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SYNTHESIS OF SEX PHEROMONES OF THE JAPANESE BEETLE AND CUPREUS CHAFER BEETLE

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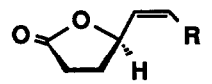
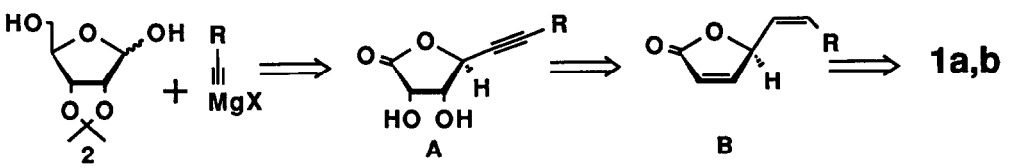
Abstract: The pheromones (**1a**,**1b**) of two insect pests, the Japanese Beetle (*Popillia japonica*, Newman) and Cupreus Chafer Beetle (*Anomala cuprea* , Hope), were synthesized. Starting from protected D-Ribose, **1a** was prepared in 8 steps with a 30% total yield. The same chemistry was demonstrated for the synthesis of **1b**.

The Japanese beetle (*Popillia japonica*, Newman) is a major insect pest of crops and various vegetables. In 1977, Tumlinson *et al.*[1] elucidated and synthesized its sex pheromone (**1a**, Japonilure). They also found that its bio-activity was dependent on the very strict enantiomeric purity of **1a**. Recently, Leal determined the structure of the sex pheromone of the cupreus chafer beetle (*Anomala cuprea* , Hope), which is also a major insect pest of vegetables in Japan, to be **1b**.[2] It is quite interesting that these two serious pests have very similar molecules as their sex pheromones. Even though several syntheses of **1a**[1,3,4,5,7,8,14] and **1b**[2,6] have been reported, it still remains a challenging task to synthesize an enantiomeric pure compound.[7]



1a; R=n-C_8H_{17}
b; n-C_6H_{13}

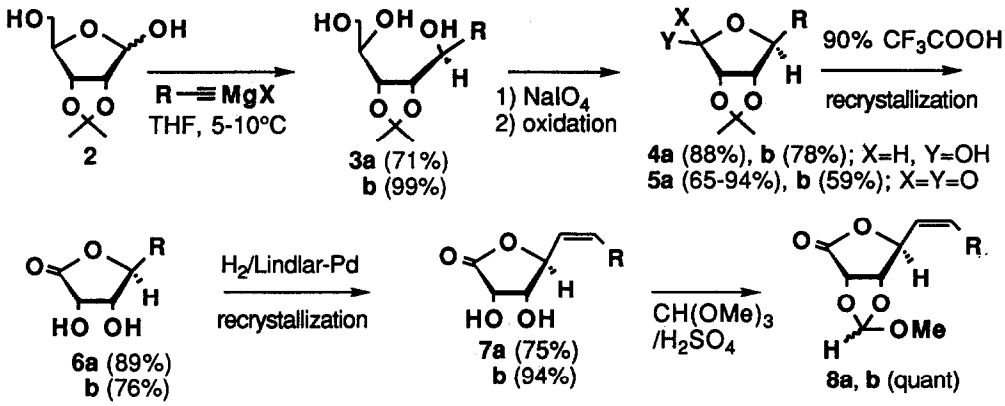


Scheme 1

As shown in Scheme 1, we planned to employ **B**[8] as a key compound in our synthesis. The required stereochemistry for this system could be prepared by coupling an acetylide anion with 2,3-protected-D-ribose. This strategy could be applied to the synthesis of **1b** as well.

