Synthesis of (1*R*,4*R*,5*S*)-(+)-Acoradiene, the Structure Proposed for the Aggregation Pheromone of the Broad-Horned Flour Beetle[‡]

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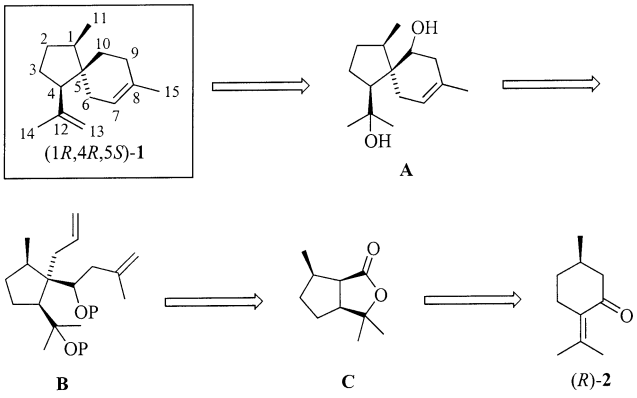
(1*R*,4*R*,5*S*)-(+)-Acoradiene {1,8-dimethyl-4-(1′-methylethenyl)spiro[4.5]dec-7-ene (**1**)}, the structure proposed for the aggregation pheromone of the broad-horned flour beetle (*Gnatocerus cornutus*), was synthesized from (*R*)-(+)-pulegone (**2**) by employing the ring-closing olefin metathesis of diene **9** as the key step, and confirming the structure of intermediate **11** by X-ray analysis. The spectral properties of (+)-**1** were different from those reported for the pheromone, whose proposed structure **1** was therefore proven incorrect.

Introduction

In 1998 Tebayashi et al. reported the isolation of 12.3 mg of the major component of the aggregation pheromone of the broad-horned flour beetle, *Gnatocerus cornutus*, a stored-products pest.[1] They proposed **1** [(+)-acoradiene] as its structure, including relative stereochemistry, on the basis of its detailed NMR studies. Because the spiro-sesquiterpene structure **1** was unique among insect pheromones, we became interested in determining its absolute stereochemistry by enantioselective synthesis. Scheme 1 shows our retrosynthetic analysis of **1**. Ring-closing olefin metathesis[2,3] to convert diene **B** into spiro-alkene **A** was chosen as the key reaction. Diene **B** was to be prepared from known lactone **C**, which could be prepared from readily available (*R*)-(+)-pulegone.[4] This paper describes an unambiguous synthesis of (1*R*,4*R*,5*S*)-**1**. The non-identity of the spectroscopic data of **1** with those reported for the natural pheromone disproves the correctness of Tebayashi's structure proposal.



Scheme 1. Structure and retrosynthetic analysis of (1*R*,4*R*,5*S*)-acoradiene

Results and Discussion

Scheme 2 summarizes our synthesis of (+)-acoradiene (**1**). (*R*)-(+)-Pulegone (**2**) was converted into the known saturated lactone **5** (*cis*,*cis*-pulegenolide) via **3** and **4** according to Wolinsky et al.[4] Allylation of **5** with lithium diisopropylamide (LDA) and allyl iodide gave **6**, which was reduced with diisobutylaluminium hydride (DIBAL-H) to furnish lactol **7**. Treatment of **7** with methallylmagnesium chloride in THF afforded diol **8** as a mixture (1:1 to 2:1) of two diastereomers. Since direct ring-closing olefin metathesis employing **8** with free hydroxy groups as a substrate was unsuccessful, the diol **8** was converted into the corresponding bis(trimethylsilyl) (TMS) ether **9**. At this stage, one of the two diastereomers of **8** was silylated more rapidly than the other, and the resulting **9** was a mixture (3:1 to 4:1) of the two diastereomers. Later, X-ray analysis of **11** revealed the major isomer of **9** to be the one with the secondary TMS-oxy group in (*S*) configuration. The (*R*)-configured hydroxy group of one of the isomer of **8** was less reactive against TMSCl than the (*S*)-hydroxy group of the other isomer of **8** due to the steric hindrance.

