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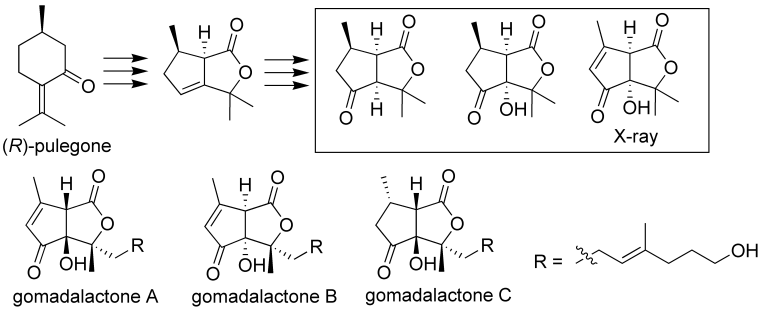

Pheromone synthesis. Part 264: Synthesis of the core 3-oxabicyclo[3.3.0]octane structures of gomadalactones A, B and C, the components of the contact sex pheromone of the white-spotted longicorn beetle, *Anoplophora malasiaca*☆

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ABSTRACT

The core bicyclic cyclopentanelactone structures of gomadalactones A, B and C with α-hydroxyketone system were synthesized from (*R*)-pulegone, employing deconjugation of an α, β-unsaturated lactone as the key step. Comparison of the CD spectra of the synthetic compounds with those of the natural products confirmed the absolute configuration of the natural pheromone components as proposed in 2007. X-ray crystallographic analysis of the model compound of gomadalactone B core structure was carried out.

☆ For Part 263. see Ref.[1]

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1. Introduction

The white-spotted longicorn beetle, *Anoplophora malasiaca* (Thomson) (Coleoptera: Cerambycidae), is a serious pest of citrus, apple, pear and willow. Its female contact pheromone components were extensively studied by Yasui and co-workers, and found to be a mixture of eight hydrocarbons, five ketones and three lactones.[2,3] Although the structures of the hydrocarbons and the ketones are all trivial, the lactones possess non-trivial and unique structures. They were given the names gomadalactone A (**1**, Figure 1), B (**2**) and C (**3**).[2] The uniqueness of their structures is represented by the presence of an angular hydroxy group at C-5.

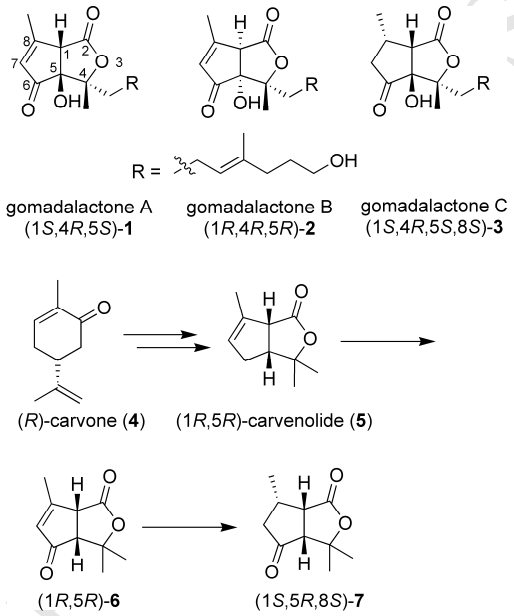
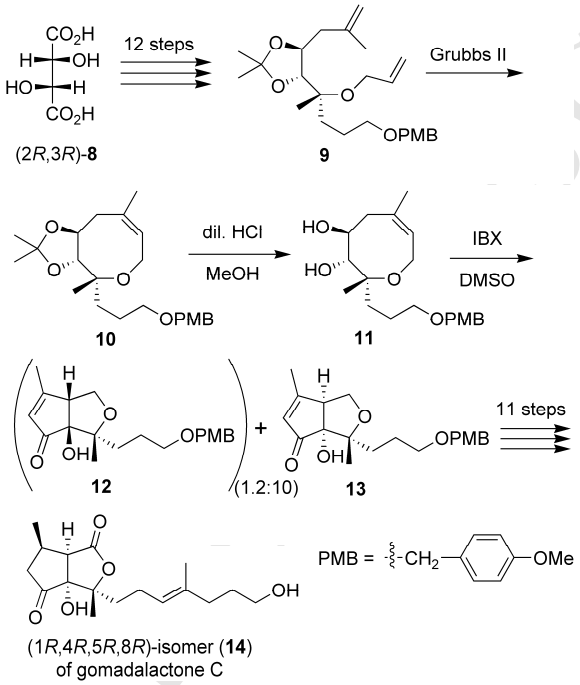


Figure 1. Structures of gomadalactones A (**1**), B (**2**) and C (**3**), and the synthesis of the model compounds **6** and **7**. The numbering system depicted in **1** is those employed in refs.[2,4]

I became interested in synthesizing **1**, **2**, and **3**, so as to establish their structures including absolute configuration. In 2007, as the first step to the goal, synthesis and CD measurements of two model compounds (1*R*,5*R*)-**6** and (1*S*,5*R*,8*S*)-**7** were reported as a short communication.[4] CD spectra of **1**, **2** and **3** were compared with those of **6** and **7**. Since **6**[5] and **7** were synthesized from (*R*)-carvone (**4**) via (1*R*,5*R*)-carvenolide (**5**), their absolute configurations were as depicted. It was therefore concluded that gomadalactones A (**1**), B (**2**) and C (**3**) must possess the absolute configuration as shown

in Figure 1.

Since the discovery of gomadalactones in 2007, there is reported only one successful synthesis of the (1*R*,4*R*,5*R*,8*R*)-isomer (**14**, Scheme 1) of gomadalactone C in a patent claimed in 2017 by Suzuki et al.[6] Their synthesis is summarized in Scheme 1. (+)-Tartaric acid (**8**) was converted to diene **9**, which afforded **10** after ring-closing olefin metathesis.



Scheme 1. Suzuki's 26-step-synthesis of the (1*R*,4*R*,5*R*,8*R*)-isomer (**14**) of gomadalactone C (**3**).

Deprotection of the acetonide group of **10** gave **11**, whose IBX oxidation resulted in transannular cyclization to give a mixture of **12** and **13**. Further conversion of **13** over eleven steps gave (1*R*,4*R*,5*R*,8*R*)-isomer (**14**) of gomadalactone C. Although only 4.4 mg of **14** was obtained without describing the $[\alpha]_D$ value, **14** was shown to be pheromonally active against *Anoplophora malasiaca*. Two additional analogues of gomadalactone C were also pheromonally active, indicating that the ligand specificity of the pheromone receptor of *A. malasiaca* does not seem to be extremely selective. Suzuki's synthesis, however, is too lengthy to be practical. I therefore decided to explore possibilities for more concise synthesis of the pheromone components **1**–**3**.

2. Results and discussion

2.1. Selection of target model compounds, and initial attempts to take advantage of the late-stage oxidation of monoterpene intermediates

Since the peculiar structural feature of gomadalactones A, B and C lies in the highly functionalized bicyclic lactones part, three bicyclic lactones **7**, **15** and **16** were selected as the target model compounds (Figure 2).

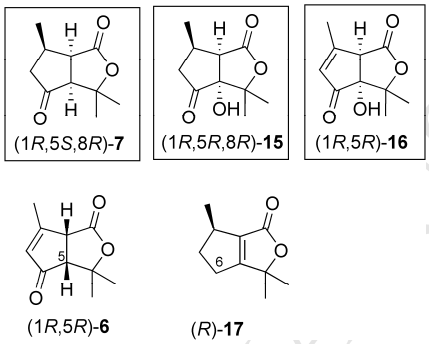
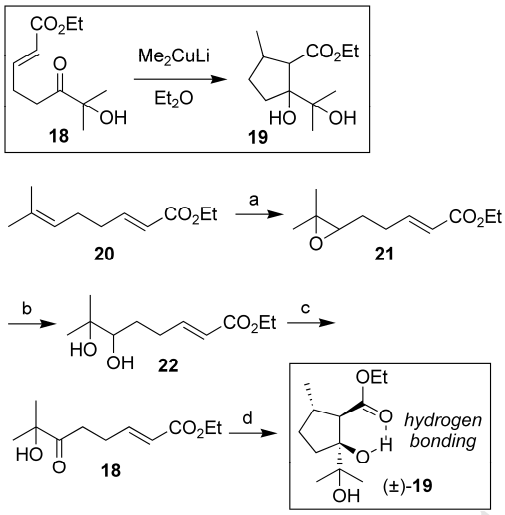


Figure 2. Structures of the target model compounds **7**, **15** and **16** and their relatives **6** and **17**.

The first attempt was to explore C–H functionalization[7] of (1*R*,5*R*)-**6**[4] or (*R*)-**17**[8]. Unfortunately, however, neither functionalization of C-5 of **6** nor that at C-6 of **17** was unsuccessful employing SeO_2, NBS or $Pb(OAc)_4$ as an oxidant. Accordingly, various additional attempts were made to introduce a hydroxy group at the angular position of bicyclic lactones as detailed in 2.2–2.5.

2.2. Cyclopentane ring formation by tandem conjugate addition/cyclization

Intramolecular ring closure is one of the classic ways to construct a ring system. Cyclization of **18** to give **19** seemed plausible by means of Me_2CuLi (Scheme 2).

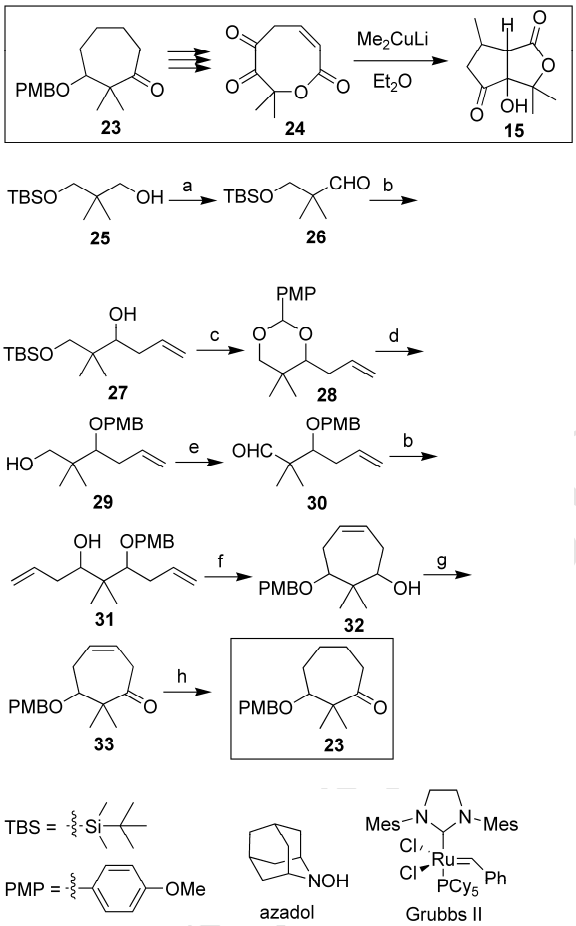


Scheme 2. Cyclopentane ring formation by tandem conjugate addition/cyclization. Reagents: (a) MCPBA, CH_2Cl_2 (86%); (b) $HClO_4$, THF, H_2O (quant.); (c) $(COCl)_2$, DMSO, CH_2Cl_2; then Et_3N (43%); (d) Me_2CuLi, Et_2O (27%).

The precursor **18** was readily available from the known ester **20**.[9,10] through epoxidation to give **21**, followed by its hydrolysis to yield diol **22**, and final Swern oxidation of **22** to furnish **18**. Treatment of **18** with Me_2CuLi in Et_2O was followed by chromatographic purification to give (±)-**19** in a modest yield of 27%. In the IR spectrum of **19**, the ester C=O group showed an absorption at 1705 cm^{-1}, clearly indicating the presence of a hydrogen bonding between the ester C=O group and the OH group at C-2. This implied that the lactone formation might not be induced between $–C(Me)_2OH$ and $–CO_2Et$. The above consideration together with the observed low yield of cyclization (27%) made me to explore other possibilities.

