Synthetic Photochemistry. LXVII.[1] A Total Synthesis of (±)-Hinesol and (±)-Agarospirol via *retro*-Benzilic Acid Rearrangement

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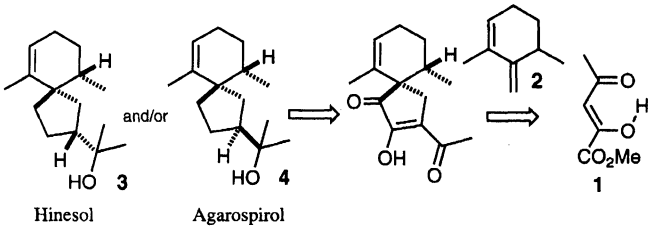
A mild base-catalyzed *retro*-benzilic acid rearrangement of a *proto*-photocycloadduct, formed in highly stereoselective photoaddition of methyl 2,4-dioxopentanoate to 1,5-dimethyl-6-methylene-1-cyclohexene, afforded a spiro[4.5]decenedione derivative. Reductive elimination of the α-dicarbonyl function and C_1-homologation furnished (±)-hinesol and (±)-agarospirol.

In the photocycloaddition reaction of methyl 2,4-dioxopentanoate (**1**), a new synthetic utility was added by recently discovered *retro*-benzilic acid rearrangement of the *proto*-photocycloadducts,[2] particularly for functionalized spiro[4.*n*]alkanes.[3]

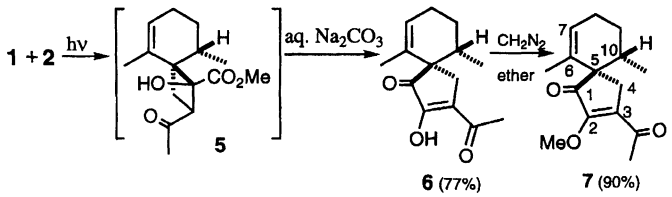
Here, as shown in the retrosynthetic scheme, Scheme 1, we show an easy conversion of the major photoproduct formed in the reaction of **1** with 1,5-dimethyl-6-methylenecyclohexene (**2**) into vetispirane derivatives,[4] hinesol (**3**), a metabolite of *Atractylodes lancea*,[5,6] and agarospirol (**4**) found in *Aquilaria agallocha*,[7] in racemic forms.

When an EtOAc solution of **1** and **2** was internally irradiated by a 400-W high-pressure Hg-lamp through a Pyrex glass filter for 7 h, a smooth reaction occurred to form isomeric *proto*-photocycloadducts,[8] the major product (**5**) of which was isolated on a silica-gel column chromatography. Interestingly, treatment of **5** with sodium carbonate in solution furnished a *retro*-benzilic acid rearrangement product, ($5R^*$,$10S^*$)-3-acetyl-2-hydroxy-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (**6**, 77%), but the treatment with triethylamine afforded none of **6** (Scheme 2). Certainly, besides the dissociation of the hydroxyl proton on the tertiary alcohol, a formation of the chelated intermediate with sodium ion could facilitate the rearrangement since the basicities of triethylamine ($pK_a=10.72$) and carbonate ($pK_{a1}=3.9$, $pK_{a2}=10.33$) are nearly the same. Previously, the rearrangement has often occurred spontaneously, and the controlled occurrence of the process under mild conditions has a synthetic value.

The major product (**6**) could be purified easily via silica-gel column chromatography. To differentiate its stereochemistry, the nuclear overhauser effect (NOE) was investigated; the methyl ether of **6**, ($5R^*$,$10S^*$)-3-acetyl-2-methoxy-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (**7**), showed a clear NOE between the C-10 secondary methyl signal at $\delta=0.75$ and a signal at $\delta=2.62$



Scheme 1.



Scheme 2.

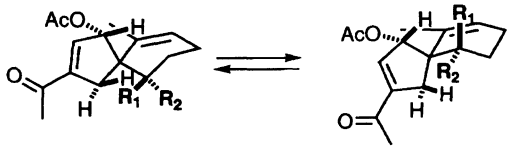
ascribable to one of the C-4 methylene protons (8%). However, deduction of the stereochemistry of **7** by the NOE should be careful; since the substituents on this functionalized cyclopentenone ring are all on the sp^2-carbons, and in view of the conformational mobility of the spirocyclic system, a bulky substituent should prefer the equatorial conformation (Scheme 3).

It is desirable to do the experiments with other derivatives. In this regard, a dihydro derivative, having hydrogens on the two vicinal carbons (C-1 and C-4) to the spiro-carbon (C-5), of **7** should give reliable information.

Thus, **7** was treated with 1,2-ethanediol and *p*-toluenesulfonic acid in benzene to give **8**, which was reduced with lithium aluminum hydride in tetrahydrofuran (THF) to give **9**. Consecutive treatment of **9** with acetic anhydride and *p*-toluenesulfonic acid gave an allylic acetal acetate (**10**) and an allylic acetate (**11**), appropriate for NOE inspections.

For the ^{1}H NMR spectrum of **11**, an irradiation with the frequency of the C-10 methyl signal (δ=0.95) caused an increase of the signal ascribable to one of the C-4 methylene protons at δ=2.49 (8%), and an irradiation with that of the C-1 methine proton (δ=6.03) showed an enhancement of the C-10 methine proton at δ=1.85 (10%). Moreover, there is an additional NOE (7.4%) between the signals of the vinylic methyl (δ=1.70) and another C-4 methylene proton (δ=2.66). These experiments firmly established the stereochemistry.

