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SYNTHESIS OF (±)-PA 22-VII, THE RACEMATE OF THE REARRANGEMENT PRODUCT OF PERSOONS'S PERIPLANONE-A†

KENJI MORI* and YASUHIRO IGARASHI

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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Abstract —— A synthesis of the racemate of **5** was achieved to prove its identity with PA 22-VII, the stable and biologically inactive rearrangement product of Persoons's periplanone-A.

Introduction

Chemistry of the sex pheromone of the American cockroach (*Periplaneta americana*) was pioneered by Ritter and Persoons.[1] A minor bioactive component of the sex pheromone was isolated, named periplanone-A, and given the structure **1** by Persoons *et al.*[2,3] Their periplanone-A was found to be quite unstable, and rearranged to give a stable and biologically inactive compound with a code name PA 22-VII.[2] Indeed, about 50% conversion was observed at 0°C in two weeks, and even at -20°C the rearrangement took place.[3]

Persoons and his co-workers gave the structure **2** for PA 22-VII,[2] the stereostructure of which was later assigned by them as depicted in **3**.[3] Macdonald's synthesis of (±)-**4** was followed by comparison of its ^{1}H NMR spectrum with that reported for PA 22-VII.[4] This enabled Macdonald *et al.* to propose **5** as the structure of the rearrangement product, PA 22-VII.[4] The same conclusion was also reported by Shizuri *et al.*[5] In order to confirm this proposal, we felt it necessary to synthesize (±)-**5**. As will be detailed in this paper, (±)-**5** was shown to be the racemate of PA 22-VII.[6]

It must be stated, however, that our recent work clarified the structure of the compound, which had been named periplanone-A by Ritter and Persoons, to be not **1** but **6**.[7] The compound **6** (new name:isoperiplanone-A[8]) was a biologically inactive thermal decomposition product of the genuine pheromone **7**,[9] which was first isolated by Hauptmann *et al.*,[9] and should now be called periplanone-A.[8]

Our retrosynthetic analysis of (±)-PA 22-VII (**5**) is shown in Fig.1. Construction of the non-conjugated diene system of **5** would be possible starting from **A**. The ketol system of **A**, in turn, might be prepared from enone **B**, which has the required tricyclic ring-system with correct stereochemistry. Preparation of the enone **B** would be feasible *via* **C**, employing the conjugate addition of the *iso*-propyl group at a certain stage after building up the tricyclic ring-system. The diketo ester **C** is the known Diels-Alder adduct between 1,3-butadiene and **D**,[10] and possesses all of the functionalities required for the preparation of **B**.

†Pheromone Synthesis ——120. Part 119, Mori, K. and Takikawa, H. *Tetrahedoron*, in press.

