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Stereochemistry of the Intramolecular Cyclization Products of Methyl 2-Bromo-5-(4-hydroxyphenyl)hexanoate: Synthesis of *trans*- and *cis*-1,4-Dimethyltetralin

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The stereochemistry of the spirodienones (**2**) obtained by the intramolecular cyclization of methyl 2-bromo-5-(4-hydroxyphenyl)hexanoate (**1**) was established by carbon-13 nuclear magnetic resonance spectral analysis and chemical transformation to *trans*- and *cis*-1,4-dimethyltetralins (**6**).

Keywords——spirodienone; methyl 4-methyl-8-oxo-spiro[4.5]deca-6,9-diene-1-carboxylate; ^{13}C-NMR; γ-effect; envelope conformation; *trans*-1,4-dimethyltetralin; *cis*-1,4-dimethyltetralin; dienol–benzene rearrangement; base-induced isomerization

We previously synthesized some spirocyclic sesquiterpenes using spirodienone compounds as effective intermediates.[1] For our current research, we selected the spirodienone esters **2a** and **2b** (methyl 4-methyl-8-oxo-spiro[4.5]deca-6,9-diene-1-carboxylate) as possible intermediates for the synthesis of acorane-alaskane type sesquiterpenes, *e.g.*, α- and β-acorenol,[2] α- and β-acoradiene,[2] and acorenone.[3]

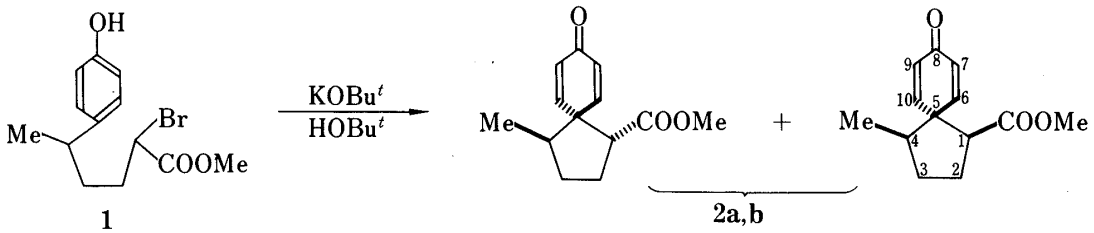


Chart 1

Compounds **2a** and **2b** have already been prepared as a mixture by the intramolecular cyclization of the phenolic bromo ester (**1**) by Corey *et al.*[4] Their stereochemistry was determined only from the base-induced isomerization without isolation of the two isomers: one (**2a**; δ 3.56 $COOCH_3$) isomerized to the other (**2b**; δ 3.45) on treatment with sodium methoxide in methanol; consequently, the latter was concluded to be the more stable *trans*-isomer.

It is known, however, that the *cis*-isomer is actually more stable than the *trans*-isomer in 1,3-dimethylcyclopentanes,[5] and in spiro[4.5]decane derivatives.[6] Thus, before addressing ourselves to the synthetic work, we prepared **2a** and **2b** according to the method of Corey and confirmed their stereochemistry. Though it was difficult to determine the stereochemistry of the *trans*- and *cis*-isomers from the proton nuclear magnetic resonance (^{1}H-NMR) spectra

TABLE I. ^{13}C-NMR Data (22.6 MHz, in $CDCl_3$) for the Spirodienones **2a** and **2b**

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C_1–CO	C_4–CH_3	OCH_3
2a	53.0	33.2	27.4	44.7	53.8	150.4[a]	129.7[b]	185.5	129.0[b]	150.9[a]	173.4	15.1	51.6
2b	54.7	31.2	25.1	46.3	55.6	146.6	130.3[c]	186.0	130.9[c]	153.8	171.8	14.3	51.5

a), *b*) and *c*) Assignments interchangeable.
Chemical shifts in ppm from tetramethylsilane.
Assignments were made with the aid of the off-resonance technique and by reference to the literature.[7]

(see Experimental), the difference between them was clearly seen in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra (see Table I).