Ring-closing olefin metathesis of **9** (as a stereoisomeric mixture) was executed by employing the (carbene)ruthenium complex (benzylidene)dichlorobis(tricyclohexylphosphane)ruthenium introduced by Grubbs,[2] and afforded oily **10** in 98% yield as a diastereomeric mixture. Treatment of **10** with tetra(*n*-butyl)ammonium fluoride (TBAF) smoothly yielded a mixture of diols **11** and **11′**, which could be separated by silica gel chromatography to give both of them as crystals. X-ray analysis of the major isomer ob-

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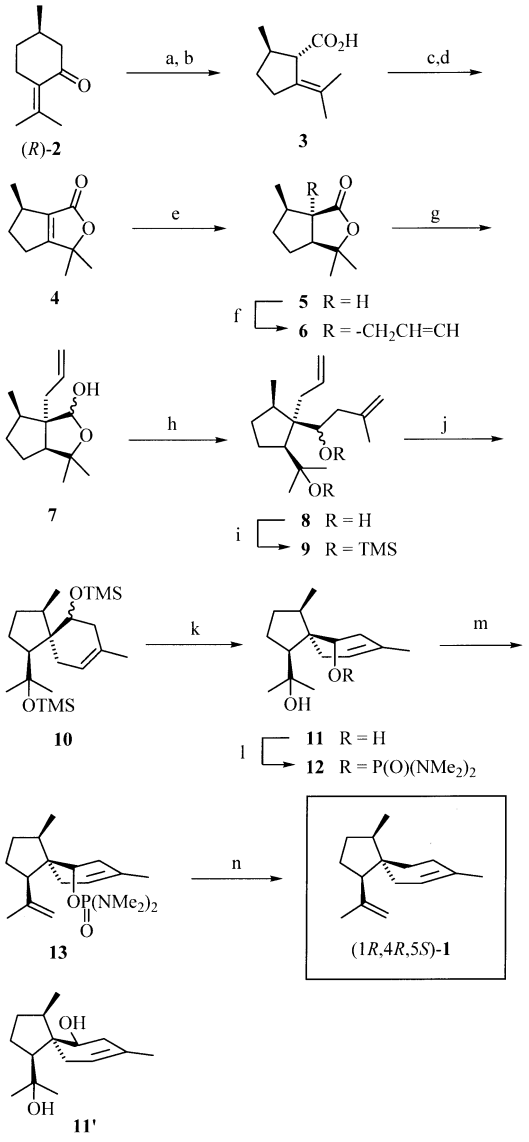

Scheme 2. Synthesis of (1*R*,4*R*,5*S*)-acoradiene (**1**); reagents: (a) Br_2, AcOH; (b) i) NaOMe, MeOH, ii) KOH, then dil. HCl (60%, 2 steps); (c) Br_2, NaOH, H_2O; (d) KO*t*Bu, *t*BuOH (39%, 2 steps); (e) H_2, PtO_2, EtOAc (99%); (f) i) LDA, THF, ii) $H_2C{=}CHCH_2I$, HMPA (96%); (g) DIBAL-H, CH_2Cl_2 (98%); (h) $H_2C{=}C(Me)CH_2MgCl$, THF (99%); (i) *n*BuLi, TMSCl, THF (84%); (j) $(Cy_3P)_2RuCl_2{=}CHPh$ (Grubbs catalyst), CH_2Cl_2 (98%); (k) TBAF, THF (α-OH, 71%; β-OH, 25%); (l) *n*BuLi, $(Me_2N)_2P(O)Cl$, TMEDA, DME (86% based on the consumed **11**); (m) $Ph_2S[OC(CF_3)_2Ph]_2$ (Martin sulfurane), CH_2Cl_2 (93%); (n) Li, $EtNH_2$, THF, *t*BuOH (50% based on the consumed **13**)

tained in 71% yield revealed it to be (1*R*,4*S*,5*R*,10*S*)-**11**, and therefore the minor isomer obtained in 25% yield was (1*R*,4*S*,5*R*,10*R*)-**11′**. Figure 1 shows the perspective view of the major isomer, which must be (1*R*,4*S*,5*R*,10*S*)-**11**, taking into account its (1*R*) configuration of (*R*)-pulegone origin.

The final stage of the synthesis was the conversion of the major product **11** to the target molecule **1**. After some experimentation, the route shown in Scheme 2 was adopted and proved successful. Accordingly, the diol **11** was monophosphorylated with *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidic chloride[5] to give **12**. The remaining free tertiary hydroxy group of **12** was then dehydrated by treatment with Martin sulfurane {bis[bis(trifluoromethyl)(phenyl)methoxy]diphenylsulfur}[6−8] to give alkene **13**. Finally, dissolving-metal reduction of **13** with lithium in ethylamine in the presence of *tert*-butyl alcohol[5] furnished (1*R*,4*R*,5*S*)-(+)-acoradiene (**1**), the proposed structure for the pheromone. The overall yield of (+)-**1** was 5.0% based on (*R*)-(+)-pulegone (**2**, 14 steps).