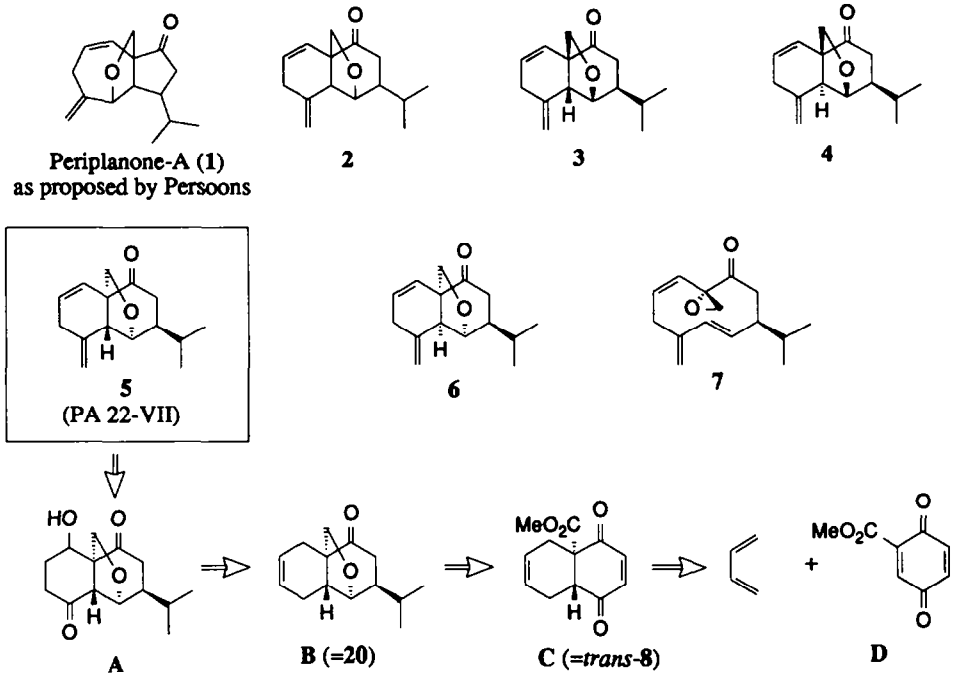


Fig.1. The target molecule and its synthetic plan.

Synthesis of the Tricyclic Intermediate (±)-20

The Diels-Alder adduct (±)-**8** (*cis,trans*-mixture) was prepared in the presence of $SnCl_4$ according to Kojima and Kato,[10] and found to be a mixture of the *cis*- and *trans*-isomers in a ratio of 1:1.2, although a ratio of 4:1 had previously been recorded.[10] An attempt to prepare *cis*-**8** in the absence of $SnCl_4$ under a high-pressure condition failed to give pure *cis*-**8**, and afforded an unidentified anomalous product. Unfortunately, the mixture **8** was not readily separable by conventional SiO_2 chromatography. Because *trans*-**8** was the desired starting material for our purpose, we treated the mixture **8** with a variety of bases such as Al_2O_3, K_2CO_3, NaOMe and Et_3N so as to enrich *trans*-**8**. All of our attempts were unsuccessful owing to the instability of *cis*-**8** under basic conditions. We therefore employed **8** (*cis,trans*-mixture) as it was generated by the Lewis acid-catalyzed Diels-Alder reaction.

The first step of the conversion of (±)-**8** (*cis,trans*-mixture) into (±)-**20** (=**B**) was how to secure a *trans*-fused bicyclic intermediate in a pure state. Fortunately, reduction of **8** (*cis,trans*-mixture) with $LiAl(O\text{-}t\text{-}Bu)_3H$ was found to give, in 39% yield, crystalline (±)-**9a** as the major product, which could be readily separated by chromatography and recrystallization from other two reduction products, (±)-**10** (7% yield) and (±)-**11** (tentative structure; 5% yield). The structure of the major product as (±)-**9a** was based on its ^1H NMR analysis (as the corresponding acetate) to observe no coupling between CHOAc and the angular proton as well as on its MnO_2 oxidation to give back *trans*-**8** (see Experimental). The assigned structure **9a** was later confirmed by its conversion to (±)-**20**.

The second phase of the work was to reduce the CO group of **9a** to give an α-oriented OH group so that it could be utilized for the construction of the α-oriented tetrahydrofuran ring of (±)-**20**. When **9a** was reduced with $NaBH_4$ in the presence of $CeCl_3$, the undesired β-OH compound (±)-**12** was produced exclusively. Treatment of