It is well known that steric compression shifts, especially γ-effects, in ^{13}C-NMR are of great use in the establishment of stereochemistry.[7] Carbon-6 in the *cis*-isomer ought to be affected by the two substituents on the cyclopentane ring, and its chemical shift should therefore lie at a somewhat higher field than that of C-10. The difference in chemical shifts of C-6 and C-10 in the unstable isomer, **2a**, is only 0.5 ppm, whereas the difference in the stable isomer, **2b**, is over 7 ppm. While C-6 of **2b** shows an upfield shift (*ca.* 4 ppm) in comparison with that of **2a**, C-10 of **2b** shows a down field shift (*ca.* 3 ppm), probably because of loss of γ-effects. These data show that the stable isomer, **2b**, is *cis*. However, this result does not agree with the assignment of Corey. Accordingly, we confirmed the accuracy of our assignment by the chemical transformation as follows. (Chart 2: This is drawn on the presumption that **2a** is *trans* and **2b** is *cis*.)

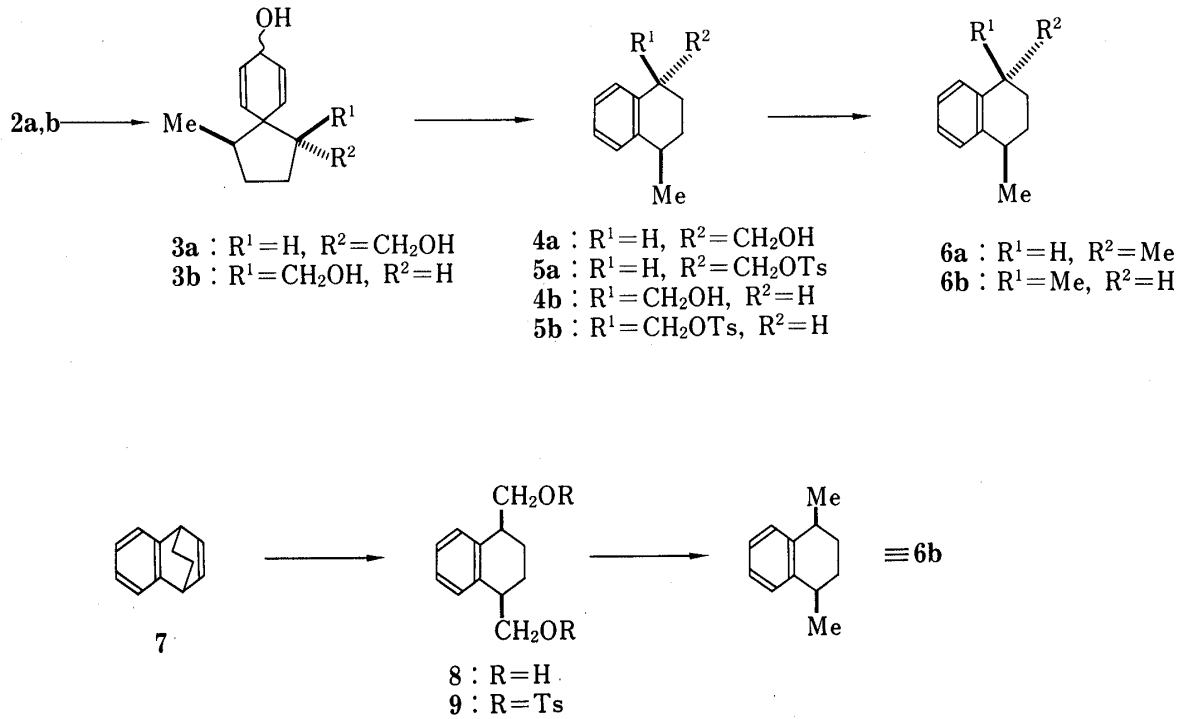
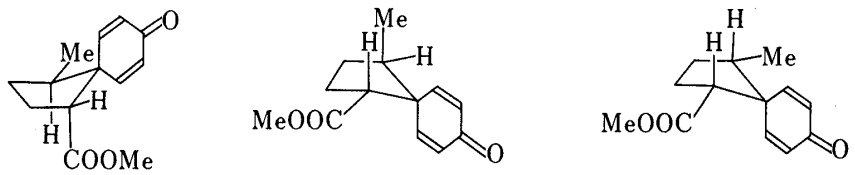


Chart 2

Lithium aluminum hydride (LAH) reduction of **2a** and **2b** gave the unstable dienic diols **3a** and **3b**, respectively, each of which was a diastereomeric mixture with regard to the configuration of the hydroxyl on the six-membered ring. Compounds **3a** and **3b** were smoothly converted to the hydroxymethyltetralin derivatives **4a** and **4b** by the dienol–benzene

rearrangement (*p*-TsOH/MeOH), and the latter compounds were tosylated to give **5a** and **5b**, respectively. Finally 1,4-dimethyltetralins **6a** and **6b** were obtained by LAH reduction of **5**. Compounds **6a** and **6b** thus obtained are mutually exclusive.