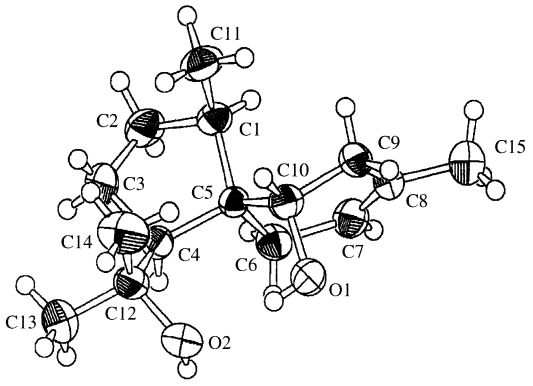

Figure 1. X-ray structure of **11**

Comparison of the physical data of (+)-acoradiene (**1**) with those reported for the natural pheromone indicated that they are different. Firstly, the specific rotation of (+)-**1** was $[\alpha]_D^{23} = +2.96$ ($c = 0.75$, hexane), while that of the natural pheromone was recorded as $[\alpha]_D = +37.1$ ($c = 1.2$, hexane). Secondly, as shown in Table 1, the reported ^1H and ^{13}C NMR spectroscopic data of the natural pheromone do not coincide with those of our synthetic **1**. We therefore conclude that structure **1** proposed for the major compon-

Table 1. NMR spectroscopic data of the natural pheromone[1] and synthetic **1**

	^1H NMR (400 MHz, $CDCl_3$)		^{13}C NMR (100 MHz, $CDCl_3$)	
C-	Natural pheromone	Synthetic **1**	Natural pheromone	Synthetic **1**
1	1.88 (m)	1.78 (m)	40.1	44.0
2	1.29 (ddd)	1.37 (m)	30.9	31.4
	1.88 (m)	1.78 (m)		
3	1.67 (m)	1.68 (m)	27.8	27.8
	1.86 (m)	1.78 (m)		
4	2.44 (t)	2.19 (t)	51.3	57.9
5			45.8	44.6
6	1.75 (s)	1.92 (dd)	31.1	39.1
		2.01 (dd)		
7	5.31 (m)	5.33 (br. t)	121.2	120.9
8			133.0	133.8
9	1.97 (s)	1.94 (m)	28.1	28.7
		1.99 (d)		
10	1.42 (dt)	1.47 (m)	27.4	24.1
11	0.86 (d)	0.94 (d)	15.4	15.8
12			148.4	147.1
13	4.61 (d)	4.72 (s)	111.7	111.8
	4.82 (s)	4.83 (t)		
14	1.71 (s)	1.77 (s)	24.2	24.1
15	1.63 (s)	1.61 (s)	23.3	23.3

ent of the aggregation pheromone of *Gnatocerus cornutus* is in error. We are currently synthesizing the stereoisomers of **1**, one of which may turn out to be the genuine pheromone.

Experimental Section

General: Melting points: uncorrected values; IR: Jasco FT/IR-410; ^{1}H NMR: Jeol JNM-LA 400 (400 MHz), Jeol JNM-LA 500 (500 MHz) (TMS at $\delta_H = 0.00$ or $CHCl_3$, $\delta_H = 7.26$ as an internal standard); ^{13}C NMR: Jeol JNM-LA 400 (100 MHz) ($CDCl_3$, $\delta_C = 77.0$ as an internal standard); MS: Jeol JMS-SX 102A and Hitachi M-80B; optical rotation: Jasco P-1020; m.p.: Yanaco MP-S3; column chromatography: Merck Kieselgel 60 Art 1.07734; TLC: 0.25 mm Merck silica gel plates (60F-254).

(3a*S*,6*R*,6a*R*)-Hexahydro-3,3,6-trimethyl-6a-(2′-propenyl)-1*H*-cyclopenta[*c*]furan-1-one (6): A solution of **5**[5] (2.00 g, 11.9 mmol) in THF (40 mL) was added to a stirred solution of LDA (11.9 mmol) in THF (15 mL) at −78 °C under argon. After stirring for 20 min, a solution of allyl iodide (2.0 mL, 21.9 mmol) in HMPA (3.0 mL) was added, and the temperature was allowed to rise to −40 °C. After stirring for 15 h at 0 °C, a saturated aqueous ammonium chloride solution was added, the organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (50 g, hexane/ethyl acetate, 60:1) to give 2.39 g (96%) of **6** as a colorless oil; $n_D^{22} = 1.4791$; $[\alpha]_D^{22} = -58.8$ ($c = 1.07$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 1755$ cm^{-1} (s, C=O), 1640 (w, C=C), 1260 (s, C−O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, $J = 7.1$ Hz, 3 H, 6-Me), 1.16 (dq, $J = 5.8$, 12.2 Hz, 1 H, 5-H$_a$), 1.34 and 1.38 (each s, 6 H, 3-Me), 1.55 (m, 1 H, 4-H$_a$), 1.80 (dt, $J = 5.8$, 12.2 Hz, 1 H, 5-H$_b$), 1.87−1.95 (m, 2 H, 4-H$_b$, 6-H), 2.34 (dd, $J = 8.3$, 14.1 Hz, 1 H, 1′-H$_a$), 2.44 (d, $J = 8.8$ Hz, 1 H, 3a-H), 2.56 (dd, $J = 6.7$, 14.1 Hz, 1 H, 1′-H$_b$), 5.15 (d, $J = 17.7$ Hz, 1 H, 3′-H$_a$), 5.16 (d, $J = 10.1$ Hz, 1 H, 3′-H$_b$), 5.79 (dddd, $J = 6.7$, 8.3, 10.1, 17.7, 1 H, 2′-H); $C_{13}H_{20}O_2$ (208.3): calcd. C 74.96, H 9.68; found C 74.56, H 9.46.