*2.3. Attempted synthesis of diketoheptenolide (**24**) via 2,2-dimethyl-3-PMBoxy-cycloheptanone (**23**)*

Suzuki et al. cleverly employed transannular cyclization (**11**→**12**, Scheme 1) to construct the bicyclic system.[6] In analogy with Suzuki's synthesis, intramolecular conjugate addition/cyclization of **24** (Scheme 3) to give **15** might solve the problem. The diketolactone **24** would be prepared from **23**. Synthesis of **23** was therefore executed as shown in Scheme 3.



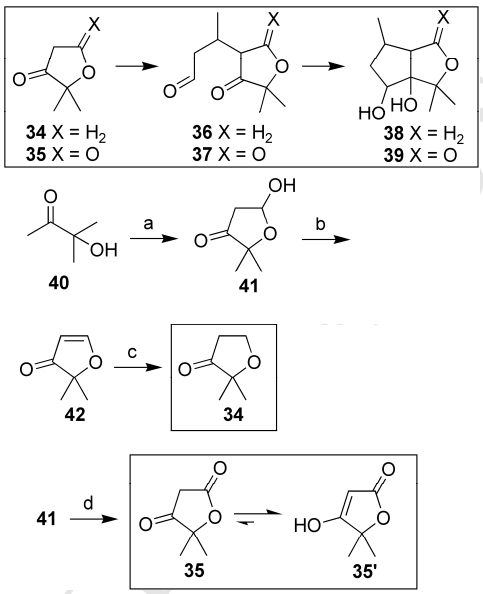
Scheme 3. Synthesis of 2,2-dimethyl-3-PMBoxycycloheptanone (**23**). Reagents: (a) azadol, $NaOCl\cdot 5H_2O$, $(n\text{-}Bu)_4NHSO_4$, CH_2Cl_2, H_2O (80%); (b) $CH_2{=}CHCH_2MgCl$, THF (73% for **27**, 91% for **31**); (c) $p\text{-}MeOC_6H_4CH(OMe)_2$, CSA, DMF (34%); (d) $(i\text{-}Bu)_2AlH$, CH_2Cl_2 (quant.); (e) azadol, $PhI(OAc)_2$, CH_2Cl_2 (75%); (f) Grubbs II, CH_2Cl_2 (92%); (g) Jones CrO_3, acetone (81%); (h) H_2, Pd-$BaSO_4$ (84%).

The known starting material **25**[11] was oxidized with $NaOCl\cdot 5H_2O$[12] in the presence of azadol[13] to give aldehyde **26**. Treatment of **26** with allylmagnesium bromide furnished **27**. *p*-Methoxybenzaldehyde dimethylacetal and camphorsulfonic acid (CSA) in DMF converted **27** to **28**, which was reduced with diisobutylaluminum hydride to give **29**. Oxidation of **29** with (diacetoxy)iodobenzene (DAIB) in the presence of azadol afforded **30**, to which was added allylmagnesium chloride yielding **31**. Ring-closing metathesis of **31** with second-generation Grubbs catalyst[14] gave **32**. Chromic acid oxidation of **32** was followed by hydrogenation to give **23** via **33**. Although the above synthetic route was straightforward, it was rather lengthy and

inefficient. The attempt to convert **23** to **24** was therefore abandoned at this stage.

*2.4. Synthesis of ketone **34** and lactone **35** and attempted Michael addition of crotonaldehyde to them*

The next plan was to synthesize ketone **34** and lactone **35** to explore the possibility of Michael addition of them to crotonaldehyde (Scheme 4). If this plan were successful, the products **36** and **37** would give bicycles **38** and **39** after reductive C–C bond formation with low-valent titanium[15] or SmI_2.[16]



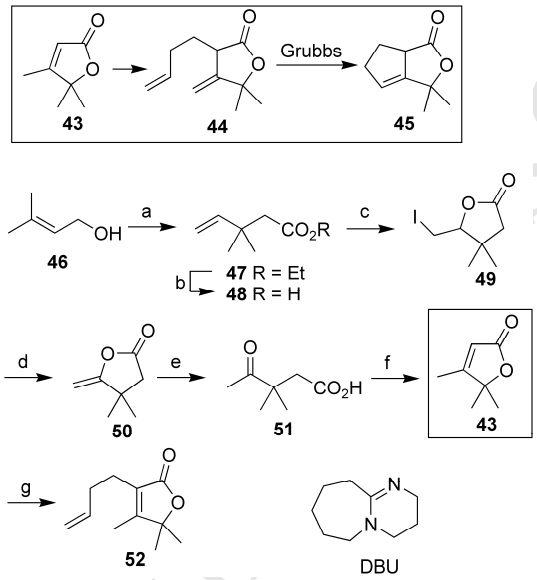
Scheme 4. Synthesis of ketone **34** and tetronic acid **35**. Reagents: (a) NaH, HCO_2Et, Et_2O (67%); (b) $MgSO_4$, $CuSO_4$ (58%); (c) H_2, Pd-C, AcOMe (77%); (d) Jones CrO_3, acetone (39%).

According to Margaretha, 3-hydroxy-3-methyl-2-butanone (**40**) was formylated to give **41**.[17] Treatment of **41** with anhydrous $CuSO_4$ and $MgSO_4$ furnished **42**. This was hydrogenated over Pd-C to give **34**. Chromic acid oxidation of **41** smoothly afforded crystalline 5,5-dimethyltetronic acid (**35**).[18,19] It must be added that the present procedure is a concise and new method for the preparation of **35**. Judging from its ^1H and ^{13}C NMR spectra in DMSO-d_6, **35** adopts entirely enolic form **35'**.

Michael addition between crotonaldehyde or acrolein and **34** or **35** was attempted under various different conditions. Unfortunately, all the attempts were in vain, and I was forced to examine another plan.

*2.5. Synthesis and alkylation of lactone **43***

It was expected that alkylation of lactone **43** with 1-iodo-3-butene would give **44** by concomitant deconjugation of the α,β-unsaturated lactone system of **43**, if the equilibration to give back the original α,β-unsaturated lactone system does not take place so quickly. The product **44** would then give the bicyclic lactone system **45** after ring-closing olefin metathesis (Scheme 5).



Scheme 5. Synthesis and alkylation of lactone **43**. Reagents: (a) $MeC(OEt)_3$, $EtCO_2H$, heat; (b) KOH, MeOH, H_2O (70%, 2 steps); (c) I_2, KI, $NaHCO_3$, H_2O (97%); (d) DBU, C_6H_6 (70%); (e) KOH, H_2O (quant.); (f) P_2O_5, H_3PO_4 (48%); (9) LDA, $CH_2=CHCH_2CH_2I$, THF (44%).

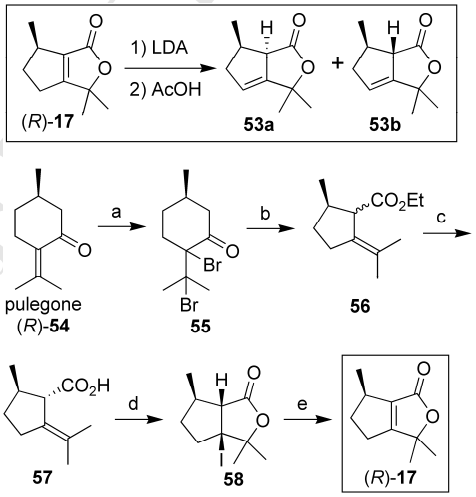
Preparation of the key lactone **43** was executed by the method published by Jäger and co-workers.[20,21] Some modifications were made to secure **43** in a multi-gram scale. Johnson-Claisen rearrangement of **46** with ethyl orthoacetate gave **47**, which was hydrolyzed to furnish **48**. Iodolactonization of **48** afforded **49**, which was treated with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) to give **50**. Alkaline hydrolysis of **50** yielded **51**. Finally **51** was heated with polyphosphoric aid (PPA) to give **43** as a low melting solid.

Treatment of **43** with lithium diisopropylamide (LDA) in THF at −75°C was followed by alkylation with 1-iodo-3-butene at −75°C for 1 h and at room temperature

for 1 h. After quenching with NH_4Cl solution, the product was purified by SiO_2 chromatography. The distilled product (44% yield) turned out to be **52**, not the desired **44**. It was thus shown that **44**, even when it was generated, rapidly isomerized to the more stable α,β-conjugated lactone **52**. The present route was therefore abandoned. At this stage it occurred to me that a compound similar to **45** might be obtained by deconjugation/protonation of (*R*)-**17** as shown in the next section.

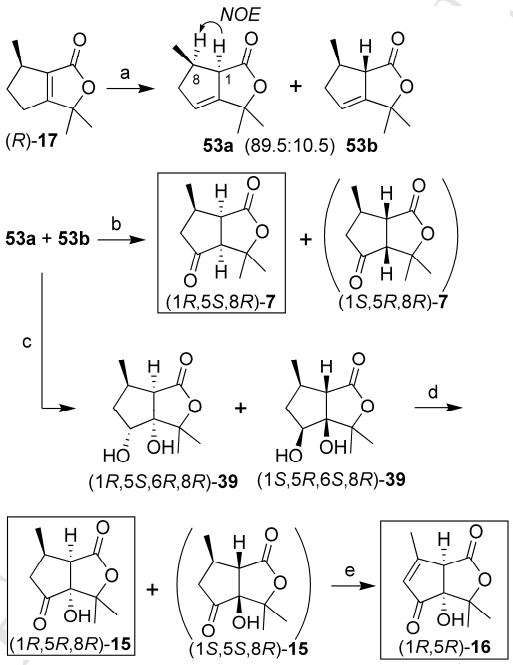
*2.6. Synthesis of the target model compounds **7**, **15** and **16** employing deconjugation/protonation of **17** as the key-step*

In order to explore the feasibility of the deconjugation/protonation of (*R*)-**17**, it was necessary to provide multi-gram quantities of (*R*)-**17**, a known lactone.[8,22] As reported by Wolinsky,[22,23] commercially available (*R*)-pulegone (**54**) was first treated with Br_2 to give **55** (Scheme 6). Sodium ethoxide in ethanol induced the Favorskii rearrangement of **55** to give a mixture of ethyl *cis*- and *trans*-pulegenate (**56**). Alkaline hydrolysis of **56** was followed by distillation of the resulting acid to give (1*S*,5*R*)-pulegenic acid (**57**). This was subjected to the conventional iodolactonization conditions. The product was purified by SiO_2 chromatography and recrystallization to give pure iodolactone (**58**). Finally, treatment of **58** with DBU in benzene afforded (*R*)-**17**. A sufficient amount (5.72 g) of (*R*)-**17** could be secured.



Scheme 6. Synthesis of pulegonolide (**17**). Reagents: (a) Br_2, AcOH; (b) NaOEt, EtOH (72%, 2 steps); (c) KOH, EtOH, H_2O (57%); (d) $NaHCO_3$, I_2, NaI (52%); (e) DBU, C_6H_6 (78%).

Deconjugation of (*R*)-**17** was examined employing either LDA or KH as the base. Since the presence of mineral oil in commercially available KH was problematic in the later purification of the product, LDA was selected as the base of choice. Acetic acid in Et_2O at −78°C was chosen as the protonation agent. Deconjugation/protonation of (*R*)-**17** with LDA/AcOH furnished a mixture of **53a** and **53b** as a solid. Protonation of the enolate with AcOH/Et_2O at −78°C was considerably stereoselective, and a mixture of the major and minor isomers (4:1–10:1) was obtained. Since this protonation proceeded under kinetic control, the structure of the major isomer was thought to be **53a**, which was verified by the observation of NOE between 1-H and 8-H as depicted in Scheme 7.