Using the method of Levene *et al.*,[9] the 2,3-hydroxyl groups of the starting material, D-ribose, were protected as dimethylacetal. Thus, 2,3-isopropylydene-D-ribose **2** was treated with 1-decynylmagnesium bromide in THF at 5-10°C to give **3a**. The NMR analysis of the resultant tri-ol **3a** showed a spectrum of only a single isomer. Mori and Kikuchi[10] also reported that the selectivity of the coupling reaction with MeMgI and 2,3-cyclohexylydene-D-ribose was very high by virtue of the bulky cyclohexylydene group. The terminal diol

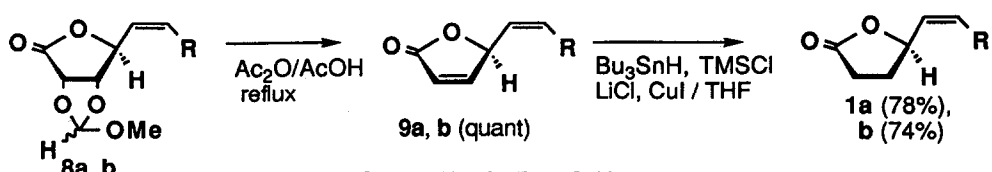
of **3a** was cleaved with sodium periodate to give lactol **4a**. In the same way, **4b** was prepared from 1-octyne and **2**. The lactol **4a** was oxidized into lactone **5a** with silver carbonate on celite (Fétizon reagent)[11]. An oxidation employing DMSO, which would be more suitable for large scale preparation, was also demonstrated. For the conversion of **4b** into **5b**, it was possible to use PDC.



3a-8a; R=n-C_8H_{17}, **3b-8b**; R=n-C_6H_{13}

Scheme 2

The lactones **5a,b** were carefully checked by NMR and TLC and they were found to be diastereomerically pure. The isopropylidene group was removed with trifluoroacetic acid/water to furnish the diol **6a** which formed crystals in a mixed solvent of diisopropyl ether and hexane. Semihydrogenation of the triple bond was performed with Pb poisoned Pd-$CaCO_3$ (Lindlar catalyst). The resulting (5*Z*)-diol **7a** was recrystallized in the same solvent system. In the case of **6b** and **7b**, recrystallization was carried out in a mixed solvent of hexane and dichloromethane. The next task in our synthesis was the deoxygenation of the 2,3-hydroxyl groups, which had served as a chiral auxiliary for the stereochemistry of the C4 position. We employed the method of Eastwood.[12] Thus, diols **7a, b** were converted to orthoesters **8a, b** using trimethyl orthoformate. Orthoesters **8a, b** were treated with acetic anhydride/acetic acid under mild reflux for several hours to afford the diene-lactones **9a, b** (=**B**). Although usual operations at room temperature were possible for **9a**, the silica-gel column chromatography of **9a** produced a significant amount of a double bond-migrated compound.



8a-1a; R=n-C_8H_{17}, **8b-1b**; R=n-C_6H_{13}

Scheme 3

With the key compound in hand, we turned our attention to the final task. We examined Midland's original conditions (Red-Al™/CuBr)[8], a combination of triethylsilane and Wilkinson's catalyst[15], and a hydridohalocuprate (*n*-Bu3SnH/CuI/LiCl/TMSCl) developed by Lipshutz *et al.*.[13] The best results were obtained from the reduction with the hydridohalocuprate. Thus, a pure Japonilure **1a** (78% yield, $[\alpha]_D$ -71.0°; the following numbers have been reported previously;[3] -63.1°, -68.1°, -69.7°, -69.93°, -70.0°, -70.4°, -70.82°, -73.9°) was successfully obtained from **9a**, and **1b** (74%, $[\alpha]_D$ -79.5°; reported[6] -80.9°) from **9b**.

The enantiomeric purity was unambiguously determined by GLC analysis with a column employing a chiral stationally phase (Chiraldex G-TA™, ASTEC) which had been used in the analysis of **1b**.[2] Our **1b** showed only one peak corresponding to the (*R*)-enantiomer and no detectable antipode peak. The Japonilure **1a** was also successfully separated on the same column at an elevated oven temperature and our sample of **1a** gave a single peak of only the (*R*)-enantiomer.