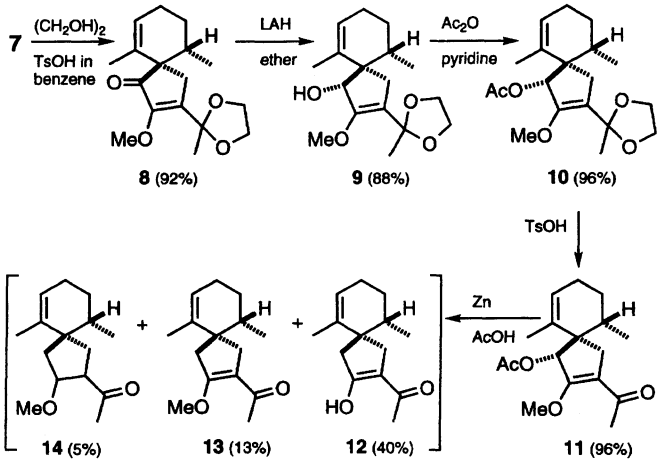
Now, the compounds **5** and its derivatives seem to be a good synthone for **3** and related vetispiranes;[9] the carbon framework of **5** constitutes fourteen out of fifteen carbons, and a C_1-homologation on the acetyl carbonyl completes the skeleton of **3** with the correct stereochemistry. Therefore, the synthetic operation with this aim should be reductive elimination of the unnecessary oxygen functions and unsaturated linkage before the homologation. However, attempted reduction of **11** with zinc in acetic acid, which should be the most direct way of removing the oxygen functions, formed three products (**12**, **13**, and **14**), but the major products, **12** and **13**, were unstable under these conditions and **14** was obtained only in 5% yield (Scheme 4).



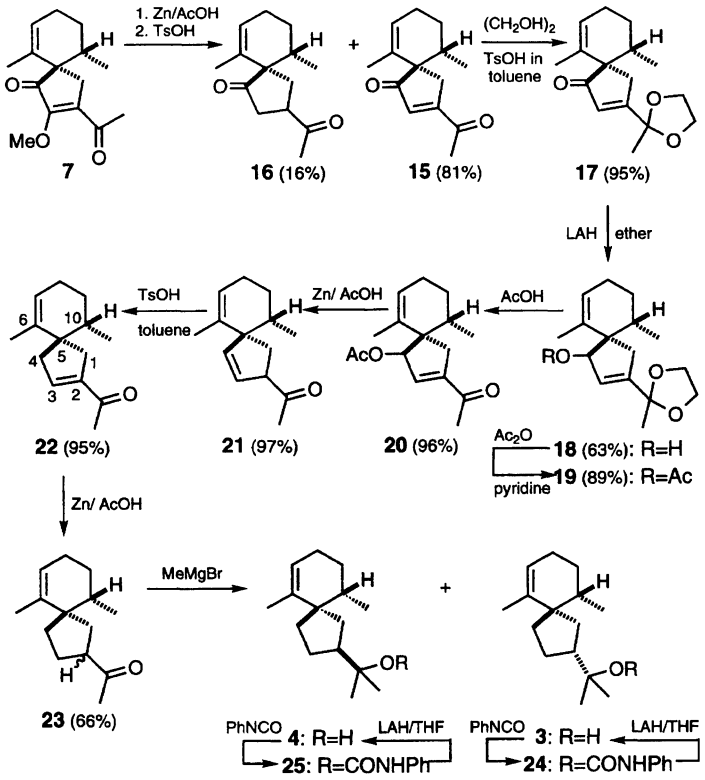
Scheme 3.

Consequently, a steadier method was desirable; the methyl ether (**7**) was at first converted into a spirocyclic β-acetylcyclopentenone, (5*R**,10*S**)-3-acetyl-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (**15**), by reduction with Zn in AcOH and following treatment with *p*-toluenesulfonic acid, together with its dihydro diketone, (5*R**,10*S**)-3-acetyl-2-methoxy-6,10-dimethylspiro[4.5]-dec-6-en-1-one (**16**).

Then, the cyclopentenone carbonyl of **15** was removed by reductions; i.e., protection of the acetyl carbonyl of **15** as a dioxolane derivative, (5*R**,10*S**)-3-(2-methyl-1,3-dioxolan-2-yl)-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (**17**) followed by reduction with lithium alminum hydride (LAH) furnished a hydroxy acetal (**18**). After acetylation and deprotection (via **19**), the resultant allylic acetate (**20**) was again reduced with zinc in acetic acid to form a β,γ-unsaturated ketone, (5*S**,10*S**)-3-acetyl-6,10-dimethylspiro[4.5]deca-1,6-diene (**21**), which could be isomerized to an α,β-unsaturated ketone, (5*S**,10*S**)-2-acetyl-6,10-dimethylspiro-[4.5]deca-2,6-diene (**22**), by treatment with TsOH in toluene (Scheme 5). The NOE experiment with **20** again confirmed the stereochemistry; i.e., irradiations of the secondary methyl signal (at δ=0.96) and the signal (at δ=5.79) of methine proton on the vicinal carbon of the spiro-carbon respectively enhanced the signal (at δ=2.51) ascribable to the one of the methylene protons on the cyclopentenone moiety (9%), and the signal (at δ=1.81) of the methine proton on the neopentyl carbon bearing the methyl group (6%).