(3a*S*,6*R*,6a*R*)-Hexahydro-3,3,6-trimethyl-6a-(2′-propenyl)-1*H*-cyclopenta[*c*]furan-1-ol (7): To a stirred solution of **6** (1.71 g, 8.21 mmol) in dry dichloromethane (30 mL) was added a solution of DIBAL-H (0.90 M in hexane, 13.7 mL, 12.3 mmol) at −78 °C under argon. After stirring for 2 h at −78 °C, a saturated aqueous solution of Rochelle's salt was added, and the temperature was gradually raised to room temperature. Water and diethyl ether were added to the reaction mixture. The organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (20 g, hexane/ethyl acetate, 40:1) to give 1.69 g (98%) of **7** as a colorless oil. The diastereomer ratio of **7** (5:1) was determined by ^{1}H NMR analysis; $n_D^{18} = 1.4858$; $[\alpha]_D^{18} = -24.9$ ($c = 1.03$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3400$ cm^{-1} (s, O−H), 1640 (m, C=C), 1260 (m, C−O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (major) and 1.13 (each d, 3 H, $J = 7.0$ and 6.8 Hz, 6-Me), 1.18 (major), 1.28, 1.35 and 1.36 (major) (each s, 6 H, 3-Me), 1.24 (m, 1 H, 5-H$_a$), 1.41 (m, 1 H, 4-H$_a$), 1.69 (m, 2 H, 4-H$_b$, 5-H$_b$), 1.83 (br. sept, $J = 6.7$ Hz, 1 H, 6-H), 2.26 (d, $J = 9.2$ Hz, 1 H, 3a-H), 2.20−2.44 (m, 2 H, 1′-H), 2.50 and 2.89 (major) (each d, $J = 2.5$ and 5.5 Hz, 1 H, OH), 5.00−5.13 (m, 2 H, 3′-H), 5.17 (d, $J = 5.5$ Hz, 1 H, 1-H) 5.78−5.95 (m, 1 H, 2′-H); $C_{13}H_{22}O_2$ (210.3): calcd. C 74.24, H 10.54; found C 74.18, H 10.68.