In conclusion, we have established a new preparation method for the (*R*, *Z*)-5-alkene-4-olide system with high optical purity.

EXPERIMENTAL

IR spectra were recorded on a JASCO FTIR 5000 spectrometer. ^{1}H-NMR spectra (300MHz) were obtained on a Bruker AC-300P in a $CDCl_3$ solution. Specific rotations were measured on a JASCO DIP-370. Melting points were measured on a Yanagimoto micro melting point apparatus or a Mitamura rikagaku photometry Auto-Melt-pointer. Silica-gel column chromatography was performed using Merck Kieselgel 60 (70-230 or 230-400 mesh for flush chromatography). GLC analyses were performed on a Shimadzu GC-14A.

(2*S*, 3*R*, 4*S*, 5*S*)-2,5-dihydroxy-3,4-isopropylidenedioxy-pentadec-6-yn-1-ol, 3a: Under a N_2 stream, 1-decyne (52ml, 288mmol) in THF (50ml) was added to ethylmagnesium bromide (1M in THF, 240ml) at 30°C over a period of 1hr. After stirring for 1hr at room temperature, the mixture was cooled to 0°C and 2,3- *O*-isopropyridene ribose (15g, 78.9mmol) n THF (50ml) was added iat 5-10°C. After the reaction mixture was stirred for 2hr at 5°C, it was added to NH_4Cl soln and extracted 3 times with ether. The combined ether layer was washed with water and brine and dried ($MgSO_4$). Solvent and residual 1-decyne were removed under a reduced pressure to give **3a** as a very viscous oil (15.7g, 70.9%), $n_D^{22.5}$ 1.4754; $[\alpha]_D^{22}$ (c=1.955, $CHCl_3$); ν max 3360 (s), 2988(m), 2930(s), 2860(s), 1222(s), 1075(s)cm^{-1}; δ 0.82 (3H, t, *J*=6.0 Hz), 1.20-1.40 (10H), 1.36 (3H, s), 1.42 (3H, s), 1.49 (2H, m), 2.24 (2H, ddd, *J*=1.9, 7.0, 7.0Hz), 3.68 (1H, dd, *J*=5.9, 11.2Hz), 3.85 (1H, dd, *J*=3.4, 11.2Hz), 3.92 (1H, ddd, *J*=3.4, 5.9, 9.2Hz).

(3*S*, 4*S*, 5*S*)-5-(1'-decynyl)-2-hydroxy-3,4-isopropylidenedioxytetrahydrofuran, 4a: An ether (50ml) soln of compound **3a** (15.7g, 47.8mmol) and 10% $NaIO_4$ soln (200ml) was vigorously stirred for 2hr at room temperature. The ether layer was separated and the aqueous layer was extracted 3 times with ether. The combined ether layer was washed with water and brine and dried ($MgSO_4$). The removal of solvent under reduced pressure afforded compound **4a** (12.46g, 88%) as a viscous oil, $n_D^{22.5}$ 1.4686; $[\alpha]_D^{22.5}$ -4.0° (c=1.487, $CHCl_3$); ν max. 3340(s), 2926(s), 2860(s), 1071(s), 1035(s) cm^{-1}; δ 0.88 (3H, t, *J*=6.6 Hz), 1.20-1.40 (12H), 1.4-1.55 (2H, m), 2.17 (2H, m), the following signals were separated due to

two diastereomers, a) 1.32, 1.46 (3H, s), 4.74, 4.89 (1H, d, *J*=5.8Hz), 4.66 (1H, br s), 5.43 (1H, d, *J*=3.5Hz), b) 1.35, 1.53 (3H, s), 4.59 (1H, d, *J*=3.5, 7.0Hz), 4.66 (1H, br s), 5.32 (1H, d, *J*=3.5Hz); (Found: C, 68.60; H, 9.72%. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52%).