Scheme 4.



Scheme 5.

Repeated reduction of **22** with zinc in acetic acid afforded an epimeric pair (1 : 1) of 2-acetyl-6,10-dimethylspiro[4.5]dec-6-enes (**23**).

Production of **22** and **23** constitutes the formal total synthesis of hinesol, as Marshal has converted them into hinesol and *epi*-hinesol (agarospirol) as an inseparable mixture.[10,11] Now, we did a homologation; by methylation with methylmagnesium bromide, **23** yielded two tertiary alcohols, which were separated as phenylurethanes (**24** and **25**) via silver nitrate-impregnated silica-gel column chromatography. Both the ^{13}C NMR spectra of **24** and **25** showed magnetic nonequivalency for *ortho*-protons of the phenyl group, with very weak nonequivalent two-carbon signals; apparently, this is due to the sterically hindered phenyl proup on the amide nitrogen. The assignments, 118.6 and 118.7 for two *ortho*-carbons of **24**, and 118.7 and 118.8 for those of **25**, were deduced from comparisons with the phenylurethane of α-terpineol.[12]

Following LAH-reduction indeed afforded **3** and **4**, respectively. These samples were identified with (±)-hinesol[13] and (±)-agarospirol[7] on the basis of the ^{1}H NMR spectral analysis.

It is noteworthy that 1-methyl-2-methylenecyclohexane was shown to give two photoadducts, in a ratio of 1 : 2, which were quantitatively converted into *retro*-benzilic acid rearrangement products.[3] Dramatic improvement of stereoselectivity in this case, as the cyclohexene **2** has an additional methyl group, made the *retro*-benzilic acid rearrangement useful.

Experimental

The elemental analyses were done by Mrs. R. Hatazoe of the Institute of Advanced Material Study, Kyushu University. The NMR spectra were measured with a JEOL GSX 270H Model spectrometer in $CDCl_3$ unless otherwise specified; the chemical shifts are expressed in δ units. The mass spectra were measured with a JEOL 01SG-2 spectrometer. The IR spectra were taken as KBr discs or liquid films inserted between NaCl plates using a JASCO IR-A102 spectrometer.

Preparation of 1,5-Dimethyl-6-methylenecyclohexene (2). To a suspension of Zn dust (20 g) and CH_2Br_2 (7 cm^3) in THF (65 cm^3) was added a CH_2Cl_2 solution (65 cm^3) of $TiCl_4$ (8 cm^3) at 25 °C. Instantaneous reaction occurred with evolution of heat and rapid development of dark brown color. After 25 min, a THF solution of 2,6-dimethylcyclohexenone (6.5 g) was added dropwise and the resulting mixture was stirred at 25 °C for 20 h. The reaction mixture was diluted with ether, poured into 1 M HCl, and extracted with ether. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, and cocentrated in vacuo. The product was passed through a silica-gel column with pentane to collect hydrocarbon and the solvent was evaporated in vacuo to give **2** [a colorless oil, 4.0 g, 62%. ^{1}H NMR δ=1.10 (3H, d, J=7 Hz), 1.82 (3H, q, J=1.7 Hz), 4.82 (1H, s), 4.90 (1H, s), and 5.64 (1H, m)], which was used for the next reaction without further purification.

Photocycloaddition of 1 to 2. Isolation of the *retro*-Benzilic Acid Rearrangement Product, (5*R, 10*S**)-3-Acetyl-2-hydroxy-6,10-dimethylspiro[4.5]-**

deca-2,6-dien-1-one (6), of the *proto*-Photocycloadduct (5). An AcOEt solution (5 cm^3) of the olefin **2** (180 mg) and **1** (100 mg) was irradiated by means of a 400 W high-pressure mercury lamp, and cooled with running water under an N_2 atmosphere for 20 h. The mixture, supposed to contain **5** and isomers, was then evaporated in vacuo, and an MeOH solution of the residue was treated with aq Na_2CO_3 for 45 min. After MeOH was removed, the residue was acidified with dil HCl and extracted with ether to give **6** [a yellow oil, 125 mg, 77%. Found: C, 72.04; H, 7.88%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. ^{1}H NMR δ=0.74 (3H, d, J=6.6 Hz), 1.25—1.45 (2H, m), 1.43 (3H, br s), 1.61 (1H, m), 2.04—2.2 (2H, m), 2.43 (1H, d, J=17.6 Hz), 2.45 (3H, s), 2.69 (1H, d, J=17.6 Hz), 5.57 (1H, m), and 9.7 (1H, br, OH); ^{13}C NMR δ=15.9, 19.0, 25.5, 27.5, 28.5, 31.1, 36.5, 54.7, 125.9, 131.5, 133.4, 159.4, 201.1, and 209.4; MS m/z (%) 234 (M^+; 100), 192 (40), 179 (29), 145 (26), 107 (65), and 91 (40); IR ν=3310, 2924, 1713, 1659, 1428, 1226, 975, 854, and 784 cm^{-1}].