Scheme 7. Synthesis of the model compounds **7**, **15** and **16**. Reagents: (a) i) LDA, THF; ii) AcOH, Et_2O (76%); (b) i) BH_3·THF, THF; ii) Jones CrO_3, acetone (8%); (c) OsO_4, NMO, acetone, *t*-BuOH, H_2O (98%); (d) (*n*-Pr)$_4$NRuO_4, NMO, CH_2Cl_2, MS 4A (7%); (e) i) KN(TMS)$_2$, PhSeBr, toluene, THF; ii) $NaIO_4$, THF, H_2O (7%).

Hydroboration of the deconjugated lactone **53a** + **53b** was followed by chromic acid oxidation to give keto lactone (1*R*,5*S*,8*R*)-**7**, whose (1*S*,5*R*,8*S*)-isomer had been reported by myself in 2007.[4] In the present case, only (1*R*,5*S*,8*R*)-**7** could be isolated as crystals in 8% yield (two steps) after chromatographic purification and

recrystallization, whereas (1*S*,5*R*,8*R*)-**7** was not observed. The physical properties of (1*R*,5*S*,8*R*)-**7** (mp, IR, ^{1}H and ^{13}C NMR spectra) as well as its magnitude of the specific rotation {$[\alpha]_D^{22}$ −309.4 (*c* 0.216, Et_2O); cf. its opposite enantiomer: $[\alpha]_D^{25}$ +319 (*c* 1.014, Et_2O)} were in good accord with the reported values of (1*S*,5*R*,8*S*)-**7**.[4]

Introduction of a hydroxy group at the angular C-5 position could be readily achieved by OsO_4-catalyzed dihydroxylation[24] of **53a** + **53b**, and the two isomers were converted almost quantitatively to a mixture of two diastereomeric dihydroxylactones (1*R*,5*S*,6*R*,8*R*)- **39** and (1*S*,5*R*,6*S*,8*R*)-**39**, respectively. Unfortunately, complete separation of these two crystalline diastereomers was difficult even after chromatography and recrystallization.

Oxidation of diol **39** to the desired model compound **15** required some experimentation. Routine oxidants such as Dess-Martin periodinane, azadol-DAIB, Swern oxidation and chromic acid oxidation did not give even a trace of **15**. In 2013 Lei and co-workers reported that Ley oxidation[25] employing tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) in the presence or absence of MS 4A in CH_2Cl_2 was effective in synthesizing α-hydroxy ketones from vicinal diols related to *Lycopodium* alkaloids.[26] To my pleasure Ley oxidation could successfully be applied to the present case, giving (1*R*,5*R*,8*R*)-**15** in reproducible yield of 7–10%. The hydroxyketolactone (1*R*,5*R*,8*R*)-**15** was crystalline, and showed a large negative rotation, mp 153–155°C, $[\alpha]_D^{16}$ −332.8 (*c* 0.035, Et_2O). Because the two diastereomers of **15** seemed to co-crystallize, it was difficult to obtain pure (1*R*,5*R*,8*R*)-**15** without contamination of a small amount of its diastereoisomer. The structure (1*R*,5*R*,8*R*)-**15** assigned to the isolated oxidation product was in accord with its ^{1}H and ^{13}C NMR data (see 4.31), and this model compound possesses the enantiomeric bicyclic nucleus part of gomadalactone C (**3**).

Finally, the third model compound (1*R*,5*R*)-**16**, which represents the nucleus portion of gomadalactone B (**2**), was synthesized from (1*R*,5*R*,8*R*)-**15** by organoselenium-based desaturation at C6-C7.[27] Treatment of **15** with excess potassium hexamethyldisilazide [$KN(TMS)_2$] in toluene/THF at −78°C gave the dianion of **15**, to which was added PhSeBr to give a phenylselenylated product at C-7. Oxidation of the selenylated ketone with $NaIO_4$ in THF/H_2O furnished crude (1*R*,5*R*)-**16** (14%) after chromatographic purification. Recrystallization of crude **16** from EtOAc/pentane gave pure (1*R*,5*R*)-**16** (7%) as pale yellow prisms, mp 132.5–133.5°C, $[\alpha]_D^{20}$ −248.7 (*c* 0.0215, EtOAc). All the spectral data of (1*R*,5*R*)-**16** were in accord with the assigned structure. The structure (1*R*,5*R*)-**16** was conclusively established by its single crystal X-ray analysis. Figure 3 shows the X-ray structure of (1*R*,5*R*)-**16**. Its

(1*R*,5*R*)-absolute configuration is clearly seen from the structure. It must be added that gomadalactone B (**2**) was isolated as an amorphous solid, and therefore its X-ray crystallographic data are unavailable. Accordingly, the X-ray data of (1*R*,5*R*)-**16** are important to precisely examine its molecular shape, which will be required in future study on the interaction between the pheromone and its receptor.

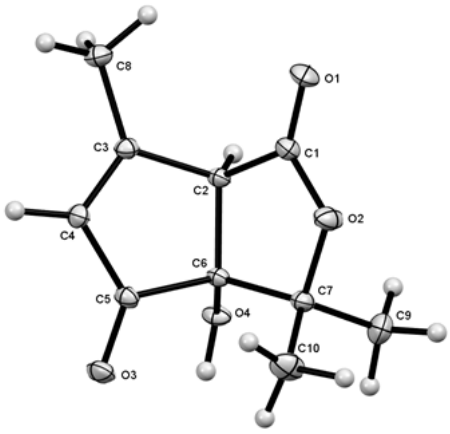


Figure 3. X-ray structure of (1*R*,5*R*)-**16**.

*2.7. CD spectral analysis of the three model compounds (1R,5S,8R)-**7**, (1R,5R,8R)-**15** and (1R,5R)-**16***

The absolute stereochemistries assigned to the three model compounds (1*R*,5*S*,8*R*)-**7**, (1*R*,5*R*,8*R*)-**15** and (1*R*,5*R*)-**16** were supported by their CD spectra. Figure 4 shows the CD spectra of **7**, **15** and **16**. The CD spectrum of the keto lactone (1*R*,5*S*,8*R*)-**7** was indeed the mirror image of that of its (1*S*,5*R*,8*S*)-isomer recorded in ref.[4] This fact supports the (1*R*,5*S*,8*R*)-stereochemistry of the keto lactone **7** reported in the present paper. In the case of (1*R*,5*R*,8*R*)-**15**, its CD spectrum is almost the mirror image of that of gomadalactone C (**3**). Finally, the CD spectrum of **16** was in good accord with that of gomadalactone B (**2**).

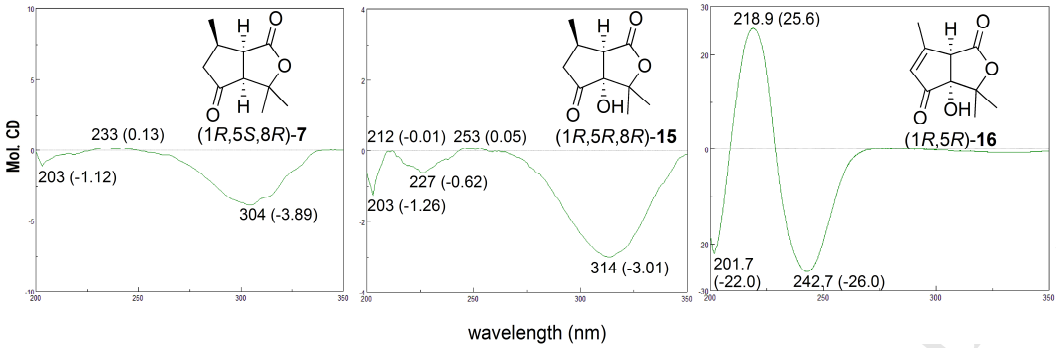


Figure 4. CD Spectra of (1*R*,5*S*,8*R*)-**7**, (1*R*,5*R*,8*R*)-**15** and (1*R*,5*R*)-**16**. They were measured in MeOH using a 10 mm cell at the concentrations of 6.6 x 10^{-5} M (**7**), 5.4 x 10^{-5} M (**15**) and 6.22 × 10^{-5} M (**16**), respectively, on a Jasco J-1500 CD spectrometer.

3. Conclusion

After several unsuccessful attempts, (*R*)-pulegone (**54**) was converted to the three model compounds **7**, **15** and **16** of the core 3-oxabicyclo[3.3.6]octane structures of gomadalactones A (**1**), B (**2**) and C (**3**). Synthesis coupled with CD and X-ray analyses allowed the assignments of absolute stereochemistries to all of the three model compounds as (1*R*,5*S*,8*R*)-**7**, (1*R*,5*R*,8*R*)-**15** and (1*R*,5*R*)-**16**. The present paper conclusively establishes the absolute configuration of gomadalactones A (**1**), B (**2**) and C (**3**), confirming my 2007 proposal.[4]

4. Experimental

4.1. General

All bps and mps are uncorrected values. Refractive indices were measured on an Atago DMT-1 refractometer. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ = 0.00 as the internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ = 77.0 as the internal standard) were recorded on a Jeol JNM-ECZ 400S/L1 spectrometer. GC-MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on Jeol JMS-700V or JMS-T100GV. Silica gel column chromatography was carried out on Merck Kieselgel 60 Art 1.00734.

*4.2. (±)-Ethyl 6,7-epoxy-7-methyl-2-octenoate (**21**)*

m-Chloroperbenzoic acid (70% purity, 4.90 g, 20 mmol) was added portionwise to a stirred and ice-cooled solution of **20** (*E*/*Z* = 94:6; 3.36 g, 18.5 mmol) in CH_2Cl_2 (30 mL). After stirring for 2 h at 0–10°C, the mixture was diluted with hexane, and

filtered. The filtrate was washed with Na_2CO_3 solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (3.95 g) was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (20:1) gave **21** (3.53 g, 96%) as a colorless oil, ν_{max} (film): 2980 (m), 2963 (m), 2929 (m), 1720 (s), 1655 (m), 1315 (m), 1267 (m), 1202 (m), 1163 (m), 1044 (m); δ_H ($CDCl_3$): 1.27 (3H, s), 1.29 (3H, t, *J* = 7 Hz), 1.31 (3H, s), 1.68–1.74 (2H, m), 2.31–2.50 (2H, m), 2.73 (1H, t, *J* = 6 Hz), 4.19 (2H, q, *J* = 7 Hz), 5.87 (1H, dd, *J* = 15, 14 Hz). HRMS calcd for $[C_{11}H_{18}O_3]^+$ (M^+): 198.1250, found: 198.1248.

*4.3. (±)-Ethyl 6,7-dihydroxy-7-methyl-2-octenoate (**22**)*

Perchloric acid (70%, 0.14 mL) was added to a vigorously stirred solution of **21** in THF (18 mL) and H_2O (10 mL). The mixture was stirred for 50 min at room temp. It was then neutralized with $NaHCO_3$, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give **22** (1.15 g, quant.) as a colorless oil, ν_{max} (film): 3427 (s), 2978 (s), 2904 (m), 1718 (s), 1653 (s), 1279 (s), 1200 (s), 1077 (s), 1044 (s), 979 (m), 928 (m); δ_H ($CDCl_3$): 1.17 (3H, s), 1.22 (3H, s), 1.29 (3H, t, *J* = 7 Hz), 1.45–1.56 (1H, m), 1.56–1.66 (1H, m), 1.80–1.90 (1H, m), 1.93–2.10 (1H, m), 2.24–2.36 (2H, m), 2.45–2.65 (2H, m), 3.35–3.42 (1H, m), 3.90–4.00 (1H, m), 4.18 (2H, q, *J* = 7 Hz), 5.58–5.60 (0.4H, m), 5.87 (0.6H, d, *J* = 16 Hz), 6.90–7.03 (1H, m). HRMS calcd for $[C_{11}H_{22}O_3]^+$ $[(M-H_2O)^+]$: 198.1256, found: 198.1257.