(2*S*, 3*R*, 4*S*)-2,3-isopropylidenedioxy-5-tetradecyn-4-olide, 5a: a) One gram of Fétizon's reagent was placed in benzene (15ml) and the water was azeotropicaly removed with benzene (10ml). To this, 4a (91mg, 0.31mmol) was added and the reaction mixture was refluxed for 8.5hr. The mixture was filtered through a celite pad and the filtrate was condensed *in vacuo* to give 5a (85mg, 94%) as a very viscous oil, $[\alpha]_D^{22.7}$ 19.5° (c=1.85, $CHCl_3$); ν max. 2994(s), 2932(s), 1798(s), 1752(s), 1226(s), 1164(s), 1151(s), 1100(s) cm^{-1}; δ 0.88 (3H, dd, *J*=7.0, 7.0Hz), 1.20-1.40 (10H), 1.45-1.55 (2H, m), 1.39 and 1.46 (3H, s), 2.21 (2H, ddd, *J*= 2.2, 7.2, 7.2Hz), 4.75 (1H, dd, *J*= 0.4, 5.2Hz), 4.86 (1H, d, *J*= 5.2Hz), 5.14 (1H, ddd, *J*= 0.4, 0.4, 1.7Hz); (Found: C, 69.31; H, 8.67%. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%).

b) To a soln of compound **4a** (13.27g, 44.8mmol) in DMSO (40ml) was added acetic anhydride (40ml). The mixture was stirred at room temperature overnight. When the starting material disappeared on TLC analysis, water (300ml) was added and the mixture was extracted 3 times with ether. The ether layer was washed with water, brine , dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica-gel to give lactone **5a** (7.35g, 65% yield)

(2*S*, 3*R*, 4*S*)-2,3-dihydroxy-5-tetradecyn-4-olide, 6a: To the acetonide lactone **5a** (5.87g, 23.3mmol) was added 90% trifluoroacetic acid (200ml) and the mixture was stirred at room temperature for 15 min. Trifluoroacetic acid was removed *in vacuo*. The residue was dissolved in ether and washed with $NaHCO_3$ soln, water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallized (hexane: diisopropyl ether=75:55, 130ml) to give diol **6a** (4.84g, 89% yield) as colorless, very fine needles, mp 97.5-98.0°C; $[\alpha]_D^{22}$ -63.4° (c=1.03, $CHCl_3$); ν max. 2994(s), 2932(s), 1798(s), 1752(s), 1226(s), 1164(s), 1151(s), 1100(s) cm^{-1}; δ 0.88 (3H, t, *J*=7.0 Hz), 1.20-1.40 (10H), 1.45-1.55 (2H, m), 1.39 and 1.46 (3H, s), 2.21 (2H, dt, *J*= 2.2, 7.2Hz), 4.75 (1H, dd, *J*= 0.4, 5.2Hz), 4.86 (1H, d, *J*= 5.2Hz), 5.14 (1H, td, *J*= 0.4, 1.7Hz); (Found: C, 66.06; H, 8.73%. Calcd. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72%).