Methylation of 6 to (5*R,10*S**)-3-Acetyl-2-methoxy-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (7).** The **6** (40 mg) was methylated with ethereal CH_2N_2 to give **7** [a yellow oil, 38 mg, 90%. Found: C, 72.11; H, 7.90%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%. ^{1}H NMR δ=0.75 (3H, d, J=7.0 Hz), 1.44 (3H, br s), 1.3—1.6 (2H, m), 1.96—2.25 (3H, m), 2.32 (1H, d, J=18.7 Hz), 2.52 (3H, s), 2.63 (1H, d, J=18.7 Hz), 4.19 (3H, s), and 5.53 (1H, m); ^{13}C NMR δ=15.9, 19.0, 25.5, 27.2, 30.7, 30.9, 36.5, 54.5, 58.6, 125.5, 133.9, 134.9, 157.5, 196.9, and 211.4; IR ν=2924, 1707, 1667, 1451, 1229, 926, 863, and 789 cm^{-1}].

An Acetal of 7 (8). An anhydrous benzene solution (30 cm^3) of **7** (100 mg), 1,2-ethanediol (1.5 cm^3), and TsOH (20 mg) was refluxed for 3.5 h. The mixture was then washed with aqueous Na_2CO_3 and extracted with ether. After removal of the solvent, the residue was chromatographed on an alumina column to give **8** [a colorless oil, 110 mg, 92%. Found: C, 70.18; H, 8.65%. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%. ^{1}H NMR δ=0.76 (3H, d, J=7.0 Hz), 1.27—1.38 (1H, m), 1.45 (3H, dt, J=2.6, 1.5 Hz), 1.45—1.62 (1H, m), 1.64 (3H, s), 1.90—2.25 (3H, m), 2.22 (1H, d, J=19.0 Hz), 2.51 (1H, d, J=19.0 Hz), 3.90—3.95 (2H, m), 3.93 (3H, s), 4.03—4.08 (2H, m), and 5.52 (1H, m); ^{13}C NMR δ=15.7, 18.8, 23.8, 25.6, 27.4, 32.5, 35.7, 53.5, 58.6, 65.1 (2C), 107.1, 125.2, 134.2, 152.9, 155.6, and 209.0; MS m/z (%) 292 (M^+; 95), 276 (16), 277 (100), 278 (90), 247 (5), 205 (9), and 87 (47); IR ν=2930, 1705, 1641, 1454, 1197, 1038, 872, 811, and 763 cm^{-1}].

Conversion of 8 into an Allyl Alcohol (9). To an anhydrous ether solution (2 cm^3) of **8** (210 mg) was added LAH (68 mg) in portions and the mixture was stirred at 0 °C for 2 h. The mixture was then treated with EtOAc and fractionated with water and ether. The organic layer was dried on $MgSO_4$ and heated in vacuo to remove the solvent. The residue was chromatographed on a Florisil column to give **9** [a colorless oil, 185 mg, 88%. Found: C, 69.10; H, 8.88%. Calcd for $C_{17}H_{24}O_4$: C, 69.36; H, 8.90%. ^{1}H NMR δ=0.92 (3H, d, J=6.6 Hz), 1.41—1.51 (1H, m), 1.56 (3H, s), 1.74 (3H, m), 1.79—2.12 (4H, m), 2.07 (1H, d, J=7.0 Hz), 2.21 (1H, dd, J=15.4, 1.8 Hz), 2.39 (1H, dd, J=15.4, 2.2 Hz), 3.78 (3H, s), 3.86—4.05 (4H, m), 4.45 (1H, ddd, J=7.0, 2.2, 1.8 Hz), and 5.75 (1H, m); ^{13}C NMR δ=15.3, 21.0, 21.8, 24.2, 25.3, 35.7, 38.7, 51.4, 57.1, 64.7, 64.8, 80.7, 107.2, 117.9, 128.3, 132.3, and 152.3; MS m/z (%) 294 (M^+; 18), 279 (100), 250 (13), 122 (34), 107 (18), and 87 (94); IR ν=3480, 2930, 1453, 1243, 949, and 857 cm^{-1}].

Acetylation of 9. Formation of an Acetal Acetate (10). To a mixed solution of Ac_2O (5 cm^3) and pyridine (8 cm^3) was added **9** (275 mg) and the solution was kept at room temperature for 24 h. The mixture was then evaporated in vacuo, and the residue was washed with aqueous $NaHCO_3$ and extracted with ether. The organic extract was chromatographed on an alumina column to give **10** [a colorless oil, 300 mg, 96%. Found: C, 68.05; H, 8.36%. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39%. ^{1}H NMR δ=0.95 (3H, d, J=6.6 Hz), 1.25—1.40 (1H, m), 1.57 (3H, s), 1.73 (3H, m), 1.70—2.00 (4H, m), 2.04 (3H, s), 2.30 (1H, dd, J=16.5, 1.5 Hz), 2.42 (1H, dd, J=16.5, 2.5 Hz), 3.58 (3H, s), 3.81—4.05 (4H, m), 5.45 (1H, m), and 5.85 (1H, m); ^{13}C NMR δ=15.8, 21.3, 21.4, 22.5, 24.1, 26.5, 34.7, 36.3, 48.7, 57.7, 64.7 (2C), 81.7, 107.0, 123.4, 124.8, 134.0, 148.8, and 170.4; MS m/z (%) 336 (M^+; 7), 321 (82), 294 (4), 277 (7), 261 (22), and 87 (100); IR ν=2932, 1739, 1460, 1231, 1039, and 861 cm^{-1}].