*4.4. (±)-Ethyl 7-Hydroxy-7-methyl-6-oxo-2-octenoate (**18**)*

A solution of DMSO (0.66 mL, 4.2 mmol, 1.1 eq) in CH_2Cl_2 (6 mL) was added dropwise to a stirred and cooled solution of $(COCl)_2$ (0.42 mL, 4.8 mmol, 1.2 eq) in CH_2Cl_2 (6 mL) at −78°C under argon. After 5 min, a solution of **22** (850 mg, 3.94 mmol) in CH_2Cl_2 (5 mL) was added to the stirred solution at −78°C. The stirring was continued for 15 min at −78°C. Subsequently, Et_3N (2.8 mL, 20 mmol, 5.0 eq) was added in one portion, and the stirring was continued for 10 min at −78°C. The temperature was gradually raised to room temperature. The mixture was diluted with Et_2O, and the Et_2O solution was washed with NH_4Cl solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (0.81 g) was chromatographed over SiO_2 (25 g). Elution with hexane/EtOAc (25:1→15:1→10:1) gave various by-products. Further elution with hexane/EtOAc (5:1) gave **18** (374 mg, 43%) as a colorless oil, ν_{max} (film): 3487 (m), 2980 (s), 1715 (s), 1655 (s), 1193 (s), 1045 (s); δ_H ($CDCl_3$): 1.26 (3H, t, *J* = 7 Hz), 1.39 (6H, s), 2.52 (2H, q, *J* = 7 Hz), 2.75 (2H, t, *J* = 7 Hz), 3.62 (1H, s), 4.18 (2H, q, *J* = 7 Hz), 5.85 (1H, dd, *J* = 1.5, 16 Hz), 6.89–6.96 (1H, m). GC-MS [column: HP-5MS,5% phenylmethylsiloxane, 0.25 mm i.d. × 30 m; carrier gas He, press 61 kPa; temp 70–230°C (+10°C/min)]: t_R 12.97 min (96%); MS (70 eV, EI): *m*/*z*: 196 (<1) $[(M-H_2O)^+]$, 171 (11), 151 (8), 128 (100), 100 (95), 82 (21), 68 (14), 59 (96),

43 (44). HRMS calcd for $[C_{11}H_{16}O_3]^+$ $[(M-H_2O)^+]$: 196.1099, found: 196.1102.

*4.5. (±)-Ethyl 2-hydroxy-2-(1-hydroxy-1-methylethyl)-6-methyl-cyclopentane-1-carboxylate (**19**)*

A solution of MeLi in Et_2O (0.75 M, 1.2 mL, 9 mmol) was added to a stirred and cooled suspension of CuI (950 mg, 5 mmol) in dry Et_2O (10 mL) at −25°C under argon. The mixture was stirred for 30 min at −5°C to generate Me_2CuLi. Subsequently, a solution of **18** (261 mg, 1.2 mmol) in dry Et_2O (4 mL) was added dropwise to the Me_2CuLi solution at −50–−40°C. The mixture was stirred for 30 min at −50–−40°C, then quenched by the addition of NH_4Cl solution, and extracted with Et_2O. The Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (232 mg) was chromatographed over SiO_2 (5 g). Elution with hexane/EtOAc (10:1) gave **19** (74 mg, 27%) as a colorless oil, ν_{max} (film): 3460 (m), 2957 (s), 2929 (s), 2870 (m), 1705 (s), 1377 (s), 1185 (s), 1026 (m), 954 (m); δ_H ($CDCl_3$): 1.05 (3H, d, *J* = 6 Hz), 1.22 (3H, s), 1.23 (3H, s), 1.29 (3H, t, *J* = 7 Hz), 1.65–1.75 (2H, m), 1.84–1.93 (1H, m), 2.05–2.14 (1H, m), 2.20 (1H, m), 2.46 (1H), 2.48–2.58 (1H, m), 4.19 (2H, q, *J* = 7 Hz), 4.57 (1H); δ_C ($CDCl_3$): 14.1, 19.1, 24.8, 25.1, 31.3, 34.9, 38.6, 55.1, 60.9, 74.5, 88.3, 177.0; GC-MS (same conditions as those used for **18**): t_R 11.7 min (76%) MS (70 eV, EI): *m*/*z*: 212 (2) $[(M-H_2O)^+]$, 171 (57), 125 (100), 115 (13), 97 (14), 83 (15), 69 (24), 59 (11), 43 (12). HRMS calcd for $[C_{12}H_{20}O_3]^+$ $[(M-H_2O)^+]$: 212.1412, found: 212.1400.

*4.6. 3-t-Butyldimethylsilyloxy-2,2-dimethylpropanol (**25**)*

Azadol (80 mg, 0.52 mmol) and **25** (22.3 g, 102 mmol) were dissolved in CH_2Cl_2 (300 mL) containing H_2O (3 mL). Crystals of $NaOCl \cdot 5H_2O$ (20.1 g, 122 mmol, 1.2 eq) was added in one portion to the stirred and ice-cooled CH_2Cl_2 solution of **25**. The color of the mixture turned red and then faded to faint yellow. The stirring was continued for 30 min. Then the reaction was quenched by the addition of $Na_2S_2O_3$ and $NaHCO_3$ (aqueous solution). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with Et_2O. The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give **26** (17.7 g, 80%) as a colorless oil, bp 66–70°C/0.5 kPa: n_D^{25} = 1.4260; ν_{max} (film): 2957 (s), 2931 (s), 2887 (m), 2858 (s), 1733 (s), 1472 (m), 1257 (m), 1104 (s), 839 (s), 777 (m); δ_H ($CDCl_3$): 0.03 (6H, s), 0.86 (9H, s), 1.04 (6H, s), 3.58 (2H, s), 9.56 (1H, s); GC-MS (same conditions as those used for **18**): t_R 8.38 min (93%); MS (70 eV, EI): *m*/*z*: 201 (<1) $[(M-CH_3)^+]$, 159 (100), 129 (29), 115 (73), 89 (9), 75 (66), 59 (13). HRMS calcd for $[C_{10}H_{21}O_2Si]^+$ $[(M-CH_3)^+]$: 201.1311, found: 201.1313.

*4.7. (±)-2,2-Dimethyl-5-hexene-1,3-diol 1-TBS ether (**27**)*

A solution of **25** (8.76 g, 40.6 mmol) in THF (30 mL) was added dropwise to a stirred and ice-cooled solution of CH_2=$CHCH_2MgCl$ in THF (1 M, 50 mL, 50 mmol) at 10–20°C. The mixture was stirred for 30 min at room temperature. It was then quenched by the addition of ice and NH_4Cl solution, and extracted with Et_2O. The Et_2O extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (10.81 g) was chromatographed over SiO_2 (80 g). Elution with hexane/EtOAc (20:1) gave **27** (7.69 g, 73%) as a colorless oil, n_D^{25} = 1.4450; ν_{max} (film): 3501 (br m), 3076 (w), 2956 (s), 2930 (s), 2886 (m), 2858 (s), 1640 (w), 1472 (m), 1254 (m), 1094 (s), 838 (s), 776 (s); δ_H ($CDCl_3$): 0.06 (6H, s), 0.96 (15H, br s), 1.26 (1H, br s), 2.08–2.11 (1H, m), 2.24–2.25 (1H, m), 3.46 (2H, m), 3.56 (1H, m), 5.06–5.13 (2H, m), 5.90–5.97 (1H, m); GC-MS (same conditions as those used for **18**): t_R 10.9 min (99%); MS (70 eV, EI): *m*/*z*: 217 (14), 159 (13), 145 (13), 109 (59), 105 (35), 89 (24), 75 (100), 73 (36), 67 (17), 41 (13). This was used for the next step without further characterization.

*4.8. (±)-2,2-Dimethyl-5-hexene-1,3-diol p-methoxybenzylidene acetal (**28**)*

Camphorsulfonic acid (150 mg, 0.6 mmol) was added to a solution of **27** (7.09 g, 27.3 mmol) and *p*-methoxybenzaldehyde dimethylacetal (9.83 g, 54 mmol) in DMF (30 mL). The mixture was stirred for 4 h at room temperature, then poured into ice and $NaHCO_3$ solution, and extracted with Et_2O. The Et_2O extract was washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (13.92 g) was fractionally distilled to give first the recovered *p*-methoxybenzaldehyde dimethylacetal (bp 100°C/0.2 kPa) and then **28** (2.96 g, 34%) as a colorless oil, bp 150–158°C/0.2 kPa; n_D^{24} = 1.5144; ν_{max} (film): 3075 (w), 2956 (m), 2838 (m), 1642 (w), 1615 (m), 1589 (w), 1518 (s), 1467 (m), 1392 (s), 1358 (m), 1303 (m), 1250 (s), 1172 (m), 1114 (s), 1036 (s), 826 (s); δ_H ($CDCl_3$): 0.80 (3H, s), 1.15 (3H, s), 2.24–2.27 (2H, m), 3.52–3.60 (2H, m), 3.69 (1H, m), 3.80 (3H, s), 5.03–5.13 (2H, m), 5.44 (1H, s), 5.91–5.98 (1H, m), 6.89 (2H, d, *J* = 8 Hz), 7.43 (2H, d, *J* = 8 Hz); GC-MS (same conditions as those used for **18**): t_R 16.43 min (91%); MS (70 eV, EI):*m*/*z*: 262 (26) [M^+] 261 (31), 221 (12), 137 (60), 136 (100), 135 (96), 109 (18), 108 (12), 81 (15), 77 (15). HRMS calcd for $[C_{16}H_{22}O_3]^+$ (M^+): 262.1569, found: 262.1531.

*4.9. (±)-2,2-Dimethyl-5-hexene-1,3-diol 3-PMB ether (**29**)*

A solution of (*i*-Bu)$_2$AlH in CH_2Cl_2 (1 M, 37 mL, 37 mmol) was added dropwise to a stirred and ice-cooled solution of **28** (2.96 g, 11 mmol) in CH_2Cl_2 (10 mL) at 5–10°C under argon. After stirring for 3 h at 5°C, the mixture was quenched with ice and dil. HCl (containing 10 mL of conc HCl), and extracted with Et_2O. The Et_2O solution was washed successively with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated

in vacuo to give **29** (2.97 g, quant.) as a colorless oil, n_D^{25} = 1.5088; ν_{max} (film): 3437 (br m), 3074 (w), 2598 (m), 2911 (m), 2873 (m), 2837 (m), 1639 (w), 1613 (m), 1586 (w), 1514 (s), 1466 (m), 1302 (m), 1249 (s), 1173 (m), 1078 (s), 1038 (s), 912 (m), 812 (m); δ_H ($CDCl_3$): 0.88 (3H, s), 0.98 (3H, s), 2.29–2.50 (2H, m), 2.76 (1H, t, *J* = 6 Hz), 3.30–3.40 (2H, m), 3.55–3.62 (1H, m), 3.80 (3H, s), 4.41 (1H, d, *J* = 7 Hz), 4.61 (1H, d, *J* = 7 Hz), 5.04–5.20 (2H, m), 5.90–6.20 (1H, m), 6.87 (2H, d, *J* = 8 Hz), 7.25 (2H, d, *J* = 8 Hz); GC-MS (same conditions as those used for **18**): t_R 17.12 min (97%); MS (70 eV, EI): *m*/*z*: 264 (<1) [M^+], 191 (10), 138 (2), 137 (5), 122 (12), 121 (100), 91 (3), 78 (5), 77 (5), 55 (2), 41 (2). HRMS calcd for $[C_{16}H_{24}O_3]^+$ (M^+): 264.1725, found: 264.1715.