(1*S*,2*R*,3*R*)-2-(1′′-Hydroxy-3′′-methyl-3′′-butenyl)-1-(1′-hydroxy-1′-methylethyl)-3-methyl-2-(2′′′-propenyl)cyclopentane (8): Methallylmagnesium chloride was prepared from methallyl chloride (5.42 g, 59.9 mmol) and magnesium (1.60 g, 65.8 mmol) in dry THF (120 mL) under argon. This reagent was added dropwise to a solution of **7** (2.49 g, 11.8 mmol) in dry THF (30 mL) at room temperature under argon. After stirring for 2 h, dil. HCl was added to the mixture, the organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic solutions were washed with water, saturated aq. $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (50 g, hexane/ethyl acetate, 400:1) to give 3.11 g (99%) of **8** as a colorless solid. The diastereomer ratio of **8** (ca. 1:1−2:1) was determined by ^{1}H NMR analysis; m.p. 56−78 °C; $[\alpha]_D^{25} = +5.13$ ($c = 1.19$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3305$ cm^{-1} (s, O−H), 1645 (m, C=C), 1635 (m, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, $J = 7.1$ Hz, 3 H, 3-Me), 1.20, 1.22, 1.39 and 1.46 (each s, 6 H, 1′-H), 1.32 (m, 1 H, 4-H$_a$), 1.75 and 1.77 (each s, 3 H, 3′′-Me), 1.83 (m, 5 H, 1-H, 3-H, 4-H$_b$, 5-H), 2.17 and 2.20 (each dd, $J = 7.8$, 14.4 and 7.3, 14.2 Hz, 1 H, 1′′′-H$_a$), 2.25 and 2.70 (each dd, $J = 10.8$, 13.8 and 11.7, 13.4 Hz, 1 H, 2′′-H$_a$), 2.34 and 2.37 (each d, $J = 13.4$ and 13.8 Hz, 1 H, 2′′-H$_b$), 2.59 and 2.78 (each dd, $J = 7.8$, 14.4 and 7.3, 14.2 Hz, 1 H, 1′′′-H$_b$), 3.02 (d, $J = 3.6$ Hz, 1/2 H, OH), 3.15 (br. s, 1/2 H, OH), 3.61, 3.94 (each d, $J = 11.7$ and 10.8 Hz, 1 H, 1′′-H), 4.10 (s, 1/2 H, OH), 4.57 (br. s, 1/2 H, OH), 4.80, 4.82, 4.87 and 4.89 (each s, 2 H, 4′′-H), 5.03 and 5.05 (each d, $J = 17.1$ and 17.6 Hz, 1 H, 3′′′-H$_a$), 5.04 and 5.06 (each d, $J = 9.5$, 10.2 Hz, 1 H, 3′′′-H$_b$), 5.85 and 5.95 (each ddt, $J = 7.3$, 9.5, 17.1 and 7.8, 10.2, 17.6 Hz, 1 H, 2′′′-H); $C_{17}H_{30}O_2$ (266.4): calcd. C 76.64, H 11.35, found C 76.67, H 11.36.

(1*S*,2*R*,3*R*)-2-(1′′-Trimethylsilyloxy-3′′-methyl-3′′-butenyl)-1-(1′-trimethylsilyloxy-1′-methylethyl)-3-methyl-2-(2′′′-propenyl)-cyclopentane (9): To a solution of **8** (3.11 g, 11.7 mmol) in dry THF (50 mL) was added a solution of *n*-butyllithium (1.6 M in hexane, 17.6 mL, 28.2 mmol) at −78 °C under argon. After the mixture had been stirred for 30 min at this temperature, TMSCl (4.45 mL, 35.1 mmol) was added to it. The resulting solution was stirred at room temperature for 18 h, and then poured into water. The organic phase was separated, and the aqueous phase was extracted with diethyl ether. The extracts and the organic phase were combined and washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (100 g, hexane/ethyl acetate, 500:1) to give 4.06 g (84%) of **9** as a colorless oil. The diastereomer ratio of **9** (ca. 3:1 to 4:1) was determined by ^{1}H NMR analysis; $n_D^{18} = 1.4791$; $[\alpha]_D^{18} = -10.0$ ($c = 1.17$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 1650$ cm^{-1} (m, C=C), 1635 (m, C=C), 1250 (s, Si−Me), 1090 (s, Si−O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07 (major), 0.08, 0.12 and 0.14 (major) (each s, 18 H, Si-Me), 0.94 and 1.04 (major) (each d, $J = 7.4$ Hz, 3 H, 3-Me), 1.32 (major), 1.35 (major), 1.39 and 1.47 (each s, 6 H, 1′-Me), 1.45 (m, 1 H, 4-H$_a$), 1.58−1.83 (m, 5 H, 1-H, 3-H, 4-H$_b$, 5-H), 1.74 (major) and 1.75 (each s, 3 H, 3′′-Me), 1.92 (dd, $J = 10.1$, 11.0 Hz, 1 H, 1′′′-H$_a$), 2.27 (dd, $J = 10.1$, 14.3 Hz, 1 H, 1′′′-H$_b$), 2.32 (d, $J = 6.4$ Hz, 1 H, 2′′-H), 2.60 (m, 1 H, 2′′-H$_b$), 3.93 and 4.23 (major) (each dd, $J = 1.8$, 9.4 and 1.8, 10.1 Hz, 1 H, 1′′-H), 4.76 (major) and 4.79 (each s, 1 H, 4′′-H), 4.81 (d, $J = 1.3$ Hz, 1 H, 4′′-H$_b$), 4.97 (major) and 4.99 (each dt, $J = 17.1$, 1.3 Hz, 1 H, 3′′′-H$_a$), 5.05 (major) and 5.06 (each dd, $J = 10.1$, 2.5 Hz, 1 H, 3′′′-H$_b$), 5.91 (m, 1 H, 2′′′-H); $C_{23}H_{46}O_2Si_2$ (410.8): calcd. C 67.25, H 11.29; found C 67.02, H 11.54.