Acid Hydrolysis of 10 to an Unsaturated Keto Acetate 11. An aq AcOH solution (1:4, 2 cm^3) of **10** (60 mg) was heated at 50 °C for 1 h. The mixture was then poured into ice-cooled aq K_2CO_3 and extracted with EtOAc. The organic layer was washed with aq NaCl, dried over Na_2SO_4, and chromatographed on a silica-gel column to give **11** [a colorless oil, 50 mg, 96%. Found: C, 69.93; H, 8.45%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%. ^{1}H NMR δ=0.95 (3H, d, J=7.0 Hz), 1.35 (1H, m), 1.70 (3H, td, J=1.8, 1.5 Hz), 1.72—2.05 (4H, m), 2.08 (3H, s), 2.39 (3H, s), 2.49 (1H, dd, J=16.3, 0.8 Hz), 2.67 (1H, dd, J=16.3, 2.0 Hz), 3.76 (3H, s), 5.49 (1H, m), and 6.03 (1H, dd, J=2.0, 1.0 Hz); ^{13}C NMR δ=15.8, 21.2, 22.0, 22.2, 26.1, 30.4, 32.9, 35.3, 48.5, 57.4, 81.6, 119.5, 125.7, 133.0, 161.2, 169.8, and 196.1; MS m/z (%) 292 (M^+; 70), 250 (100), 232 (79), 217 (66), 189 (95), 157 (31), 107 (21), and 91 (13). IR ν=2924, 1744, 1634, 1387, 1103, 975, 820, and 744 cm^{-1}].

Attempted Reduction of 11 with Zn in AcOH. Formation of 12, 13, and 14. To an AcOH solution (2 cm^3) of **11** (50 mg) was added Zn powder (190 mg) and the mixture was kept refluxing for 4 h. The mixture was then filtered, the residue was washed with $NaHCO_3$ and extracted with ether, and the organic layer was evaporated in vacuo. The residue was chromatographed on a silica-gel column to give **12** [a colorless oil, 15 mg, 40%. Found: C, 75.90; H, 9.14%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%. ^{1}H NMR δ=0.89 (3H, d, J=7.0 Hz), 1.39—1.74 (4H, m), 1.63 (3H, td, J=2.2, 1.0 Hz), 1.99 (3H, s), 1.94—2.03 (1H, m), 2.00 (1H, m), 2.33 (1H, d, J=18.9 Hz), 2.37 (1H, dd, J=15.2, 0.7 Hz), 2.50 (1H, dd, J=15.2, 0.7 Hz), 2.69 (1H, d, J=18.9 Hz), and 5.38 (1H, m); ^{13}C NMR δ=16.0, 19.8, 21.1, 24.4, 27.2, 33.2, 39.4, 44.1, 47.7, 110.8, 123.3, 138.5, 176.4, and 202.5; MS m/z (%) 220 (M^+; 65), 178 (62), 122 (64), 108 (34), 98 (29), and 70 (100); IR ν=3495, 2924, 1689, 1453, 1234, 963, 842, and 807 cm^{-1}], and a mixture of **13** [a colorless oil, 13 mg, 37%. ^{1}H NMR δ=0.89 (3H, d, J=7.0 Hz), 1.49 (1H, m), 1.63 (3H, br, s), 1.95—2.05 (4H, m), 2.32 (3H, s), 2.34 (1H, dd, J=14.9, 1.8 Hz), 2.54 (1H, dd, J=14.9, 1.8 Hz), 2.56 (1H, dd, J=18.4, 1.8 Hz), 2.91 (1H, dd, J=18.4, 1.8 Hz), 3.85 (3H, s), and 5.33 (1H, m)] and **14** [a colorless oil, 2 mg, 5%. ^{1}H NMR δ=0.88 (3H, d, J=7.0 Hz), 1.43—1.54 (7H, m), 1.54 (3H, br s), 1.94—2.04 (4H, m), 2.31 (3H,

s), 3.58 (3H, s), 4.04 (1H, dd, J=16.9, 11.4), and 5.50 (1H, m)].

Reduction of 7 with Zn in AcOH. Formation of ($5R^*$,$10S^*$)-3-Acetyl-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (15) and ($5R^*$,$10S^*$)-3-Acetyl-2-methoxy-6,10-dimethylspiro[4.5]dec-6-en-1-one (16). To an AcOH solution (20 cm^3) of **7** (750 mg) was added Zn power (2.0 g). After 5 min, the mixture was filtered and the filtrate was evaporated in vacuo. The residue was extracted with ether, and the organic layer was evaporated in vacuo. The mixture was then dissolved in benzene (300 cm^3), containing TsOH (300 mg), and was refluxed for 5 h. The mixture was then washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After removing the solvent, the residue was chromatographed on a silica-gel column to give **15** [a yellow oil, 120 mg 81%. Found: C, 76.80; H, 8.05%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%. ^{1}H NMR δ=0.72 (3H, d, J=7.0 Hz), 1.42 (3H, br s), 1.23—1.6 (2H, m), 1.97—2.27 (3H, m), 2.51 (3H, s), 2.54 (1H, dd, J=20, 2.2 Hz), 2.84 (1H, dd, J=20, 1.8 Hz), 5.56 (1H, m), and 6.66 (1H, dd, J=2.2, 1.8 Hz); ^{13}C NMR δ=15.8, 19.0, 25.6, 27.5, 27.8, 35.6, 36.2, 57.8, 125.6, 133.6, 137.4, 168.9, 197.0, and 215.3; MS m/z (%) 218 (M^+; 12), 122 (100), 107 (71), 93 (30), 79 (13), and 71 (10); IR ν=2926, 1712, 1686, 1370, 1169, 881, 843, and 801 cm^{-1}] and **16** [a yellow oil, 110 mg, 16%. ^{1}H NMR δ=0.92 (3H, d, J=7.0 Hz), 1.32 (1H, m), 1.52 (3H, m), 1.52—1.61 (1H, m), 1.90—2.53 (6H, m), 2.67 (1H, dd, J=18.7, 6.7 Hz), 3.30 (1H, m), and 5.52 (1H, dd, J=2.9, 1.5 Hz) for a-isomer; 0.80 (3H, d, J=7.0 Hz), 1.21 (1H, m), 1.61 (3H, m), 1.52—1.67 (1H, m), 1.90—2.55 (6H, m), 2.64 (1H, dd, J=18.7, 6.5 Hz), 3.16 (1H, m), and 5.47 (1H, dt, J=4.4, 1.5 Hz) for b-isomer; ^{13}C NMR δ=17.3, 19.5, 24.7, 26.6, 28.9, 33.5, 35.6, 41.8, 46.2, 58.6, 125.6, 133.4, 207.9, and 221.3 for a-isomer; 17.1, 20.8, 24.9, 26.7, 28.7, 33.6, 35.9, 41.7, 46.1, 58.5, 124.7, 134.9, 207.7, and 221.5 for b-isomer].