*4.10. (±)-2,2-Dimethyl-3-p-methoxybenzyloxy-5-hexenal (**30**)*

Diacetoxyiodobenzene (3.50 g, 11 mmol) was added quickly to a solution of **29** (2.70 g, 10 mmol) and azadol (20 mg, 0.13 mmol) in CH_2Cl_2 (70 mL) with stirring and ice-cooling. The mixture was stirred for 10 min at 5–10°C, when it became homogeneous. It was then diluted with Et_2O, washed successively with $Na_2S_2O_3$/$NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (6.6 g) was chromatographed over SiO_2 (50 g). Elution with hexane gave iodobenzene (1.58 g), and further elution with hexane/EtOAc (50:1–10:1) gave **30** (2.00 g, 75%) as a colorless oil, n_D^{26} = 1.5074; ν_{max} (film): 3075 (w), 2960 (m), 2936 (m), 2909 (m), 2871 (m), 2873 (m), 2709 (w), 1726 (s), 1640 (w), 1613 (m), 1586 (w), 1514 (s), 1466 (m), 1302 (m), 1249 (s), 1173 (m), 1083 (s), 1037 (s), 916 (m), 822 (m); δ_H ($CDCl_3$): 1.05 (3H, s), 1.11 (3H, s), 1.30–2.40 (2H, m), 3.58 (1H, t, *J* = 5 Hz), 3.80 (3H, s), 4.40 (1H, d, *J* = 7 Hz), 4.58 (1H, d, *J* = 7 Hz), 5.08–5.20 (2H, m), 5.82–5.98 (1H, m), 6.86 (2H, d, *J* = 9 Hz), 7.21 (2H, d, *J* = 9 Hz), 9.55 (1H, s): GC-MS (same conditions as those used for **18**): t_R 16.40 min (95%); MS (70 eV, EI): *m*/*z*: 262 (<1) [M^+], 150 (5), 137 (9), 122 (11), 121 (100), 91 (3), 78 (5), 77 (6), 41 (3). HRMS calcd for $[C_{16}H_{22}O_3]^+$ (M^+): 262.1569, found: 262.1561.

*4.11. 5,5-Dimethyl-6-p-methoxybenzyloxy-1,8-nonadien-4-ol (**31**)*

A solution of **30** (2.00 g, 7.5 mmol) in THF (5 mL) was added to a stirred and ice-cooled solution of CH_2=$CHCH_2MgCl$ in THF (1 M, 15 mL, 15 mmol) under argon. The mixture was stirred and heated for 1 h at 40°C. After cooling, it was poured into ice and NH_4Cl solution, and extracted with Et_2O. The Et_2O solution was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (2.56 g) was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (20:1) gave **31** (2.10 g, 91%) as a colorless oil, n_D^{26} = 1.5132; ν_{max} (film): 3481 (br m), 3074 (w), 2973 (m), 2912 (m), 2876 (m), 1639 (m), 1613 (m), 1586 (w), 1514 (s), 1249 (s),

1065 (s), 1037 (s), 912 (m), 822 (m); δ_H ($CDCl_3$): 0.84 (1.7H, s), 0.86 (1.3H, s), 0.97 (1.7H, s), 1.00 (1.3H, s), 1.69 (0.4H, s), 2.00–2.60 (4H, m), 2.78 (0.6H, s), 3.30–3.48 (1H, m), 3.54–3.72 (1H, m), 3.79 (3H, s), 4.38–4.48 (1H, m), 4.60–4.68 (1H, m), 5.02–5.20 (4H, m), 5.80–6.04 (2H, m), 6.80–6.90 (2H, m), 7.20–7.30 (2H, m); GC-MS (same conditions as those used for **18**): t_R 19.03 min (100%); MS (70 eV, EI): *m*/*z*: 191 (3), 138 (6), 137 (8), 122 (12), 121 (100), 109 (3), 78 (3), 77 (3), 43 (3), 41 (3). HRMS calcd for $[C_{19}H_{28}O_3]^+$ (M^+): 304.2038, found: 304.2033.

*4.12. 2,2-Dimethyl-5-cycloheptene-1,3-diol 1-p-methoxybenzyl ether (**32**)*

Grubbs II catalyst (42 mg, 0.005 mmol, 0.7 mol%) was added to a solution of **31** (2.08 g, 6.8 mmol) in CH_2Cl_2 (50 mL). The solution was stirred and heated under reflux for 1 h under argon. (Evolution of $H_2C{=}CH_2$ ceased after 30 min.) The mixture was concentrated in vacuo, and the residue was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (20:1–10:1) gave **32** (1.74 g, 92%) as a colorless oil, n_D^{27} = 1.5178; ν_{max} (film): 3451 (br m), 3022 (w), 2956 (m), 2933 (m), 2910 (m), 2870 (m), 2837 (m), 1655 (w), 1613 (m), 1586 (w), 1514 (s), 1465 (m), 1302 (m), 1249 (s), 1173 (m), 1072 (s), 1037 (s), 822 (m); δ_H ($CDCl_3$): 0.97 (2H, s), 1.049 (1H, s), 1.056 (1H, s), 1.23 (2H, s), 1.56 (0.35H, br s), 1.69 (0.65H, br s), 2.25–2.58 (4H, m), 3.26–3.32 (1H, m), 3.58 (1H, d, *J* = 7 Hz), 3.80 (3H, s), 4.24–4.34 (1H, m), 4.52–4.58 (1H, m), 5.60–5.80 (2H, m), 6.84–6.90 (2H, m), 7.22–7.28 (2H, m); GC-MS (same conditions as those used for **18**): t_R 19.38 min (100%); MS (70 eV, EI): *m*/*z*: 258 (1.5) [$(M-H_2O)^+$], 137 (4), 122 (11), 121 (100), 91 (2), 78 (3), 77 (4), 55 (2), 43 (2), 41 (1). HRMS calcd for $[C_{17}H_{24}O_3]^+$ (M^+): 276.1725, found: 276.1414.

*4.13. (±)-2,2-Dimethyl-3-p-methoxybenyloxy-5-cyclo hepten-1-one (**33**)*

Jones chromic acid (8 M in oxygen, 2 mL, 16 meq) was added to a stirred and ice-cooled solution of **32** (1.58 g, 5.7 mmol) in acetone (20 mL) at 5–10°C. The mixture was stirred for 10 min, then concentrated in vacuo, and partitioned between Et_2O and water. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give **33** (1.27 g, 81%) as a colorless oil, n_D^{26} = 1.5156; ν_{max} (film): 2969 (m), 2934 (m), 2907 (m), 2870 (m), 2836 (m), 1703 (s), 1655 (w), 1613 (m), 1586 (w), 1514 (s), 1465 (m), 1302 (m), 1249 (s), 1173 (m), 1090 (m), 1036 (m), 822 (m); δ_H ($CDCl_3$): 1.13 (3H, s), 1.21 (3H, s), 2.40–2.62 (2H, m), 3.12–3.26 (1H, m), 3.36–3.50 (1H, m), 3.68 (1H, m), 3.81 (3H, s), 4.38 (1H, d, *J* = 7 Hz), 4.61 (1H, d, *J* = 7 Hz), 5.59 (2H, m), 6.87 (2H, d, *J* = 9 Hz), 7.24–7.36 (2H, m); δ_C ($CDCl_3$): 21.1, 23.9, 29.9, 41.7, 52.8, 55.4, 71.5, 80.7, 113.8, 122.0, 127.5, 129.2, 130.6, 159.2, 211.3; GC-MS (same conditions as those used for **18**): t_R 18.88 min (100%); MS (70 eV, EI): *m*/*z*: 274 (2) [M^+], 138 (2), 137 (6), 122 (9),

121 (100), 91 (3), 78 (4), 77 (4), 43 (1), 41 (1), 41 (2). HRMS calcd for $[C_{17}H_{22}O_3]^+$ (M^+): 274.1569, found: 274.1556.

*4.14. (±)-2,2-Dimethyl-3-p-methoxybenzyloxy-1-cyclroheptanone (**23**)*

Palladium on barium sulfate (5%, 150 mg) was added to a solution of **33** (1.23 g, 4.5 mmol) in EtOAc (5 mL)/hexane (10 mL). The mixture was stirred under H_2 (balloon) for 1 h at room temperature. The mixture was passed through a column of SiO_2 (10 g), and the column was washed with hexane/EtOAc (15:1). The eluent was concentrated in vacuo to give **23** (1.03 g, 84%) as a colorless oil, n_D^{26} = 1.5153; ν_{max} (film): 2935 (s), 2863 (m), 1699 (s), 1612 (m), 1514 (s), 1465 (m), 1302 (m), 1249 (s), 1173 (m), 1100 (m), 1074 (m), 1036 (m), 821 (m); δ_H ($CDCl_3$): 1.09 (3H, s), 1.14 (3H, s), 1.50–1.70 (3H, m), 1.70–1.90 (3H, m), 2.42–2.52 (1H, m), 2.60–2.70 (1H, m), 3.43–3.50 (1H, m), 3.81 (3H, s), 4.32 (1H, d, *J* = 12 Hz), 4.60 (1H, d, *J* = 12 Hz), 6.88 (2H, d, *J* = 7 Hz), 7.27 (2H, d, *J* = 7 Hz); δ_C ($CDCl_3$): 20.9, 24.7, 25.4, 26.1, 28.6, 41.3, 52.6, 55.3, 71.1, 82.5, 113.9, 129.2, 130.7, 159.2, 217.0; GC-MS (same conditions as those used for **18**): t_R 18.94 min (100%); MS (70 eV, EI): *m*/*z*: 276 (<1) [M^+], 140 (5), 137 (14), 125 (2), 122 (10), 121 (100), 91 (2), 78 (3), 77 (4), 55 (2), 41 (3). HRMS calcd for $[C_{17}H_{24}O_3]^+$ (M^+): 276.1725, found: 276.1754.

*4.15. 2-Hydroxy-5,5-dimethyltetrahydrofuran-4-one (**41**)*

A solution of **40** (24.0 g, 235 mmol) and ethyl formate (26.0 g, 351 mmol) in Et_2O (20 mL) was added dropwise over 1 h to a stirred and ice-cooled suspension of NaH (60% NaH in mineral oil, 19.2 g, 480 mmol) in Et_2O (400 mL) under argon. The H_2 evolved was released frequently. The mixture was stirred for 4 h at room temperature to give a thick solid mass. It was then acidified with ice and conc H_2SO_4 (16 mL, 29.4 g, 300 mmol) diluted with water (160 mL). The mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (35.9 g) was distilled to give **41** (20.7 g, 67%) as a colorless oil, bp 80–84°C/0.4 kPa; n_D^{23} = 1.4471 (ref.[17] n_D^{25} = 1.4424); ν_{max} (film): 3425 (br s), 2981 (m), 2934 (m), 2871 (w), 1759 (s), 1460 (m), 1379 (m), 1361 (m), 1200 (m), 1173 (m), 1146 (m), 1112 (s), 1058 (m), 984 (s), 965 (m), 927 (m); δ_H ($CDCl_3$): 1.24 (3H, s), 1.39 (3H, s), 2.52 (1H, d, *J* = 18 Hz), 2.78 (1H, dd, *J* = 6, 18Hz), 3.70 (1H, br s), 5.78 (1H, d, *J* = 6 Hz); δ_C ($CDCl_3$): 24.9, 26.3, 43.0, 80.6, 94.3, 216.2; GC-MS (same conditions as those used for **18**): t_R 4.57 min (99%); MS (70 eV, EI): *m*/*z*: 102 (14) [$(M-H_2O)^+$], 71 (4), 69 (4), 59 (100), 44 (16), 43 (34). HRMS calcd for $[C_6H_{10}O_3]^+$ (M^+): 130.0630, found: 130.0631.