Because very little is known about the stereochemistry of 1,4-dimethyltetralins,[8] we prepared *cis*-1,4-dimethyltetralin stereoselectively by an unambiguous route. Ozonolysis of benzobicyclo[2.2.2]octadiene (**7**)[9] and subsequent direct sodium borohydride reduction of the resulting ozonide afforded *cis*-1,4-bis(hydroxymethyl)tetralin (**8**). Tosylation of **8** followed by LAH reduction gave *cis*-1,4-dimethyltetralin, which was identical to **6b** in infrared (IR) and ^{1}H-NMR spectra. Consequently, it is evident that **2a** is *trans* and **2b** is *cis*.[10] The ^{1}H-NMR signals for the two methyl groups in **6a** and **6b** appeared equivalently, at δ 1.24 and 1.27, respectively, in carbon tetrachloride.



I II III

Chart 3

When the cyclopentane ring in the *trans*-isomer adopts the envelope conformation[5b] in which the spiro carbon occupies the tip of the flap, either the methyl or the methoxycarbonyl group takes an axial orientation (probably in equilibrium between conformers I and II in Chart 3). On the other hand, the *cis*-isomer preferentially takes the envelope conformation III in which two substituents occupy the equatorial positions. This conformation is probably the most stable among all conformations, including those of the *trans*-isomer. The result of the isomerization experiments and the higher field shifts (γ-effects) in the ^{13}C-NMR due to C-1 and C-4 in the *trans*-isomer are in good accordance with these considerations.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi 124 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Hitachi R-22 (90 MHz) and Hitachi R-900 (22.6 MHz), respectively, with tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. Electron-impact mass spectra (EI-MS), chemical ionization mass spectra (CI-MS), and high resolution mass spectra (High-MS) were obtained with a JEOL JMS-D300 mass spectrometer. For preparative thin layer chromatography (PTLC) and column chromatography, Merck Kieselgel PF_{254} and Merck Kieselgel 60 (70—230 mesh) were used, respectively.

Methyl (1*R, 4*R**)-4-Methyl-8-oxo-spiro[4.5]deca-6,9-diene-1-carboxylate (2a) and Methyl (1*R**, 4*S**)-4-Methyl-8-oxo-spiro[4.5]deca-6,9-diene-1-carboxylate (2b)**——Compounds **2a** and **2b** were prepared according to the method of Corey.[4] The phenolic α-bromo ester (**1**) was treated with 1.2 eq of *tert*-BuOK in *tert*-BuOH at 60 °C for 2 h to give a mixture of **2a** and **2b** in 60% yield as a *ca.* 1 : 1 mixture, which was separated on a Lobar column (*n*-hexane : AcOEt = 5 : 1). Compound **2a** was almost wholly converted to **2b** by treatment with a catalytic amount of NaOMe in MeOH at 50 °C for 1.5 h. Prolonged treatment resulted in a decrease of recovery of the dienones. **2a** IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1670, 1630. UV λ_{max}^{EtOH} nm (ε): 242 (13,900). ^{1}H-NMR (CCl_4) δ: 0.86 (3H, d, J = 7, C_4–CH_3), 1.4—2.7 (5H, m), 2.91 (1H, br t, J = 6.5, C_1–H), 3.59 (3H, s, OCH_3), 6.0—6.9 (4H, m, olefinic protons). MS *m/z*: 220 (M^+). **2b** IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1670, 1630. UV λ_{max}^{EtOH} nm (ε): 243 (14,000). ^{1}H-NMR (CCl_4) δ: 0.79 (3H, d, J = 6, C_4–CH_3), 1.4—2.6 (5H, m), 3.01 (1H, br t, J = 9, C_1–H), 3.48 (3H, s, OCH_3), 5.9—6.8 (4H, m, olefinic protons). MS *m/z*: 220 (M^+).