(2*S*, 3*R*, 4*S*, 5*Z*)-2,3-dihydroxy-5-tetradecen-4-olide, 7a: To the compound **6a** (1.924g, 7.58mmol) in EtOH (20ml) was added Pb poisoned 5%-Pd/$CaCO_3$ (Lindlar catalyst, 40mg). The mixture was vigorously stirred under a H_2 atmosphere. After consumption of H_2 had ceased, the soln was filtered through a celite pad. The filtrate was concentrated *in vacuo*. Recrystallization (hexane: diisopropylether=20:30, 50ml) provided **7a** as colorless very fine needles (1.45g, 74.6% yield), mp 73.0-73.5°C; $[\alpha]_D^{23}$ -90.4° (c=0.979, $CHCl_3$); ν max. (KBr disk), 3420, 3300(br s), 2958(s), 2928(s), 2856(s), 1660(w), 1756(s), 1466, 1431(w), 1185(s), 1156(s), 922(s) cm^{-1}; δ 0.88 (3H, t, *J*=7.0 Hz), 1.20-1.50 (12H), 2.1-2.25 (2H, m), 4.22 (1H, d, *J*=4.7Hz), 4.53 (1H, d, *J*= 4.7Hz), 5.23 (1H, d, *J*=9.2Hz), 5.31 (1H, dddd, *J*=10.4, 9.0, 1.4, 1.4Hz), 5.75 (1H, ddd, *J*= 10.4, 7.8, 7.8Hz); (Found: C, 65.49; H, 9.48%. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44%).

(2*S*, 3*R*, 4*S*, 5*Z*)-2,3-methoxymethylidenedioxy-5-tetradecen-4-olide, 8a: To a soln of **7a** (598mg, 2.33mmol) in trimethyl orthoformate (10ml) was added conc. H_2SO_4 (2μl). The mixture was stirred

for 15 min. at room temperature. The reaction mixture was diluted with ether, washed with $NaHCO_3$ soln, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Compound **8a** was obtained as a colorless oil (770mg, quantitative) and subjected to the next reaction without further purification, n_D^{24} 1.4666; $[\alpha]_D^{24}$ -81.4° (c=0.950, $CHCl_3$); ν max. 2926(s), 2858(s), 1787(s), 1660(w), 1195(s), 1123(s), 1077(s), 984(s), 977(s) cm^{-1}; δ 0.88 (3H, t, *J*=7.0 Hz), 1.20-1.50 (12H), 2.15-2.25 (2H, m), the following signals were separated due to two diastereomers; a) 3.32 (3H, s), 4.52 (1H, dd, *J*= 0.85, 6.5Hz), 4.84 (1H, d, *J*=6.5Hz), 5.31 (1H, d, *J*=10.7Hz), 5.41 (1H, br d, *J*=9.2Hz), 5.77 (1H, dddd, *J*=1.0, 7.5, 7.5, 10.7Hz), 5.90 (1H, br s), b) 3.36 (3H, s), 4.67 (1H, d, *J*=5.5Hz), 4.92 (1H, d, *J*=5.5Hz), 5.25-5.34 (3H), 5.91 (1H, br s); (Found: C, 64.10; H, 9.03%. Calcd. for $C_{16}H_{26}O_5$: C, 64.41; H, 8.71%).

(4*S*, 5*Z*)-tetradeca-2,5-dien-4-olide, 9a: A soln of orthoester **8a** (1.23g, 4.80mmol) in acetic anhydride (21ml) and acetic acid (864μl) was gently refluxed until TLC showed no starting **8a**. The soln was concentrated *in vacuo* and **9a** was obtained as a slightly yellow oil (1.21g, quantitative) which was immediately subjected to the next step without purification, ν max. 2926(s), 2860(s), 1794(s), 1760(s), 1480(m), 1156(s), 1094(s), 1019(s), 818(s) cm^{-1}; δ 0.88 (3H, t, *J*=6.5Hz), 1.25-1.50 (12H), 2.1-2.35 (2H, m), 5.14 (1H, dddd, *J*=1.6, 1.6, 9.1, 9.1Hz), 5.8 (2H, m), 6.14 (1H, dd, *J*=2.0, 5.6Hz), 7.33 (1H, dd, *J*=1.6, 5.6Hz).