*4.16. Δ^2-5,5-Dimethyldihydrofuran-4-one (**42**)*

Powdered $CuSO_4$ (20 g, 125 mmol) and $MgSO_4$ (5 g, 42 mmol) were added to a

stirred solution of **41** (16.0 g, 123 mmol) in Et_2O (200 mL) containing ten drops of conc HCl, and the mixture was stirred for 2 d at room temperature. The mixture was filtered, and the solid was washed with Et_2O. The combined filtrate and washings were concentrated (Vigreux column) under atmospheric pressure, and the residue was distilled to give **42** (7.65 g, 58%) as a colorless oil, bp 63–65°C/4.4 kPa, n_D^{25} = 1.4478; ν_{max} (film): 3110 (w), 3067 (w), 2982 (m), 2934 (w), 2870 (w), 1706 (s), 1562 (s), 1454 (w), 1379 (m), 1365 (m), 1279 (w), 1198 (s), 1172 (s), 1089 (v), 1043 (m), 953 (w), 848 (w), 795 (m), 513 (m); δ_H ($CDCl_3$): 1.37 (6H, s), 5.58 (1H, d, *J* = 2 Hz), 8.13 (1H, d, *J* = 2 Hz); δ_C ($CDCl_3$): 22.7, 87.6, 104.8, 176.3, 207.8; GC-MS (same conditions as those used for **18**): t_R 3.91 min (94%); MS (70 eV, EI): *m*/*z*: 112 (100) [M^+], 71 (24), 69 (8), 58 (23), 54 (53), 43 (57), 42 (11), 41 (13). HRMS calcd for $[C_6H_8O_2]^+$ (M^+): 112.0524, found: 112.0530.

*4.17. 2,2-Dimethyltetrahydrofuran-3-one (**34**)*

Palladium-charcoal (10%, 1.0 g) was added to a solution of **42** (13.1 g, 117 mmol) in AcOMe (40 mL), and the mixture was stirred under H_2 atmosphere (balloon) for 6 h at room temperature, when H_2 uptake ceased. The mixture was filtered through Celite, and the Celite layer was washed with AcOMe. The filtrate was concentrated (Vigreux column), and the residue was distilled to give 10.24 g (77%) of **34** as a colorless oil, bp 65–66°C/4.0 kPa, n_D^{25} = 1.4240; ν_{max} (film): 2979 (m), 2932 (w), 2876 (w), 1757 (s), 1715 (sh), 1182 (s), 1103 (s), 1018 (m), 968 (m), 834 (m), 508 (m), δ_H ($CDCl_3$): 1.20 (6H, s), 2.52 (2H, t, *J* = 7 Hz), 4.11 (2H, t, *J* = 7 Hz); δ_C ($CDCl_3$): 22.4, 35.9, 61.5; 79.2, 217.7; GC-MS (same conditions as those used for **18**): t_R 3.80 min (95%); MS (70 eV, EI): *m*/*z*: 114 (9) [M^+], 86 (43), 58 (20), 43 (100). HRMS calcd for $[C_6H_{10}O_2]^+$ (M^+): 114.0681, found: 114.0687.

*4.18. 5,5-Dimethyltetronic acid (5,5-dimethyltetrahydrofuran-2,4-dione (**35**)*

Jones chromic acid (8 M for oxygen, 39 mL, 312 meq) was added dropwise over 10 min to a stirred and ice-cooled solution of **41** (20.7 g, 159 mmol) at 10–15°C. The mixture was stirred for further 10 min at 5–10°C. It was then concentrated in vacuo. The residue was diluted with water, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual semi-solid (18.9 g) was recrystallized from EtOAc/hexane to give **35** (8.00 g, 39%) as colorless rhombs, mp 145–146°C (ref.[18] mp 151–152°C; ref.[19] mp 142–143°C; ν_{max} (nujol): 2600–2400 (br m), 1748 (w), 1697 (s), 1677 (s), 1651 (m), 1558 (s), 1304 (s), 1235 (m), 1194 (m), 1109 (m), 985 (m), 800 (m); δ_H (DMSO-d_6, 500 MHz): 1.38 (6H, s), 4.79 (1H, s), 12.65 (1H, br s); δ_C (DMSO-d_6, 126 MHz): 24.0, 81.3, 86.0, 171.8, 185.2. HRMS calcd for $[C_5H_8O_3]^+$ (M^+): 128.0473, found; 128.0469.

*4.19. 3,3-Dimethyl-4-pentenoic acid (**48**)*

A stirred mixture of **46** (68.8 g, 0.80 mol), $MeC(OEt)_3$ (194.4 g, 1.20 mol) and $EtCO_2H$ (2 mL) was gradually heated to raise up the inner temperature at 145°C, while ca. 150 mL of EtOH was removed by distillation. An additional amount of $EtCO_2H$ (2 mL) was then added, and the mixture was stirred and heated at 145–150°C for 3 h, while removing ca 40 mL of EtOH. After cooling below 60°C, dil HCl (1 mL of conc HCl and 100 mL of water) was added to the mixture to destroy excess $MeC(OEt)_3$. (Addition of conc HCl as reported in ref.[20] damages the product **47**, and therefore dil HCl must be used.) Then the mixture was stirred and heated at 120°C (bath temperature to remove 120 mL of a mixture of EtOAc, EtOH and water to give crude **47**. The crude **47** was diluted with MeOH (180 mL) and water (300 mL), and KOH (93.0 g, 1.66 mol) was added portionwise with stirring. The mixture was stirred and heated under reflux for 2 h, then concentrated under atmospheric pressure removing 320 mL of distillates at bath temperature of 110°C. After cooling, neutral impurities were removed by extraction with Et_2O. The aqueous layer was diluted with ice and water, and acidified with conc HCl (160 mL, 1.92 mol). The separated acid was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give **48** (71.2 g, 70%) as a colorless oil, bp 80–90°C/1.7 kPa; ν_{max} (film): ~3086–2674 (br s), 2967 (s), 1710 (s), 1640 (m), 1415 (m), 1250 (m), 998 (m), 916 (m); δ_H ($CDCl_3$): 1.16 (6H, s), 2.33 (2H, s), 4.95–5.02 (2H, m), 5.87–5.94 (1H, m); δ_C ($CDCl_3$): 27.0, 36.1, 46.7, 111.2, 146.6, 178.6. The ^{13}C NMR data were identical with those reported in ref.[20]

*4.20. 5-Iodomethyl-4,4-dimethyltetrahydrofuran-2-one (**49**)*

Powdered $NaHCO_3$ (75.0 g, 0.89 mol) was added portionwise to a vigorously stirred mixture of **48** (71.2 g, 0.56 mol) in water (1.5 L). After the addition, the vigorous stirring was continued for 15 min to dissolve **48** as its Na salt. Subsequently, NaI (19.6 g, 0.13 mol) was added to the aqueous solution. Iodine (141 g, 0.55 mol) was added portionwise over 4 h to the stirred mixture. The flask was wrapped with aluminum foil, and the stirring was continued for 3 d at room temperature. It was then extracted with CH_2Cl_2. The extract was washed with 10% $Na_2S_2O_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to give **49** (137.1 g, 97%) as a colorless oil, ν_{max} (film): 2964 (m), 1783 (s), 1467 (m), 1417 (m), 1286 (m), 1232 (m), 1200 (m), 1177 (s), 1122 (s), 991 (s), 972 (s), 929 (m), 736 (m), 622 (m); δ_H ($CDCl_3$): 1.10 (3H, s), 1.28 (3H, s), 2.47 (2H, s), 3.21–3.25 (1H, m), 3.29–3.33 (1H, m), 4.39–4.42 (1H, m); δ_C ($CDCl_3$): −0.7, 20.8, 26.1, 40.0, 44.7, 87.9, 174.2. The NMR data were in good accord with those reported in ref. [20]

*4.21. 3,3-Dimethyl-4-penten-4-olide (**50**)*

A solution of DBU (89.6 g, 0.59 mol) in C_6H_6 (100 mL) was added dropwise to a stirred solution of **49** (137.1 g, 0.556 mol) in C_6H_6 (500 mL). The mixture was stirred and heated under reflux for 2 h. After cooling, the mixture was filtered to remove precipitated DBU·HI salt, and the solid was washed thoroughly with Et_2O. The combined filtrate and washings were washed with dil HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give **50** (52.0 g, 76%) as a colorless oil, bp 60–61°C/0.6 kPa, ν_{max} (film): 2970 (m), 2932 (w), 2874 (w), 1806 (s), 1670 (s), 1466 (w), 1419 (w), 1371 (w), 1257 (m), 1232 (m), 1199 (m), 1096 (s), 981 (s), 843 (m); δ_H ($CDCl_3$): 1.33 (6H, s), 2.50 (2H, s), 4.30 (1H, s), 4.66 (1H, s); δ_C ($CDCl_3$): 28.0, 39.1, 43.0, 86.2, 165.9, 173.2. The ^{13}C NMR data were in good accord with those reported in ref.[20]

*4.22. 3,3-Dimethyl-4-oxopentanoic acid (**51**)*

A solution of KOH (30.8 g, 0.55 mol) in water (200 mL) was slowly added to stirred **50** (51.9 g, 0.41 mol). Exothermic hydrolysis of **50** took place. The mixture was stirred for 15 min at room temperature, acidified with conc HCl (50 mL, 0.55 mol) and ice, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), and concentrated in vacuo to give **51** (61.2 g, quant) as a colorless oil, ν_{max} (film): ~3500–~2650 (m), 2975 (s), 1708 (s), 1366 (m), 1241 (m), 1172 (s), 1127 (m), 923 (m); δ_H ($CDCl_3$): 1.22 (6H, s), 2.17 (3H, s), 2.60 (2H, s); δ_C ($CDCl_3$): 25.0, 25.3, 43.8, 45.9, 177.2, 213.0. The ^{13}C NMR data were in good accord with those reported in ref.[21].

*4.23. 3,4-Dimethyl-2-penten-4-olide (**43**)*

Polyphosphoric acid was prepared by adding P_2O_5 (90 g, 0.63 mol) to 85% H_3PO_4 (60 mL), and heating the stirred mixture at 110°C for 1 h. The oily **51** (18.6 g, 0.13 mol) was added slowly to the stirred polyphosphoric acid, and the mixture was stirred and heated at 130°C for 30 min. After cooling, the mixture was diluted with ice and water, saturated with NaCl, and extracted with Et_2O. The extract was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give **43** (7.78 g, 48%) as a slightly yellowish solid, bp 73–75°C/0.3 kPa, mp 40–41°C; ν_{max} (film): 3104 (w), 1737 (s), 1665 (m), 1642 (m), 1460 (s), 1385 (m), 1368 (m), 1275 (m), 1171 (m), 1091 (m), 968 (s), 735 (m), 588 (m); δ_H ($CDCl_3$): 1.42 (6H, s), 2.01 (3H, s), 5.66 (1H, s); δ_C ($CDCl_3$): 13.0, 24.6, 87.4, 115.6, 172.2, 173.3. The ^{13}C NMR data were in good accord with those reported in ref.[21]. HRMS calcd for $[C_7H_{10}O_2]^+$ (M^+): 126.0681, found: 126.0681.

*4.24. 2-(3-Butenyl)-3,4-dimethyl-2-penten-4-olide (**52**)*

A solution of lithium diisopropylamide (1.5 M in THF/heptane/toluene, 20 mL, 30

mmol) was added dropwise to a stirred and cooled solution of **43** (3.78 g, 30 mmol) in THF (10 mL) at −75°C under argon. The mixture was stirred and −75°C for 30 min. Then a solution of 1-iodo-3-butene (6.00 g, 33 mmol) in THF (15 mL) was added dropwise over 10 min to the stirred and cooled mixture at −75°C. After stirring for 1 h at −75°C, the mixture was further stirred for 1 h at room temperature. It was then quenched with NH_4Cl solution. The mixture was diluted with water, and extracted with Et_2O. The Et_2O solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (5.95 g) was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (5:1) gave **52** (2.35 g, 44%). A portion of the crude **52** was distilled to give pure **52** as a colorless oil, bp 104–106°C/0.2 kPa; n_D^{24} = 1.4734; ν_{max} (film): 3078 (w), 2979 (m), 2932 (w), 2869 (w), 1749 (s), 1679 (m), 1640 (w), 1291 (m), 1202 (m), 1073 (m), 969 (m), 912 (m); δ_H ($CDCl_3$): 1.35 (6H, s), 1.87 (3H, s), 2.21–2.26 (4H, m), 4.89–4.97 (2H, m), 5.66–5.73 (1H, m); δ_C ($CDCl_3$): 11.1, 22.9, 24.8, 24.9, 32.0, 85.6, 115.7, 125.1, 137.2, 164.8, 173.1; GC-MS (same conditions as those used for **18**): t_R 18.21 min (91%); MS (70 eV, EI): *m/z*: 180 (21) [M^+], 165 (45), 135 (45), 121 (74), 107 (32), 93 (48), 79 (35), 43 (100). HRMS Calcd for $[C_{11}H_{16}O_2]^+$ (M^+): 180.1150, found: 180.1149.

