 3700—2300, 2931, 2860, 1709 (CO), 1448, 1281, 1041 cm⁻¹. MS m/z (%): 213 (M⁺, 0.4), 195 (19), 167 (51), 135 (100). High MS Calcd for C₁₂H₂₀O₃: 212.1413. Found: 212.1416.

(1S,10R)-7-Oxatricyclo[8.2.1.0⁶]tridecan-8-one (13) A solution of **12** (130 mg, 0.613 mmol) in xylene (0.5 ml) was added to a mixture of triphenylphosphine (241 mg, 0.920 mmol), 2,2'-dipyridyl disulfide (202 mg, 0.920 mmol), and xylene (1.5 ml) at room temperature under a nitrogen atmosphere. Stirring was continued for 30 min, then the mixture was refluxed for 6 h and the solvent was removed *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt=6/1 to give the lactones (**13**) as a diastereoisomeric mixture (88.7 mg, 75%). Further purification of this colorless oil by HPLC (Waters 6000A pump, μ -Polasil, hexane/AcOEt=8/1, flow rate: 4 ml/min] gave pure **13a** ($t_R=3.9$ min) and **13b** ($t_R=4.6$ min), each as a colorless oil. **13a**: $[\alpha]_D^{25} -91.3^\circ$ ($c=1.00$, CHCl₃). ¹H-NMR (CDCl₃) δ : 1.20—2.08 (13H, m), 2.11 (1H, d, $J=12.9$ Hz), 2.28—2.42 (1H, m, C10-H), 2.44 (1H, dd, $J=16.5, 2.0$ Hz, C9-H_a), 2.85 (1H, ddd, $J=16.5, 6.6, 2.0$ Hz, C9-H_b),

4.05 (1H, dd, $J=12.0, 3.4$ Hz, C6-H). ¹³C-NMR (CDCl₃) δ : 23.0 (CH₂), 25.5 (CH₂), 28.4 (CH₂), 29.5 (CH₂), 31.9 (C10), 36.5 (CH₂), 39.2 (CH₂), 40.4 (CH₂), 44.3 (C9), 48.2 (C1), 88.2 (C6), 174.6 (CO). IR (KBr): 2935, 2864, 1716 (CO), 1450, 1408, 1354, 1227, 1142, 1047 cm⁻¹. MS m/z (%): 194 (M⁺, 5), 166 (42), 151 (100). Anal. Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.87; H, 9.29. **13b**: $[\alpha]_D^{25} -169^\circ$ ($c=1.00$, CHCl₃). ¹H-NMR (CDCl₃) δ : 1.05—2.13 (14H, m), 2.22—2.36 (1H, m, C10-H), 2.51 (1H, d, $J=16.2$ Hz, C9-H_a), 2.85 (1H, ddd, $J=16.2, 7.6, 2.0$ Hz, C9-H_b), 4.19 (1H, dd, $J=11.2, 5.3$ Hz, C6-H). ¹³C-NMR (CDCl₃) δ : 23.2 (CH₂), 24.4 (CH₂), 29.9 (CH₂), 23.0 (CH₂), 30.8 (CH₂), 31.2 (C10), 38.5 (CH₂), 43.5 (C9), 47.1 (C1), 52.8 (CH₂), 85.9 (C6), 174.9 (CO). IR (KBr): 2937, 2858, 1720 (CO), 1452, 1367, 1230, 1169, 1055, 1012 cm⁻¹. Anal. Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.80; H, 9.30.

Ethyl [(5S)-6-(*p*-Tolylthio)spiro[4.5]deca-1,6-dien-2-yl]acetate, Ethyl [(5S)-6-(*p*-Tolylthio)spiro[4.5]deca-2,6-dien-2-yl]acetate, and Ethyl [(5S)-6-(*p*-Tolylthio)spiro[4.5]dec-6-en-2-ylidene]acetate (14**)** A mixture of **6** (396 mg, 0.683 mmol), LiCl (58.1 mg, 1.37 mmol), PdCl₂ (122 mg, 0.688 mmol), DMF (2.5 ml), and THF (11 ml) was refluxed for 12 h under a nitrogen atmosphere. After filtration through a pad of Celite and removal of the solvents, the residue was diluted with ether. The mixture was washed with a saturated NaHCO₃ solution, water, and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt=10/1 to give **14** as a regioisomeric mixture (214 mg, 91%). Colorless oil. ¹H-NMR (CDCl₃) δ : 1.0—3.2 (18H, m), 4.07—4.22 (2H, m), 5.20—6.04 (2H, m), 7.04—7.34 (4H, m). IR (KBr): 2929, 1736 (CO), 1713 (CO), 1655 (Ar and C=C), 1490 cm⁻¹. MS m/z (%): 343 (M⁺ + 1, 100), 219 (15), 146 (20). High MS Calcd for C₂₁H₂₆O₂S: 342.1651. Found: 342.1649.

Ethyl [(5S)-6-Oxospiro[4.5]dec-1-en-2-yl]acetate, Ethyl [(5S)-6-Oxospiro[4.5]dec-2-en-2-yl]acetate, and Ethyl [(5S)-6-Oxospiro[4.5]decan-2-ylidene]acetate (15**)** A mixture of **14** (230 mg, 0.673 mmol), 10% HCl solution (1.0 ml), and CH₃CN (3.0 ml) was heated at 60 °C for 40 min. The reaction was quenched with a saturated NaHCO₃ solution. After removal of the solvent *in vacuo*, the resulting mixture was extracted with ether. The extract was washed with water and brine, dried, then concentrated *in vacuo*. The residue was purified by column chromatography with hexane/AcOEt=5/1 to give the ketone (**15**) as a regioisomeric mixture (130 mg, 82%). Colorless oil. ¹H-NMR (CDCl₃) δ : 1.18—3.37 (17H, m), 4.06—4.24 (2H, m), 5.34—5.96 (1H, m). IR (KBr): 2929, 1736 (CO), 1709 (CO), 1655 (C=C), 1448 cm⁻¹. MS m/z (%): 237 (M⁺ + 1, 100), 191 (98), 111 (100). High MS Calcd for C₁₄H₂₀O₃: 236.1412. Found: 236.1415.

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