(1*R*,4*S*,5*R*)-10-Trimethylsilyloxy-4-(1′-trimethylsilyloxy-1′-methylethyl)-1,8-dimethylspiro[4.5]dec-7-ene (10): To a solution of **9** (3.15 g, 7.67 mmol) in CH_2Cl_2 (1.5 L) was added a solution of Grubbs catalyst [$(Cy_3P)_2RuCl_2$=CHPh] (520 mg, 0.632 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (60 g, hexane/ethyl acetate, 500:1) to give 2.89 g (98%) of **10** as a colorless oil. The diastereomer ratio of **10** (ca. 3:1−4:1) was determined by ^{1}H NMR analysis; n_D^{22} = 1.4731; $[\alpha]_D^{23}$ = +2.13 (*c* = 1.14, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 1250 cm^{-1} (s, Si−Me), 1090 (s, Si−O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08, 0.09 (major), 0.10 (major) and 0.12 (each s, 18 H, Si-Me), 0.93 (major) and 1.20 (each d, *J* = 6.7 and 7.0 Hz, 3 H, 1-Me), 1.25, 1.30 (major), 1.38 and 1.41 (major) (each s, 6 H, 1′-Me), 1.89−2.08 (m, 3 H, 6-H, 9-H_a), 2.18 and 2.43 (major) (each br dd, *J* = 7.3, 16.8 Hz, 1 H, 9-H_b), 4.13 (major) and 4.62 (each br dd, *J* = 4.6, 7.3 and 7.3, 9.4 Hz, 1 H, 10-H), 5.24 (major) and 5.30 (each br s, 1 H, 7-H); $C_{21}H_{42}O_2Si_2$ (382.7): calcd. C 65.90, H 11.06, found C 66.22, H 11.39.

(1*R*,4*S*,5*R*)-10-Hydroxy-4-(1′-hydroxy-1′-methylethyl)-1,8-dimethylspiro[4.5]dec-7-ene (11): To a solution of **10** (5.00 g, 13.1 mmol) in THF (100 mL) was added a solution of TBAF (1.0 M in THF, 55.0 mL, 55.0 mmol). The mixture was stirred for 12 h at room temperature, then poured into water, and extracted with diethyl ether. The extracts and the organic phase were combined, washed with water, saturated aq. $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (100 g, hexane/ethyl acetate, 5:1) to give 2.22 g (71%) of **11** and 795 mg (25%) of **11′** as colorless solids. The major isomer **11** was further purified by recrystallization from diethyl ether to give pure **11** as colorless needles.

11: R_f = 0.33 (hexane/ethyl acetate, 1:1); m.p. 182−184 °C; $[\alpha]_D^{22}$ = −63.5 (*c* = 1.17, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3240 cm^{-1} (s, O−H), 3125 (s, O−H); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.1 Hz, 3 H, 1-Me), 1.22 and 1.39 (each s, 6 H, 1′-Me), 1.29 (m, 1 H, 2-H_a), 1.46 (m, 1 H, 3-H_a), 1.66 (br. s, 3 H, 8-Me), 1.73−1.88 (m, 4 H, 1-H, 2-H_b, 3-H_b, 4-H), 1.92 (dd, *J* = 4.6, 17.9 Hz, 1 H, 6-H_a), 2.05 (d, *J* = 17.9 Hz, 1 H, 6-H_b), 2.23 (dq, *J* = 18.0, 2.4 Hz, 1 H, 9-H_a), 2.40 (br. d, *J* = 18.0 Hz, 1 H, 9-H_b), 3.00 (br. s, 1 H, OH), 4.36 (s, 1 H, 10-H), 5.21 (br. s, 1 H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 23.1, 25.4, 28.7, 31.3, 33.2, 37.3, 38.1, 39.8, 51.0, 61.3, 67.2, 74.1, 120.6, 130.3; $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99, found C 75.65, H 11.05. The structure of (10*S*)-**11** was solved by X-ray crystallographic analysis (vide infra).

11′: R_f = 0.55 (hexane/ethyl acetate, 1:1); m.p. 129−130 °C; $[\alpha]_D^{22}$ = −16.4 (*c* = 1.09, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3170 cm^{-1} (s, O−H); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 7.1 Hz, 3 H, 1-Me), 1.26 and 1.47 (each s, 6 H, 1′-Me), 1.53 (m, 1 H, 2-H_a), 1.66 (br. s, 3 H, 8-Me), 1.67 (m, 1 H, 3-H_a), 1.82 (m, 1 H, 2-H_b), 1.87−1.95 (m, 3 H, 1-H, 3-H_b, 4-H), 2.20−2.41 (m, 4 H, 6-H, 9-H), 4.50 (dd, *J* = 6.4, 10.4 Hz, 1 H, 10-H), 5.22 (br. s, 1 H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 22.5, 26.2, 29.7, 32.5, 32.8, 38.3, 43.2, 44.0, 50.7, 59.9, 71.5, 72.8, 120.3, 132.6; $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99, found C 75.20, H 10.89.