*4.25. (1S,5R)-trans-Pulegenic acid (**57**)*

*4.25.1 (R)-Pulegone dibromide (**55**)*

Bromine (19 mL, 370 mmol) was added dropwise over 30 min to a stirred and ice-cooled solution of **54** (54.2 g, 357 mmol) in glacial AcOH (75 mL) at 5–15°C. The mixture was stirred for 30 min after the addition of Br_2, poured into ice-water, and extracted with pentane. The pentane solution was washed with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and filtered to give a pentane solution of **55**.

*4.25.2. A cis/trans-mixture of ethyl pulegenates (**56**)*

The above solution of **55** was added dropwise to a stirred and heated solution of NaOEt (68 g, 1 mol) in EtOH (400 mL). After distilling off the pentane, the mixture was stirred and heated at 80–100°C for 2 h to remove 100 mL of EtOH. After cooling, the mixture was poured into ice and 10% HCl (500 mL), and extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 50.4 g (72%) of **56** as a 1:3 mixture of *cis*/*trans*-isomers of **56** as judged by GC analysis (same conditions as those used for **18**): t_R 16.23 min (77%), 16.56 min (23%).

*4.25.3. (1S,5R)-trans-Pulegenic acid (**57**)*

A solution of KOH (20 g, 357 mmol) in water (60 mL) was slowly added to a solution of **56** (50.4 g, 257 mmol) in 95% EtOH (200 mL). The mixture was stirred and heated under reflux for 3 h, and EtOH was removed by distillation. After cooling,

the residue was diluted with water, and extracted with Et_2O to remove neutral impurities. The Et_2O layer was extracted with water. The combined aqueous solution was acidified with conc HCl (40 mL, 480 mmol) and ice. The mixture was extracted with Et_2O. The Et_2O solution was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give **57** (24.5 g, 57%) as a colorless oil, ν_{max} (film): ~3500– ~2500 (br m), 2956 (s), 1701 (s), 1456 (m), 1415 (m), 1375 (m), 1292 (m), 1213 (m), 952 (w), 893 (w), 813 (w), 707 (w); δ_H ($CDCl_3$): 1.08 (3H, d, *J* = 7 Hz), 1.64 (3H, s), 1.67 (3H, s), 1.90–2.05 (2H, m), 2.23–2.45 (3H, m), 2.97 (1H, d, *J* = 5 Hz); δ_C ($CDCl_3$): 19.9, 21.67, 21.74, 30.4, 33.8, 40.9, 55.6, 126.9, 133.9, 182.2; GC-MS (same conditions as those used for **18**): t_R 17.45 min (89%); MS (70 eV, EI): *m*/*z*: 168 (35) [M^+], 125 (14), 123 (100), 107 (21), 91 (10), 81 (56), 67 (13), 41 (13).

*4.26. Iodolactone (**58**)*

A solution of I_2 (76.2 g, 0.3 mol) and NaI (135.0 g, 0.9 mol) in water (300 mL) was added over 10 min to a stirred solution of **57** (24.5 g, 0.146 mol) and $NaHCO_3$ (12.6 g, 0.150 mol) in a mixture of Et_2O (400 mL) and H_2O (400 mL) at room temperature. The mixture was stirred for 4 d at room temperature, while the flask was wrapped with an aluminum foil. Then sodium thiosulfate was added to destroy the excess I_2, and the Et_2O layer was separated. The aqueous layer was extracted with Et_2O. The Et_2O solution was successively washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give a solid residue (37 g). This was recrystallized from pentane to give **58** (22.2 g, 52%) as colorless needles, mp 55–56°C; $[\alpha]_D^{22}$ +1.82 (*c* 1.65, Et_2O); ν_{max} (nujol): 1775 (s), 1375 (s), 1267 (s), 1225 (m), 1209 (m), 1120 (m), 1078 (s), 1029 (m), 947 (s), 802 (m), 731 (m), 607 (m); δ_H ($CDCl_3$): 1.39 (3H, d, *J* = 7 Hz), 1.49 (3H, s), 1.74 (3H, s), 1.78–1.94 (2H, m), 2.10–2.20 (2H, m), 2.55–2.65 (1H, m), 2.88 (1H); δ_C ($CDCl_3$): 21.1, 23.0, 33.0, 34.9, 37.1, 42.3, 53.0, 63.1, 86.9, 177.4. GC (same conditions as those used for **78**): t_R 22.66 min (100%); MS (70 eV, EI): *m*/*z*: 167 (100), 123 (67), 95 (15), 91 (12), 81 (64), 43 (23). HRMS calcd for $[C_{10}H_{15}O_2I]^+$ (M^+): 294.0117, found: 294.0109.

*4.27. Unsaturated lactone (**17**)*

1,8-Diazabicyclo[5.4.0]-7-undecene (DBU, 12.0 g, 65.9 mmol) was added to a solution of **58** (12.12 g, 41.2 mmol) in C_6H_6 (120 mL). The mixture was stirred for 3 h at room temperature. White precipitates of DBU·HI salt appeared soon afterwards (exothermic). Subsequently the mixture was acidified with dil HCl and ice. The benzene layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic solution was washed successively with water, $NaHCO_3$ solution and

brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from pentane to give **17** (5.72 g, 78%) as colorless prisms, mp 43–43.5°C, $[\alpha]_D^{20}$ +6.39 (*c* 1.32, Et_2O); ν_{max} (nujol): 1766 (s), 1663 (m), 1336 (m), 1279 (m), 1182 (m), 1124 (m), 1049 (m), 1006 (s), 902 (m), 786 (m), 615 (m), 575 (m); δ_H ($CDCl_3$): 1.18 (3H, d, *J* = 7 Hz), 1.44 (3H, s), 1.46 (3H, s), 1.90–2.00 (1H, m), 2.38–2.56 (2H, m), 2.60–2.72 (1H, m), 2.92–3.02 (1H, m): δ_C ($CDCl_3$): 19.3, 25.0, 26.4, 33.9, 38.1, 83.3, 139.3, 168.6, 180.4. GC (same conditions as those used for **18**): t_R 17.30 min (100%); MS (70 eV, EI): *m*/*z*: 151 (28), 123 (100), 107 (7), 79 (14), 43 (21). HRMS calcd for $[C_{10}H_{14}O_2]^+$ (M^+): 166.0994, found: 166.1004.

*4.28. Unsaturated lactone **53a** + **53b***

Deconjugation/protonation of (*R*)-**17** to a mixture of **53a**/**53b** could be achieved either KH or lithium diisopropylamide (LDA) as a base. The use of LDA was more convenient, and therefore recorded here.

A solution of LDA (TCI, 1.5 M in THF/heptane/toluene; 54 mL, 81 mmol) was added dropwise to a stirred and cooled solution of (*R*)-**17** (9.64 g, 58 mmol) in THF (100 mL) over 10 min at −60 to −50°C under argon. The mixture was stirred at −78°C for 30 min, and then the dry ice/acetone bath was removed to raise the inner temperature to 0°C. The resulting enolate solution was taken into a syringe, and added over 5 min to a stirred and cooled solution of AcOH (24 mL) in Et_2O (200 mL) at −78°C under argon. The solution was stirred for 5 min, poured into iced-water, and extracted with Et_2O. The Et_2O extract was washed successively with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 12.1 g of an oil. This was chromatographed over SiO_2 (90 g). After washing the column with hexane to remove toluene and heptane, a mixture of **53a**/**53b** (7.30 g, 76%) was eluted with hexane/EtOAc (10:1). The oily **53a**/**53b**, n_D^{23} = 1.4770, solidified in a deep freezer, although its recrystallization from pentane was unsuccessful: $[\alpha]_D^{23}$ −36.5 (*c* 1.52, Et_2O); ν_{max} (film): 3060 (w), 2977 (s), 2931 (s), 2871 (s), 2850 (s), 1765 (s), 1675 (m), 1460 (m), 1371 (m), 1297 (s), 1219 (s), 1194 (s), 1125 (s), 1104 (m), 1083 (s), 1036 (m), 963 (s), 898 (m), 846 (m), 593 (m), 552 (m); δ_H ($CDCl_3$): 0.95 (3H, d, *J* = 7 Hz), 1.47 (3H, s), 1.53 (3H, s), 2.14 (1H, m). 2.70–2.80 (1H, m), 2.85–2.93 (1H, m), 3.82–3.89 (1H, br), 5.58–5.62 (1H, m); The minor isomer (**53b**) showed its C*H*$_3$CH at δ1.28 (3H, d, *J* = 7 Hz); δ_C ($CDCl_3$): 16.3, 26.1, 26.5, 35.5, 45.2, 54.4, 83.6, 121.6, 147.4, 173.9; GC-MS (same conditions as those used for **18**): t_R 15.37 min (10.5%), 15.81 min (89.5%); MS (70 eV, EI): *m*/*z*: 166 (11) [M^+], 122 (26), 121 (33), 107 (100), 105 (26), 9 (37), 79 (23), 43 (15); The two isomers showed entirely similar MS spectra. HRMS calcd for $[C_{10}H_{14}O_2]^+$ (M^+): 166.0994, found: 166.1006.

*4.29. Ketolactone (1R,5S,8R)-**7***

A solution of **53a**/**53b** (1.53 g, 9.2 mmol) in Et_2O (15 mL) was added dropwise over 5 min to a stirred and ice-cooled solution of BH_3·THF in THF (0.9 M, 10 mL, 9.0 mmol) at 9–15°C under argon. The mixture was stirred for 75 min at 5–8°C. Excess BH_3·THF was then destroyed by slow addition of water (3 mL). After stirring for 5 min, the mixture was concentrated in vacuo (rotary evaporator). The residue was diluted with Et_2O (20 mL), acetone (10 mL) and water (10 mL), and stirred vigorously under ice-cooling. Jones chromic acid (8 M in oxygen, 9 mL, 72 mmol) was added dropwise to the stirred mixture, and the stirring was continued for 20 min. After destroying excess CrO_3 with MeOH, the mixture was diluted with water, and extracted with Et_2O. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (1.06 g) was chromatographed over SiO_2 (10 g). Elution with hexane gave 0.26 g of an oil, and further elution with hexane/EtOAc (20:1) gave 0.58 g of an oil. Subsequently, elution with hexane/EtOAc (20:1) gave 0.72 g of an oil, from which crystals of (1*R*,5*S*,8*R*)-**7** separated. Recrystallization from EtOAc/pentane gave 140 mg (8%) of (1*R*,5*S*,8*R*)-**7** as colorless rhombs, mp 85–86°C (ref.[4]: mp 83.0–84.0°C for its opposite enantiomer); $[\alpha]_D^{22}$ −309.4 (*c* 0.216, Et_2O); [ref.[4]: $[\alpha]_D^{25}$ +319 (*c* 1.014, Et_2O) for its opposite enantiomer]. Its IR, ^1H and ^{13}C NMR spectra were identical with those reported for the enantiomer.[4]: ν_{max} (nujol): 1764 (s), 1741 (s), 1375 (m), 1257 (m), 1204 (m), 1170 (m), 1135 (m), 1109 (m), 1086 (m), 968 (m), 935 (m), 747 (m); δ_H ($CDCl_3$): 1.40 (3H, d, *J* = 7 Hz), 1.41 (3H, s), 1.45 (3H, s), 1.94 (1H, dd, *J* = 16, 13 Hz). 2.43–2.58 (2H, m), 2.73 (1H, d, *J* = 9 Hz), 3.43 (1H, dd, *J* = 9, 7Hz); δ_C ($CDCl_3$): 15.8, 24.4, 30.9, 32.1, 46.8, 47.2, 58.4, 83.6, 174.8, 213.7; GC-MS (same conditions as those used for **18**): t_R 18.99 min (98.5%); MS (70 eV, EI): *m*/*z*: 182 (15) [M^+], 113 (10), 97 (17), 96 (100), 81 (36), 69 (24), 43 (12). HRMS calcd for $[C_{10}H_{18}O_3]^+$ (M^+): 182.0943, found: 182.0942.