Protective Acetalization of 15 to ($5R^*$,$10S^*$)-3-(2-Methyl-1,3-dioxolan-2-yl)-6,10-dimethylspiro[4.5]deca-2,6-dien-1-one (17). An anhydrous benzene solution (100 cm^3) of **16** (140 mg), 1,2-ethanediol (3 cm^3), and TsOH (100 mg) was refluxed for 4 h. The mixture was then washed with aqueous Na_2CO_3 and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on a Florisil column to give **17** [a colorless oil, 160 mg, 95%. Found: C, 73.60: H, 8.40%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%. ^{1}H NMR δ=0.74 (3H, d, J=6.6 Hz), 1.30 (1H, m), 1.44 (3H, dt, J=2.5, 1.5 Hz), 1.55 (1H, m), 1.60 (3H, s), 1.95—2.25 (3H, m), 2.40 (1H, dd, J=19.4, 2.2 Hz), 2.67 (1H, dd, J=19.4, 1.8 Hz), 3.81—3.99 (2H, m), 4.02—4.12 (2H, m), 5.54 (1H, m), and 6.20 (1H, t, J=2.0 Hz); ^{13}C NMR δ=15.7, 18.9, 23.6, 25.6, 27.7, 35.6, 36.5, 57.6, 65.1 (2C), 107.1, 125.2, 130.5, 134.1, 180.0, and 213.9; MS m/z (%) 262 (M^+; 33), 274 (14), 122 (5), 107 (5), 91 (6), 87 (100), and 73 (10); IR ν=2960, 1704, 1624, 1452, 1166, 948, 873, and 798 cm^{-1}].

Conversion of 17 to an Allylic Alcohol (18) via LAH-Reduction. To an anhydrous ether solution (6 cm^3) of **17** (350 mg) was added LAH (230 mg) in portions at 0 °C and the mixture was kept stirred for 1 h. The mixture was then treated with EtOAc and filtered. The filtrate was heated in vacuo and chromatographed on an alumina column to afford **18** [a colorless oil, 225 mg, 63%. Found: C, 72.50; H, 8.91%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%. ^{1}H NMR δ=0.94 (3H, d, J=7.0 Hz), 1.46 (1H, m), 1.50 (3H, s), 1.69 (3H, dt, J=2.2, 1.5 Hz), 1.85—2.1 (5H, m), 2.28 (1H, dt, J=16.5, 2.3 Hz), 2.52 (1H, ddd, J=16.5, 2.1, 1.0 Hz), 3.86—4.05 (4H, m), 4.47 (1H, m), and 5.71 (2H, m); ^{13}C NMR δ=15.9, 21.1, 21.8, 23.7, 25.5, 38.6, 39.2, 56.0, 64.8, 65.0, 84.9, 107.1, 127.5, 129.7, 132.4, and 144.8; MS m/z (%) 264 (M^+; 33), 246 (46), 202 (50), 174 (12), 155 (32), 109 (23), and 87 (100); IR ν=3494, 2924, 1375, 1219, 987, 865, and 806 cm^{-1}].

Acetylation of 18 to 19. To a mixed solution of Ac_2O (1 cm^3) and pyridine (3 cm^3) was added **18** (50 mg). The solution was kept at room temperature for 24 h. The mixture was then evaporated in vacuo, and the residue was washed with aq $NaHCO_3$ and extracted with ether. The combined organic portion was chromatographed on a Florisil column to give **19** [a colorless oil, 52 mg, 89%. Found: C, 70.67; H, 8.48%. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55%. ^{1}H NMR δ=0.95 (3H, d, J=7.0 Hz), 1.32 (1H, m), 1.51 (3H, s), 1.68 (3H, td, J=1.8, 1.5 Hz), 1.68 (1H, m), 1.83—2.06 (3H, m), 2.00 (3H, s), 2.38 (1H, dt, J=17.0, 1.8 Hz), 2.40 (1H, dt, J=17.0, 1.8 Hz), 3.83—4.04 (4H, m), 5.46 (1H, m), 5.79 (1H, dd, J=4.4, 2.2 Hz), and 6.51 (1H, m); ^{13}C NMR δ=16.2, 21.2, 21.4, 22.9, 23.7, 26.9, 37.0, 37.9, 53.3, 64.8, 64.9, 86.2, 106.9, 124.1, 125.3, 134.4, 148.4, and 170.8; MS m/z (%) 306 (M^+; 5), 246 (92), 231 (100), 202 (12), 184 (13), 174 (14), and 159 (6); IR ν=2930, 1733, 1452, 1105, 949, 870, and 804 cm^{-1}].