(*R*, *Z*)-5-tetradecen-4-olide, Japonilure, 1a:

a) with hydridohalocuprate: Cuprous iodide (570mg, 3.0mmol) and LiCl (dried at 130°C *in vacuo*, 318mg, 7.5mmol) were dissolved in THF (10ml) under an Ar stream. After stirring for 30min at room temperature, the mixture was cooled to -60°C and to this was added diene **9a** (336mg, 1.51mmol) in THF (3.5ml) followed by TMSCl (0.8ml, 6mmol). After stirring for 10min, n-Bu_3SnH (freshly distilled, 1.5ml, 5.5mmol) was added over a period of 5min. The reaction mixture was allowed to warm to 0°C during the next 30min. To this, 10% KF soln (20ml) was added and the mixture was stirred for 15min. The reaction mixture was filtered through a celite pad. The filtrate was extracted with THF and the combined THF layers were concentrated *in vacuo*. The residue was stirred with 10% KF soln (30ml) for 15min then ether was added and the mixture was stirred for an additional 15min. The mixture was filtered through a celite pad and the filtrate was extracted twice with ether and the combined ether layer was washed with water, brine and dried ($MgSO_4$). Solvent was removed *in vacuo* and the residue was chromatographed over silica-gel (270-400mesh, 10g, n-hexane ethyl acetate=98:2-96:4) to give pure Japonilure (265mg, 78% yield). The IR and NMR spectra were identical to reported data.[3] n_D^{22} 1.4666; $[\alpha]_D^{26}$ -71.0° (c=5.387, $CHCl_3$); (Found: C, 74.82; H, 10.86%. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%).

b) with Red-Al™ and cuprous bromide: A soln of Red-Al™ (3.4M in toluene, 1.05ml, 3.56mmol) was added dropwise to a suspension of cuprous bromide (511mg, 3.56mmol) in THF (8.9ml) under an Ar stream at 0°C. 2-Butanol (1.23ml) was then added all at once followed by **9a** (102mg, 0.46mmol) in THF (1.6ml). After 10min at -78°C, the mixture was stirred at - 20°C for 1hr, quenched by the addition of water (1ml), and poured into sat. NH_4Cl soln. The mixture was extracted with ether twice and the combined ether layers were washed with water, brine and dried ($MgSO_4$). Solvent was removed *in vacuo* and the residue was chromatographed over silica-gel (270-400mesh, 10g, n-hexane ethyl acetate=96:4-90:10) to give **1a** (75mg, 73% yield); $[\alpha]_D^{26}$ -67.1° (c=0.98, $CHCl_3$). The IR and NMR spectra were identical to reported data.[3]

c) with triethylsilane and Wilkinson's catalyst: Tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst, 38mg, 0.023mmol) was added to a soln of 9a (180mg, 0.81mmol) and Et_3SiH (155μl, 0.972mmol) in benzene (3ml) under an Ar stream. After stirring at 65°C for 75min, the mixture was directly subjected to silica-gel chromatography (270-400mesh, 10g, n-hexane ethyl acetate=96:4-92:8). Thirteen mg of **1a** was obtained (7%). The IR and NMR spectra were identical to reported data.[3]

Determination of the enantiomeric purity of 1a by GLC: A GLC analysis of **1a** was achieved using the column with a chiral stationary phase (Chiraldex G-TA™, ASTEC, 20m x 0.25mmI.D., 0.125um column) and operated at a constant 145°C using He as the carrier gas at $2kg/cm^2$. (*R*)-**1a** was eluted at 38 min. and (*S*)-**1a** at 46 min. The reference racemic **1a** was prepared in the same manner as described by Senda and Mori[14] without a chiral auxiliary.

(2*R*, 3*R*, 4*S*, 5*S*)-2,5-dihydroxy-3,4-isopropylidenedioxy-tridec-6-yn-1-ol, 3b: In the same manner as described for **3a**, triol **3b** was prepared from 1-octyne (32ml, 24.2g, 220mmol) , n-hexylmagnesium bromide (2M in ether, 100ml, 200mmol) and 2,3- *O*-isopropyridene ribose **2** (10g, 52.7mmol) and THF (100ml). The obtained **3b** (15.6g, 99% yield) was a very viscous oil, $n_D^{23.9}$ 1.4568; $[\alpha]_D^{27}$ -36.0° (c=1.00, $CHCl_3$); ν max. 3338(s), 2980(m), 2934(s), 2864(s), 2238(w), 1222(s), 1073(s) cm^{-1}.