*4.30. Dihydroxylactone (1R,5S,6R,8R)-**39** + (1S,5R,6S,8R)-**39***

An aqueous solution of 4-methylmorpholine-*N*-oxide (50%, 4.8 M, 5 mL, 24 mmol) and OsO_4 (1% solution in *t*-BuOH, 2 mL = 20 mg OsO_4, 0.08 mmol) were added to a stirred solution of **53a**/**53b** (2.50 g, 15 mmol) in a mixture of acetone (30 mL), *t*-BuOH (10 mL) and water (2 mL) at room temperature under argon. The mixture was stirred for 9 d under argon. Subsequently, Na_2SO_3·$7H_2O$ was added to destroy excess NMO and OsO_4. The mixture was diluted with brine, and extracted with EtOAc. The EtOAc solution was dried ($MgSO_4$), and concentrated in vacuo to give a residue (4.17 g). This was chromatographed over SiO_2 (30 g). Elution with hexane gave 0.14 g of an oil, and further elution with hexane/EtOAc (5:1–2:1) gave 3.06 g (98%) of

a mixture of (1*R*,5*S*,6*R*,8*R*)-**39** and (1*S*,5*R*,6*S*,8*R*)-**39** as a solid. This was recrystallized from acetone/pentane to give 1.93 g of the 1st crop as colorless prisms, mp 112–114°C; $[\alpha]_D^{20}$ −54.8 (*c* 0.70, Et_2O) 0.61 g of 2nd crop and 0.25 g of the 3rd crop. Analytical data of the 1st crop were as follows: ν_{max} (nujol): 3443 (m), 3304 (m), 1742 (s), 1380 (m), 1281 (m), 1266 (m), 1232 (m), 1197 (w), 1119 (m), 1096 (m), 1086 (m), 1027 (m), 864 (m); δ_H ($CDCl_3$, major signals): 1.18 (3H, d, *J* = 7 Hz) 1.42 (3H, s), 1.43 (3H, s), 1.62–1.72 (1H, m), 2.01–2.10 (1H, m), 2.58–2.70 (1H, m), 2.72 (1H, br), 2.97 (1H, d, *J* = 9 Hz), 3.61 (1H, s-like), 4.41 (1H, dd, *J* = 12, 6 Hz); δ_C ($CDCl_3$, major signals): 16.3, 21.8, 25.5, 30.9, 41.6, 53.1, 72.1, 85.3, 86.2, 174.5; GC-MS (same conditions as those used for **18**): t_R 23.99 min [10.1%, (1*S*,5*R*,6*S*,8*R*)-**39**], 24.74 min [89.9%, (1*R*,5*S*,6*R*,8*R*)-**39**]; MS of the major isomer (= that of the minor isomer, 70 eV, EI): *m*/*z*: 130 (37), 114 (100), 99 (61), 96 (49), 81 (45), 70 (23). HRMS calcd for $[C_{10}H_{16}O_4]^+$ (M^+): 200.1049, found for the major isomer: 200.1060, found for the minor isomer: 200.1039. GC of the 2nd crop showed it to be a 3:1 mixture of (1*R*,5*S*,6*R*,8*R*)-**39** and (7*S*,5*R*,6*S*,8*R*)-**39**. The 3rd crop contained substantial amount of impurities different from **39**.

*4.31. Hydroxyketolactone (1R,5R,8R)-**15***

4-Methylmorpholine *N*-oxide (Aldrich, 1.89 g, 14 mmol), powdered MS 4A (2.84 g)

and $(n\text{-Pr})_4NRuO_4$ (98 mg, 0.28 mmol) were added to a stirred and ice-cooled solution of (1*R*,5*S*,6*R*,8*R*)-**39**/(1*S*,5*R*,6*S*,8*R*)-**39** (3:1, 559 mg, 2.8 mmol) in CH_2Cl_2 (15 mL). After the initial exothermic reaction, the mixture was stirred for 2 h at room temperature. Then the dark-colored mixture was poured onto a column of SiO_2 (20 g) in hexane. Elution with hexane and hexane/EtOAc (5:1) gave nothing. Further elution with hexane/EtOAc (3:1) gave 102 mg (18%) of (1*R*,5*R*,8*R*)-**15** as a solid. This was recrystallized from EtOAc/pentane to give 50 mg (9%) of (1*R*,5*R*,8*R*)-**15** as colorless rhombs, mp 153–155°C (sinter at 120°C); $[\alpha]_D^{16}$ −332.8 (*c* 0.035, Et_2O); ν_{max} (film): 3427 (m), 1744 (s), 1308 (m), 1061 (m), 1033 (m), 897 (m); δ_H ($CDCl_3$, major isomer): 1.29 (3H, s), 1.40 (3H, d, *J* = 7 Hz), 1.45 (3H, s), 2.19 (1H, dd, *J* = 16, 2 Hz), 2.50–2.61 (2H, m), 2.81 (1H, s), 3.15 (1H, dd, *J* = 7, 2 Hz); δ_C ($CDCl_3$, major isomer): 15.5, 23.2, 25.6, 30.6, 45.9, 51.7, 85.0, 85.7, 172.4, 214.9; GC-MS (same conditions as those used for **18**): t_R 18.85 min [87%, (1*R*,5*R*,8*R*)-**15**], 19.00 min [13%, (1*S*,5*S*,8*R*)-**15**]; MS (70 eV, EI): *m*/*z*:113 (13), 112 (100), 97 (21),84 (21), 69 (72), 59 (14), 43 (22). The two isomers showed the same MS spectra. HRMS calcd for $[C_{10}H_{14}O_4]^+$ (M^+): 198.0892, found: 198.0906 (major isomer), 198.0901 (minor isomer).

*4.32. Unsaturated hydroxyketolactone (1R,5R)-**16***

A solution of $KN(TMS)_2$ (0.5 M, 11% in toluene, 24 mL, 12 mmol) was added dropwise to a stirred and cooled solution of (1*R*,5*R*,8*R*)-**15** (654 mg; 3 mmol) in THF (15 mL) at −78–−65°C under argon. The mixture was stirred for 15 min at −78°C. Subsequently a solution of PhSeBr (1.18 g, 5 mmol) in THF (5 mL) was added dropwise to the stirred mixture at −78°C, and the stirring was continued for 1 h at −78°C. Then the mixture was quenched with NH_4Cl solution and extracted with Et_2O. The Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil (2.12 g). This was chromatographed over SiO_2 (40 g). Elution with hexane/EtOAc (2:1) gave 670 mg (quant based on the consumed **15**) of C-7 phenylselenylated product. Further elution with hexane/EtOAc (2:1) gave 340 mg (52%) of the recovered **15**. A solution of the crude phenylselenoketone (670 mg, 1.4 mmol) in THF (16 mL) was added dropwise to the vigorously stirred solution of $NaIO_4$ (2.14 g, 10 mmol) in H_2O (8 mL). The solution was stirred for 1 h at room temperature to give a suspension of $NaIO_3$. The suspension was diluted with Na_2CO_3 solution, and extracted with Et_2O. The Et_2O solution was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil (370 mg). This was chromatographed over SiO_2 (20 g). After some unidentified materials, elution with hexane/EtOAc (2:1) gave 42 mg (14% based on **15**) of (1*R*,5*R*)-**16** as crystals. This was recrystallized (EtOAc/pentane) to give 20 mg (7%) of pure (1*R*,5*R*)-**16** as pale yellow prisms, mp 132.5–133.5°C; $[\alpha]_D^{20}$ −248.7 (*c* 0.0215, EtOAc); ν_{max} (nujol): 3370 (m), 1766 (s), 1698 (vs), 1615 (m), 1376 (m), 1254 (m), 1133 (m), 1088 (m), 964 (w), 907 (w), 873 (w), 729 (w); δ_H ($CDCl_3$): 1.34 (3H, s), 1.53 (3H, s), 1.65 (1H, s), 2.36 (3H, s), 3.03 (1H, s), 3.67 (3H, s), 6.06 (1H, s-like), 7.27 (1H, s), δ_C ($CDCl_3$): 18.0, 24.4, 25.7, 59.8, 83.4, 87.9; 128.9, 170.4, 173.8; 204.8; GC-MS (same conditions as those used for **18**): t_R 20.14 min (98.9%); MS (70 eV, EI): *m*/*z*: 152 (31), 138 (25), 110 (100), 109 (43), 82 (87), 70 (19), 53 (20), 39 (22). HRMS calcd for $[C_{10}H_{12}O]^+$ (M^+): 196.0736, found: 196.0747.

4.33. CD spectral measurements

Instrument: Jasco J-1500; Solvent: MeOH; Cell length: 10 mm; Temp: 21.56°C. (A) (1*R*,5*S*,8*R*)-**7**: *c* 6.6 × 10^{-5} M; Mol. CD (1) 304 nm, −3.889; (2) 233 nm, 0.13247; (3) 203 nm, −1.12416. (B) (1*R*,5*R*,8*R*)-**15**: *c* 5.4 × 10^{-5} M; Mol. CD (1) 314 nm, −3.0068; (2) 253 nm, 0.05325; (3) 227 nm, −0.61590; (4) 212 nm, −0.01093; (5) 203 nm, −1.2648. (C) (1*R*,5*R*)-**16**: *c* 6.22 × 10^{-5} M; Mol. CD (1) 242.7 nm, −26.0; (2) 218.9 nm 25.6; (3) 201.7 nm, −22.0.

*4.34. X-Ray crystal structure analysis of (1R,5R)-**16***

Crystal data: $C_{10}H_{12}O_4$, *FW* = 196.20, monoclinic $P2_1$, a = 6.35336 (9), b =

6.60462 (9), c = 11.70119 (17) Å, β = 104.8324 (15) °, V = 474.639 (12) Å^3; D_X = 1.373 g cm^{-3}; Z = 2; μ(Mo Kα) = 0.106 mm^{-1}, T = 90 K. Block shaped pale yellow crystals were grown from ethyl acetate solution of (1*R*,5*R*)-**16**. A single crystal with the dimensions of 0.28 × 0.21 × 0.09 mm was mounted on a glass capillary and set on a Rigaku AFC-8 diffractometer equipped with a Saturn70CCD detector. The diffraction data were collected using MoKα radiation, which was monochromated by a multi-layered confocal mirror. The unit cell dimensions were determined using 21363 reflections with $3.55 \leq 2\theta \leq 65.53$ °. The diffraction data of 23728 within $3.60 \leq 2\theta \leq 65.04$ ° were collected and merged to give 3326 unique reflections with the R_{int} of 0.0317. The structure was solved by a dual-space method and refined on F^2 by a least-squares method by the programs SHELXT-2018/2[28] and SHELXL-2018/3,[29] respectively. The anisotropic and isotropic temperature factors were applied for non-hydrogen and hydrogen atoms, respectively. The final R values on 3291 unique reflections ($2\theta_{max}$ = 65.04°) with $I > 2\sigma(I)$ are 0.0249 and 0.0678 for $R(F)$ and $wR(F^2)$, respectively. The absolute structure of the crystal was determined by anomalous dispersion effects (χ = 0.00 (16))[30,31] Supplementary crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC) under the numbers CCDC 1901767, and can be obtained free of charge from via https://www.ccdc.cam.ac.uk/structures.

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