Hydrolysis of 19 to α,β-Unsaturated Keto Acetate 20. An aqueous AcOH solution (1:4, 2 cm^3) of **19** (20 mg) was heated at 60 °C for 2 h. The mixture was poured into ice-cooled aq K_2CO_3, and extracted with EtOAc. The organic layer was washed with NaCl solution, dried over Na_2SO_4, and chromatographed on a silica-gel column to give **20** [a colorless oil, 18 mg, 96%. Found: C, 73.20; H, 8.28%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%. ^{1}H NMR δ=0.96 (3H, d, J=7.0 Hz), 1.31 (1H, m), 1.60 (3H, td, J=1.8, 1.5 Hz), 1.58—2.11 (4H, m), 2.05 (3H, s), 2.35 (3H, s), 2.51 (1H, dt, J=17.2, 2.2 Hz), 2.64 (1H, ddd, J=17.2, 2.2, 1.5 Hz), 5.46 (1H, m), 5.79 (1H, q, J=2.2 Hz), and 6.51 (1H, m); ^{13}C NMR δ=16.3, 21.2, 21.5, 22.8, 26.7, 26.9, 36.9 (2C), 53.1, 85.4, 124.8, 133.6, 139.6, 146.1, 170.7, and 196.6; MS m/z (%) 262 (M^+; 52), 202 (18), 159 (100), 122 (56), 108 (48), 93 (86), and 71 (54); IR ν=2924, 1741, 1676, 1452, 1231, 974, 841, and 805 cm^{-1}].

Reduction of 20 with Zn in AcOH to a Spirocyclic Dienone, ($5S^*$,$10S^*$)-3-Acetyl-6,10-dimethylspiro[4.5]deca-1,6-diene (21). To an AcOH solution (8 cm^3) of **20** (50 mg) was added Zn powder (400 mg), and the mixture was refluxed for 40 min. The mixture was then filtered, the residue was washed with ether, the combined organic solution was fractionated with ether and aqueous $NaHCO_3$, and the organic layer was evaporated in vacuo. The residue was chromatographed on a silica-gel column to give **21** [a colorless oil, 38 mg, 97%. ^{1}H NMR δ=0.74 (3H, d, J=7.0 Hz), 1.25—1.35 (1H, m), 1.48 (3H, m), 1.45—2.1 (6H, m), 2.12 (3H, s), 3.59 (1H, m), 5.35 (1H, m), 5.40 (1H, dd, J=5.5, 1.5 Hz), and 5.75 (1H, dd, J=5.5, 2.0 Hz) for a-isomer; 0.69 (3H, d, J=7.0 Hz), 1.21—1.35 (1H, m), 1.48 (3H, m), 1.4—2.1 (6H, m), 2.11 (3H, s), 3.47 (1H, m), 5.31 (1H, m), 5.39 (1H, dd, J=5.5, 1.3 Hz) and 5.76 (1H, dd, J=5.5, 2.0 Hz) for b-isomer; ^{13}C NMR δ=16.0, 20.5, 25.7, 27.7, 28.3, 31.3, 36.8, 57.3, 60.3, 122.3, 128.4, 138.4, 141.1,

and 208.6 for a-isomer; 16.4, 19.9, 25.0, 27.5, 28.3, 31.7, 36.6, 57.5, 60.1, 122.0, 127.7, 138.6, 140.8, and 209.0 for b-isomer].

Isomerization of 21 into an α,β-Unsaturated Ketone, (5S*,10S*)-2-Acetyl-6,10-dimethylspiro[4.5]-deca-2,6-diene (22). A toluene solution (25 cm^3) of **21** (38 mg) and TsOH (30 mg) was refluxed for 4 h. The mixture was then washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After removing the toluene in vacuo, the residue was chromatographed on a silica-gel column to give **22** [a yellow oil, 36 mg, 95%. ^1H NMR δ=0.85 (3H, d, J=7.0 Hz), 1.27—1.42 (1H, m), 1.45—1.75 (2H, m), 1.58 (3H, dt, J=1.8, 1.5 Hz), 1.94—2.0 (2H, m), 2.31 (3H, s), 2.35 (1H, d, J=16 Hz), 2.43 (1H, dm, J=19 Hz), 2.58 (1H, dm, J=16 Hz), 2.77 (1H, dm, J=19 Hz), 5.32 (1H, m), and 6.68 (1H, m); ^{13}C NMR δ=16.0, 19.3, 24.9, 26.5, 27.5, 37.5, 39.4, 44.9, 48.0, 121.9, 139.4, 143.5, 145.4, and 196.6; IR ν=1669, 1628, 1383, 1172, 981, 831, and 801 cm^{-1}].