(3*S*, 4*S*, 5*S*)-5-(1'-octynyl)-2-hydroxy-3,4-isopropylidenedioxyterahydrofuran, 4b: In the same manner as described for **4a**, lactol **4b** was prepared from **3b** (15.3g, 51.0mmol), 10% $NaIO_4$ soln (200ml) and ether (10ml). The lactol **4b** (10.6g, 78% yield) was obtained as a colorless oil, $n_D^{22.4}$ 1.7062; $[\alpha]_D^{25}$ -5.9° (c=1.00, $CHCl_3$); ν max. 3416(s), 2936(s), 2864(s), 2230(s), (w), 1073(s), 1035(s)cm^{-1}

(2*S*, 3*R*, 4*S*)-2,3-isopropylidenedioxy-5-dodecyn-4-olide, 5b: To a soln of lactol **4b** (1.00g, 3.74mmol) in CH_2Cl_2 (10ml) was added PDC (4.21g, 11.2mmol) and molecular sieves 4Å (4.21g) The mixture was stirred at room temperature for 5.5hr. When TLC analysis showed no starting material, ether (100ml) was added to the mixture and the whole mixture was passed through a florisil pad. The filtrate was washed with sat. $CuSO_4$ soln, water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica-gel to give lactone **5b** (590mg, 59% yield) as a viscous oil, $n_D^{21.9}$ 1.7062; $[\alpha]_D^{25}$ 14.6° (c=1.00, $CHCl_3$); ν max. 2990(m), 2936(s), 2240(w), 1798(s), 1224(m), 1164(s), 1151(s), 1100(s) cm^{-1}; δ 0.90 (3H, t, *J*=7.0Hz), 1.20-1.60 (8H), 1.40 and 1.47 (3H, s), 2.22 (2H, ddd, *J*=2.0, 7.1, 7.1Hz), 4.75 (1H, d, *J*=5.2Hz), 4.86 (1H, d, *J*=5.2Hz), 5.15 (1H, dd, *J*=2.0, 2.0Hz); (Found: C, 67.66; H, 8.36%. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%).

(2*S*, 3*R*, 4*S*)-2,3-dihydroxy-5-dodecyn-4-olide, 6b: In the same manner as described for **6a**, diol **6b** was prepared from acetonide lactone **5b** (590mg, 2.22mmol) and 90% trifluoroacetic acid (20ml). Residual solid was recrystallized (hexane: dichloromethane) to give diol **6b** (381mg, 76% yield) as a very fine needle, mp 103.0-104.0 °C; $[\alpha]_D^{25}$ -68.2° (c=1.07, $CHCl_3$); ν max. (KBr) 3426(br), 3300(br), 2930(m), 2864(m), 2240(w), 1760(s), 1185(s), 1152(m), 1011(m), 932(m) cm^{-1}; δ 0.89 (3H, t, *J*=6.9Hz), 1.20-1.60 (8H), 2.22 (2H, ddd, *J*=2.0, 7.0, 7.0Hz), 2.89 (1H, br s), 2.96 (1H, br s), 4.46 (1H, d, *J*=4.6Hz),

4.69(1H, d, *J*=4.6Hz), 5.09 (1H, dd, *J*=2.0, 2.0Hz); (Found: C, 63.27; H, 7.89%. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%).