(1*R*,4*S*,5*R*,10*S*)-4-(1′-Hydroxy-1′-methylethyl)-1,8-dimethylspiro[4.5]dec-7-en-10-yl *N*,*N*,*N*′,*N*′-Tetramethylphosphorodiamidate (12): To a solution of **11** (1.00 g, 4.20 mmol) in dry DME (40 mL) and TMEDA (10 mL) was added a solution of *n*-butyllithium (1.59 M in *n*-hexane, 5.80 mL, 9.22 mmol) at 0 °C under argon. After the mixture had been stirred for 10 min at this temperature, $(Me_2N)_2$-POCl (90%, 0.76 mL, 4.62 mmol) was added to it at 0 °C under argon. The resulting solution was stirred at room temperature for 2 h, and then poured into ice-cooled dil. HCl. The organic phase was separated, and the aqueous phase was extracted with diethyl ether. The extracts and the organic phase were combined and washed with water, saturated aq. $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (30 g, hexane/ethyl acetate, 3:1) to give 821 mg (86% based on the consumed **11**) of **12** as a colorless solid with recovery of **11** (390 mg); m.p. 79−81 °C; $[\alpha]_D^{25}$ = −16.3 (*c* = 1.03, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3365 cm^{-1} (s, O−H), 2805 (m, N−Me), 1685 (w, C=C), 1215 (vs, P=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7.0 Hz, 3 H, 1-Me), 1.18 and 1.33 (each s, 6 H, 1′-Me), 1.32 (m, 1 H, 2-H_a), 1.54 (quint, *J* = 9.7 Hz, 1 H, 3-H_a), 1.63 (s, 3 H, 8-Me), 1.71−1.90 (m, 4 H, 1-H, 2-H_b, 3-H_b, 4-H), 2.03 (br. d, *J* = 18.6 Hz, 1 H, 6-H_a), 2.18 (br. d, *J* = 18.6 Hz, 1 H, 6-H_b), 2.35 (br. d, *J* = 18.6 Hz, 1 H, 9-H_a), 2.62, 2.64 and 2.66 (each s, 12 H, NMe), 2.75 (br. d, *J* = 18.6 Hz, 1 H, 9-H_b), 4.08 (s, 1 H, OH), 4.98 (q, *J* = 4.3 Hz, 1 H, 10-H), 5.30 (br. s, 1 H, 7-H); $C_{19}H_{37}N_2O_3P$ (372.5): calcd. C 61.27, H 10.01, N 7.52, found C 61.36, H 10.02, N 7.32.

(1*R*,4*S*,5*R*,10*S*)-1,8-Dimethyl-4-(1′-methylethenyl)spiro[4.5]dec-7-en-10-yl *N*,*N*,*N*′,*N*′-Tetramethylphosphorodiamidate (13): To a solution of **12** (608 mg, 1.63 mmol) in dry CH_2Cl_2 (60 mL) was added Martin sulfurane (2.0 g, 2.97 mmol) at room temperature. The mixture was stirred for 10 h at room temperature, then poured into saturated aq. $NaHCO_3$ and extracted several times with $CHCl_3$. The extracts and the organic phase were combined and washed with water, saturated aq. $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (10 g, hexane/ethyl acetate, 3:1) to give 537 mg (93%) of **13** as a colorless solid with a low m.p. (< 25 °C); $[\alpha]_D^{20}$ = +26.5 (*c* = 0.99, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 2805 cm^{-1} (m, N−Me), 1640 (m, C=C), 1225 (vs, P=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.4 Hz, 3 H, 1-Me), 1.43 (m, 1 H, 2-H_a), 1.60 (s, 3 H, 8-Me), 1.76 (m, 1 H, 3-H_a), 1.84 (br. t, *J* = 6.4 Hz, 1 H, 1-H), 1.88 (s, 3 H, 1′-Me), 1.95−2.11 (m, 2 H, 2-H_b, 6-H_a), 2.17−2.33 (m, 3 H, 3-H_b, 6-H_b, 9-H_a), 2.58−2.67 (m, 2 H, 4-H, 9-H_b), 2.59, 2.61, 2.62, and 2.64 (each s, 12 H, NMe), 4.71 (dt, *J* = 5.5, 7.3 Hz, 1 H, 10-H), 4.86 and 4.91 (each s, 2 H, 2′-H), 5.26 (br. s, 1 H, 7-H); $C_{19}H_{35}N_2O_2P$ (354.5): calcd. C 64.38, H 9.95, N 7.90, found C 64.07, H 10.31, N 7.54.