(1*R, 4*R**)-1-Hydroxymethyl-4-methyl-1,2,3,4-tetrahydronaphthalene (4a)**——An ether solution of **2a** (153 mg) was added to a stirred suspension of LAH (80 mg) and dry ether (20 ml) at 0 °C, and the mixture was stirred for 1 h at 0 °C. After the addition of ether (20 ml), sat. Rochelle salt solution was slowly added in small portions to the well-stirred reaction mixture until the greyish precipitates turned white. The ether layer separated by decantation was dried

over a mixture of Na_2SO_4 and $CaCO_3$, and evaporated under reduced pressure at room temperature to give a crude unstable dienic diol **3a**. Compound **3a**, without purification, was treated with a catalytic amount of *p*-TsOH in MeOH (5 ml) at room temperature for 3 h. Sat. $NaHCO_3$ solution (5 ml) was added to the reaction mixture. After removal of the MeOH under reduced pressure, the residue was extracted with AcOEt. The extract was washed, dried and evaporated, and the product was purified by PTLC (*n*-hexane: AcOEt = 5 : 1) to give **4a** (91 mg) as a colorless oil in 74% yield. **3a** IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3420. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.83 (each d, J=7, total 3H), 1.0—2.4 (m), 3.2—3.8 (2H, m), 4.43 (1H, m), 5.4—6.1 (4H, m). **4a** $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3400, 1490, 1030. ^{1}H-NMR ($CDCl_4$) δ: 1.23 (3H, d, J=7, C_4–CH_3), 1.3—2.2 (4H, m, –CH_2CH_2–), 2.64 (1H, s, OH), 2.6—3.0 (2H, m, benzylic methine protons), 3.55 (2H, d, J=6, –$C\underline{H}_2$OH), 6.96 (4H, s-like, aromatic protons). MS *m/z*: 176 (M^+), 145 (base). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.82; H, 9.21.

(1*R, 4*S**)-1-Hydroxymethyl-4-methyl-1,2,3,4-tetrahydronaphthalene (4b)**——Compound **4b** was prepared in a manner similar to that described for **4a** from **2b** *via* **3b** as a colorless oil in 84% yield. **3b** IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400. ^{1}H-NMR ($CDCl_3$) δ: 0.71, 0.76 (each d, J=7, total 3H), 1.1—2.4 (m), 3.4—3.6 (2H, m), 3.53 (2H, s), 4.47 (1H, m), 5.4—6.2 (4H, m). **4b** IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3410, 1490, 1035. ^{1}H-NMR (CCl_4) δ: 1.25 (3H, d, J=7, C_4–CH_3), 1.4—2.1 (4H, m, –CH_2CH_2–), 2.35 (1H, s, OH), 2.56—3.00 (2H, m, benzylic methine protons), 3.64 (2H, d, J=6, –$C\underline{H}_2$OH), 6.8—7.2 (4H, m, aromatic protons). MS *m/z*: 176 (M^+), 145 (base). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.66; H, 9.26.

(1*R, 4*R**)-4-Methyl-1,2,3,4-tetrahydro-1-*p*-toluenesulfonyloxymethylnaphthalene (5a) and (1*R**, 4*S**)-4-Methyl-1,2,3,4-tetrahydro-1-*p*-toluenesulfonyloxymethylnaphthalene (5b)**——Tosylation of **4a** and **4b** was performed in the usual way (2 eq of *p*-TsCl in pyridine). The crude products were purified by PTLC (*n*-hexane : AcOEt = 1 : 1) to give **5a** (92%) and **5b** (89%), respectively. **5a** IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1600, 1495, 1375, 1195, 1180. ^{1}H-NMR (CCl_4) δ: 1.19 (3H, d, J=7, C_4–CH_3), 1.3—2.1 (4H, m, –CH_2CH_2–), 2.36 (3H, s, Ar–CH_3), 2.6—3.2 (2H, m, benzylic methine protons), 3.75—4.15 (2H, AB in ABX, –CH_2OTs), 6.75—7.05 (4H, m, aromatic protons), 7.1—7.7 (4H, AA′BB′ type aromatic protons). MS *m/z*: 330 (M^+), 158 (base). High-MS *m/z*: 330.1299 (M^+, Calcd for $C_{19}H_{22}O_3S$: 330.1291). **5b** IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1610, 1500, 1380, 1200, 1190. ^{1}H-NMR (CCl_4) δ: 1.22 (3H, d, J=7, C_4–CH_3), 1.3—2.0 (4H, m, –CH_2CH_2–), 2.40 (3H, s, Ar-CH_3), 2.6—3.2 (2H, m, benzylic methine protons), 3.82—4.21 (2H, AB in ABX, –CH_2OTs), 6.8—7.1 (4H, m, aromatic protons), 7.1—7.7 (4H, AA′BB′ type aromatic protons). MS *m/z*: 330 (M^+), 145 (base). High-MS *m/z*: 330.1303 (M^+, Calcd for $C_{19}H_{22}O_3S$: 330.1291).