(2*S*, 3*R*, 4*S*, 5*Z*)-2,3-dihydroxy-5-dodecen-4-olide, 7b: In the same manner as described for **7a**, **7b** was prepared from **6b** (1.02g, 4.51mmol) in EtOH (20ml) using Pb poisoned 5%-Pd/$CaCO_3$ (Lindlar catalyst, 40mg) Recrystallization (hexane: dichloromethane) provided **7b** as very fine needles (967mg, 94% yield), mp 72.0-73.0°C; $[\alpha]_D^{24}$ -90.4° (c=1.00, $CHCl_3$); ν max. (KBr) 3440(br), 3314(br), 2956(s), 2922(s), 2856(s), 1777(s), 1763(s), 1653(w), 1466(w), 1437(w), 1187(s), 1156(s), 926(s) cm^{-1}; δ 0.89 (3H, t, *J*=6.9Hz), 1.20-1.50 (8H), 2.05-2.25 (2H, m), 2.87 (1H, br s), 3.13 (1H, br s), 4.23 (1H, d, *J*=4.7Hz), 4.52 (1H, d, *J*=4.7Hz), 5.20-5.40 (2H, m), 5.70-5.85 (1H, m); (Found: C, 62.87; H, 8.60%. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%).

(2*S*, 3*R*, 4*S*, 5*Z*)-2,3-methoxymethylidenedioxy-5-dodecen-4-olide, 8b: In the same manner as described for **8a**, **8b** was prepared from diol **7b** (641mg, 2.81mmol), trimethyl orthoformate (10ml) and conc. H_2SO_4 (2μl). Compound **8b** was obtained as a colorless oil (760mg, quantitative) and subjected to the next reaction without further purification, ν max. 2960(s), 2932(s), 2860(s), 1792(s), 1659(s), 1466(m), 1193(s), 1123(s) cm^{-1}.

(4*S*, 5*Z*)-dodeca- 2,5-dien-4-olide, 9a: In the same manner as described for **9a**, diene **9b** was prepared from orthoester **8b** (1.50g, 5.55mmol), acetic anhydride (25ml) and acetic acid (1ml). The required material was obtained as a slightly yellow oil (1.16g, quantitative) and subjected to the next reaction without further purification. ν max. 2928(s), 2860(s), 1794(s), 1760(s), 1466(w), 1158(s), 1094(m), 1025(m), 818(m) cm^{-1}; δ 0.89 (3H, t, *J*=6.9Hz), 1.20-1.50 (8H), 2.05-2.35 (2H, m), 5.14 (1H, dddd, *J*=1.5, 1.5, 9.1, 9.1Hz), 5.71-5.85 (2H), 6.14 (1H, dd, *J*=2.0, 5.6Hz), 7.32 (1H, dd, *J*=1.5, 5.6Hz).

(*R*, *Z*)-5-dodecene-4-olide, 1b: In the same manner as described for **1a**, **1b** was prepared from CuI (1.95g, 10.2mmol), LiCl (dried at 130°C *in vacuo*, 1.09g, 25.7mmol) in THF (40ml), diene **9b** (1.16g, 5.98mmol) in THF (21ml), TMSCl (2.72ml, 20.4mmol) and n-Bu_3SnH (freshly distilled, 5.04ml, 16.0mmol). The lactone **1b** was obtained (875mg, 74% yield) as a colorless oil, $n_D^{24.8}$ 1.4627; $[\alpha]_D^{21}$ -79.5° (c=0.99, $CHCl_3$), $[\alpha]_D^{26}$ -61.2° (c=1.08, n-hexane). The IR and NMR spectra were identical with the reported data.[6] (Found: C, 73.35; H, 10.34%. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%).

Determination of the enantiomeric purity of 1b by GLC:[2] A GLC analysis of **1b** was achieved using the column a chiral stationary phase (Chiraldex G-TA™, ASTEC, 20m x 0.25mmI.D., 0.125um column) and operated at a constant 130°C using He as the carrier gas at $2kg/cm^2$. (*R*)-**1b** was eluted at 31.5 min. and (*S*)-**1a** at 42 min. The reference racemic **1b** was prepared in the same manner as described by Leal[2] without a chiral auxiliary.

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