Reduction of 22 with Zn in AcOH. Formation of 23. To an AcOH solution (3 cm^3) of **22** (24 mg) was added Zn powder (160 mg) and the mixture was, while stirring, refluxed for 0.5 h. The mixture was then filtered and the residue was washed with ether. The combined organic fractions were washed with aq Na_2CO_3, and the organic layer was evaporated in vacuo. The residue was chromatographed on a silica-gel column to afford **23** [a colorless oil, 16 mg, 66%. ^1H NMR δ=0.93 (3H, d, J=7.0 Hz), 1.67 (3H, m), 2.17 (3H, s), and 5.35 (1H, m) for a-isomer; 0.89 (3H, d, J=7.0 Hz), 1.68 (3H, m), 2.16 (3H, s), and 5.28 (1H, m) for b-isomer, together with common signals at 1.37—2.04 (11H, m), and 2.86—3.02 (1H, m); ^{13}C NMR δ=16.0, 20.5, 23.8, 27.6, 29.0, 29.1, 35.8, 36.9, 38.5, 49.4, 53.2, 122.5, 138.5, and 210.8 for a-isomer; 15.3, 19.7, 22.3, 27.3, 29.0, 29.4, 35.0, 36.2, 38.9, 49.1, 54.7, 121.5, 138.9, and 210.8 for b-isomer; IR ν=2920, 1737, 1453, 1240, 942, and 802 cm^{-1}].

Grignard Reaction of 23. Formation of 3 and 4. To a THF solution (1 cm^3) of **23** (16 mg) was added CH_3MgBr (0.3 cm^3 of 0.1 M hexane solution) at room temperature, and stirred for 0.5 h. The mixture was then treated with aq NH_4Cl, extracted with EtOAc, and washed with aq NaCl. The organic extract chromatographed on a silica-gel column to afford a 1 : 1-mixture of mixture **3** and **4**.

Separation of 3 and 4 via Phenylurethanes (24 and 25). A pyridine solution (1 cm^3) of the above mixture of **3** and **4** (8 mg) and PhNCO (46 mg) was stirred for 24 h under an N_2 atmosphere. The mixture was then heated in vacuo to remove the volatile material, and the residue (10 mg, 81%) was chromatographed on a silica-gel column with benzene. However, no indication of fractionation was observed.

Subsequently, the mixture was chromatographed on an $AgNO_3$-impregnated silica-gel column with hexane and EtOAc (15 : 1) as the eluate to afford a phenylurethane **24** [a colorless oil, 5.4 mg, 88%. ^1H NMR δ=0.92 (3H, d, J=6.6 Hz), 1.35—2.1 (11H, m), 1.54 (6H, s), 1.70 (3H, m), 2.37 (1H, m), 5.33 (1H, m), 6.37 (1H, br s), 7.03 (1H, t, J=7.2 Hz), and 7.25—7.4 (4H, m); ^{13}C NMR δ=15.4, 20.5, 22.5, 24.2, 24.4, 27.2, 27.7, 35.5, 38.5, 39.2, 48.1, 51.9, 84.2, 118.6, 118.7, 120.8, 123.1, 129.0 (2C), 138.3, 139.9, and 152.8] and another phenylurethane **25** [a colorless oil, 4.5 mg, 74%. ^1H NMR δ=0.94 (3H, d, J=6.6 Hz), 1.35—2.05 (11H, m), 2.37 (1H, m), 1.54 (6H, s), 1.70 (3H, dm, J=1.8 Hz), 2.48 (1H, m), 5.26 (1H, m), 6.37 (1H, br s, NH), 7.03 (1H, M), and 7.26—7.35 (4H, m); ^{13}C NMR δ=16.2, 19.9, 24.2, 24.3, 24.4, 27.7, 27.9, 33.1, 35.5, 36.6, 48.5, 50.3, 84.4, 118.7, 118.8, 121.9, 123.1, 129.0 (2C), 138.3, 139.8, and 152.8], respectively.

LAH-Reduction of 24 to 3. Similarly, a THF solution (5 cm^3) of **24** (3 mg) and LAH (50 mg) was refluxed for 3 h. The reaction mixture was then treated with EtOAc and filtered. The residue was washed with ether, and the filtrate was chromatographed on a silica-gel column to give **3** [a colorless oil, 3 mg, 92%. ^1H NMR δ=0.92 (3H, d, J=7.0 Hz), 1.21 (6H, s), 1.17—1.81 (10H, m), 1.68 (3H, m), 1.84—2.17 (3H, m), and 5.32 (1H, br s); ^{13}C NMR δ=15.3, 20.5, 22.5, 27.2, 27.6, 28.4, 29.7, 35.7, 38.7, 39.2, 48.4, 53.2, 71.9, 120.7, and 140.0].

LAH-Reduction of 25 to 4. A THF solution (5 cm^3) of **25** (5 mg) and LAH (50 mg) was refluxed for 3 h. The reaction mixture was then treated with EtOAc and filtered. The residue was washed with ether, and the filtrate was chromatographed on a silica-gel column to give **4** [a colorless oil, 2 mg, 92%. ^1H NMR δ=0.91 (3H, d, J=7.0 Hz), 1.21 (6H, s), 1.17—1.81 (10H, m), 1.68 (3H, m), 1.84—2.17 (3H, m), and 5.25 (1H, br s); ^{13}C NMR δ=16.2, 19.9, 24.2, 27.7, 28.0 (2C), 28.4, 33.3, 35.8, 36.7, 48.8, 51.4, 72.0, 121.7, and 140.0].

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