(1*R, 4*R**)-1,4-Dimethyl-1,2,3,4-tetrahydronaphthalene (6a)**——A solution of **5a** (96 mg) in dry ether (5 ml) was added to a suspension of LAH (33 mg) and dry ether (20 ml), and the mixture was refluxed for 4 h under stirring. After work-up similar to that described for **4a** and purification by PTLC (*n*-hexane), **6a** was obtained in 91% yield (43 mg) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3050, 3010, 2950, 2930, 2860, 1490, 1465, 1440, 1375, 1030, 665. ^{1}H-NMR (CCl_4) δ: 1.24 (6H, d, J=7, CH_3 ×2), 1.2—1.8, 1.8—2.3 (each 2H, m, –CH_2CH_2–), 2.84 (2H, m, benzylic methine protons), 6.94 (4H, s-like, aromatic protons). MS *m/z*: 160 (M^+), 118 (base). High-MS *m/z*: 160.1237 (M^+, Calcd for $C_{12}H_{16}$: 160.1253).

(1*R, 4*S**)-1,4-Dimethyl-1,2,3,4-tetrahydronaphthalene (6b)**——Compound **6b** was prepared in a manner similar to that described for **6a** from **5b** in 84% yield as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3080, 3040, 2980, 2950, 2880, 1500, 1475, 1465, 1455, 1385, 1035, 715, 675. ^{1}H-NMR (CCl_4) δ: 1.27 (6H, d, J=7, CH_3 ×2), 1.4—2.1 (4H, m, –CH_2CH_2–), 2.80 (2H, m, benzylic methine protons), 6.7—7.1 (4H, m, aromatic protons). MS *m/z*: 160 (M^+), 117 (base). High-MS *m/z*: 160.1253 (M^+, Calcd for $C_{12}H_{16}$: 160.1253).

(1*R, 4*R**)-1,4-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (8)**——Dry ozone produced by passing oxygen through an ozonizer was introduced into a solution of benzobicyclo[2.2.2]octadiene (**7**; 914 mg) in dry ether (10 ml) and absolute MeOH (20 ml) at 0 °C until the starting material was no longer detectable on TLC. Then the excess ozone was removed by flushing the reaction mixture with dry N_2. $NaBH_4$ (1.1 g) was added at 0 °C, and the mixture was stirred overnight. Acetic acid and water were added to the mixture, and the MeOH was removed under reduced pressure. The residue was extracted with AcOEt, and the extract was washed with sat. $NaHCO_3$ and sat. NaCl, then dried, and evaporated. The residue was purified by column chromatography ($CHCl_3$: MeOH = 7 : 1) to give **8** (889 mg) in 79% yield as colorless crystals (mp 80—81 °C from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3420, 1495, 1035. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (4H, m, –CH_2CH_2–), 2.83 (2H, s, OH), 2.88 (2H, m, benzylic methine protons), 3.74 (4H, d, J=6, –$C\underline{H}_2$OH ×2), 6.8—7.5 (4H, m, aromatic protons). MS *m/z*: 192 (M^+), 143 (base). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.11; H, 8.39.

(1*R, 4*S**)-1,4-Bis(*p*-toluenesulfonyloxymethyl)-1,2,3,4-tetrahydronaphthalene (9)**——Tosylation of **8** was performed in the usual way using 6 eq of *p*-TsCl. The crude product was purified by PTLC ($CHCl_3$) to give **9** in 90% yield as colorless crystals (mp 105—106 °C from cyclohexane–benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605, 1500, 1375, 1195, 1180. ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.99 (4H, m, –CH_2CH_2–), 2.42 (6H, s, Ar-CH_3 ×2), 3.07 (2H, m, benzylic methine protons), 3.88—4.29 (4H, AB in ABX, –CH_2OTs ×2), 6.99 (4H, s-like, aromatic protons), 7.15—7.73 (8H, AA′BB′ type aromatic protons ×2). CI-MS *m/z*: 501 ($M^+ + 1$), 157 (base). *Anal.* Calcd for $C_{26}H_{28}O_6S_2$: C, 62.39; H, 5.64; S, 12.79. Found: C, 62.39; H, 5.64; S, 12.72.

***cis*-1,4-Dimethyltetralin**——LAH (6 eq) reduction of **9** in tetrahydrofuran (THF) was performed in a manner similar to that described for **5a** to give *cis*-1,4-dimethyltetralin in 80% yield. This product was identical with **6b** on the

basis of the IR and ^{1}H-NMR spectra.

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