(1*R*,4*R*,5*S*)-1,8-Dimethyl-4-(1′-methylethenyl)spiro[4.5]dec-7-ene (1) [(+)-Acoradiene]: To a stirred and cooled solution of Li (15 mg, 2.16 mmol) in dry $EtNH_2$ (3.0 mL) was added dropwise a solution of **13** (77 mg, 0.217 mmol) in *t*BuOH (83 μL) and dry THF (1.0 mL) at −78 °C under argon. After stirring for 2 h at −78 °C, the reaction was quenched by the addition of water at −78 °C, which destroyed excess Li. The mixture was poured into water and extracted with diethyl ether. The extracts and the organic phase were combined and washed with water, saturated aq. $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (2.0 g, hexane) and further purified by chromatography on $AgNO_3$-impregnated silica gel (4.0 g, hexane) to give 16 mg (50% based on the consumed **13**) of **1** as a colorless oil with recovery of **13** (21 mg); n_D^{22} = 1.5011; $[\alpha]_D^{23}$ = +2.96 (*c* = 0.75, hexane) {ref.[1] $[\alpha]_D$ = +37.1 (*c* = 1.2, hexane)}; GLC [column: NB-5® (0.25 mm × 30 m); at 40−200 °C, +5 °C/min; carrier gas: He, press 90 kPa]: t_r = 27.5 min (> 99% pure); IR (CCl_4 solution): $\tilde{\nu}_{max}$ = 3075 cm^{-1} (w), 2960 (vs), 2930 (s), 2875 (s), 1635 (w, C=C), 1455 (m), 1435 (m), 1375 (m), 890 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H, 1-Me), 1.35 (m, 1 H, 2-H_a), 1.47 (m, 2 H, 10-H), 1.61

(s, 3 H, 8-Me), 1.68 (m, 1 H, 3-H_a), 1.70−1.84 (m, 3 H, 1-H, 2-H_b, 3-H_b), 1.77 (s, 3 H, 1′-Me), 1.86−2.06 (m, 4 H, 6-H, 9-H), 2.19 (t, J = 8.7 Hz, 1 H, 4-H), 4.72 (s, 1 H, 2′-H_a), 4.83 (t, J = 1.2 Hz, 1 H, 2′-H_b), 5.33 (br. t, J = 1.2 Hz, 1 H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 23.3, 24.1, 27.8, 28.7, 31.4, 39.1, 44.0, 44.6, 57.9, 111.8, 120.9, 133.8, 147.1; $C_{15}H_{24}$ (204.4): calcd. C 88.16, H 11.84, found C 87.96, H 11.87; $C_{15}H_{24}$: calcd. 204.1879; found 204.1884 (HRMS).

X-ray Analysis of 11: The crystal used for data collection was a colorless needle with approximate dimensions 0.90 × 0.50 × 0.20 mm. All the data were obtained with a Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo-K_α radiation. Unit cell parameters were determined by least-squares refinement of the optimized setting angles of 25 reflections in the range 12.6° < θ < 15.0°. Crystal data for **11**: $C_{15}H_{26}O_2$, M = 238.37, monoclinic, space group $P2_1$, a = 9.615(4), b = 6.967(4), c = 11.221(2) Å, β = 109.9(2) °, V = 706.6(4) Å^3, Z = 2, D_c = 1.120 Mg·m^{-3}, F(000) = 264, μ(Mo-K_α) = 0.717 cm^{-1}. The intensities were measured using ω/2θ scan techniques up to 55°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors. Absorption and decay correction was not applied. Of the 1858 independent reflections collected, 1215 reflections with $I > 2.0\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct methods using the TEXSAN crystallographic software package.[9] All non-H atoms were found in the Fourier map. The refinement of atomic parameters was carried out by full-matrix least-squares refinement, using anisotropically temperature factors for all non-H atoms. All H atoms, except for those attached to O atoms, were located geometrically, and not refined. The H atoms attached to O atoms were found in the difference Fourier map and refined isotropically. The final refinement converged with R = 0.038 and Rw = 0.040 for 160 parameters. Atomic scattering factors were taken from "International Tables for X-ray Crystallography".[10] The supplementary material includes the lists of atomic coordinates for the non-H atoms, the bond lengths and angles of **11** with their e.s.d.s in parentheses.[11]

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[11] Further details of the crystal structure investigation are deposited to the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-164147. Copies of the data can be obtained free of change on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

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