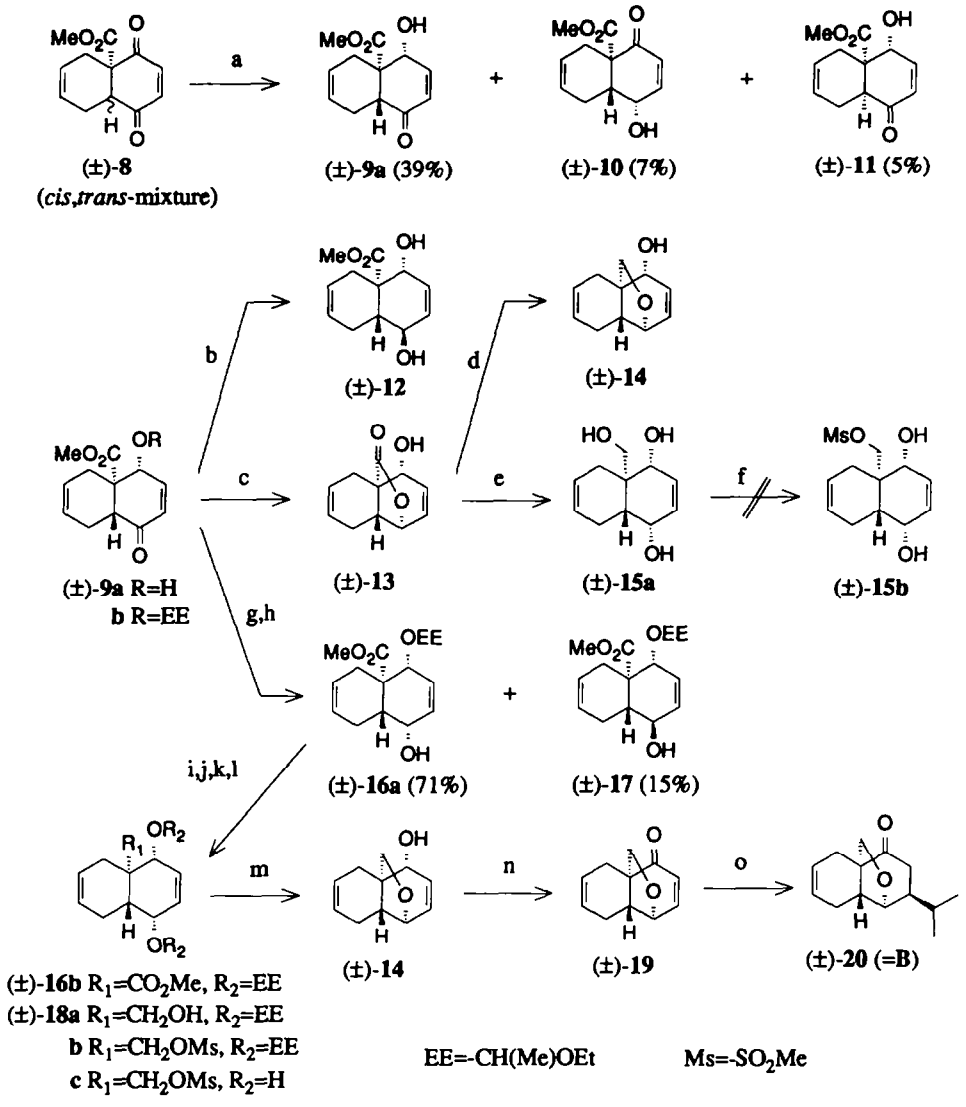


Fig.2. Synthesis of the tricyclic intermediate (±)-**20**.

Reagents: a)LiAl(O*t*-Bu)$_3$H, THF, 0-5°C. b)NaBH$_4$, CeCl$_3$, MeOH, 0-5°C. c)LiB(*s*-Bu)$_3$H, THF, -78°C. d)i)DIBAL, Toluene, -78°C. ii)Et$_3$SiH, BF$_3$•Et$_2$O, CH$_2$Cl$_2$, -78°C. e)NaBH$_4$, MeOH, THF, reflux. f)MsCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 0-5°C. g)Ethyl vinyl ether, PPTS, CH$_2$Cl$_2$, r.t., quant. h)NaBH$_4$, CeCl$_3$, THF, 0-5°C. i)Ethyl vinyl ether, PPTS, CH$_2$Cl$_2$, r.t., 77%. j)LiAlH$_4$, Et$_2$O, 0°C-r.t., 87%. k)MsCl, Py, CH$_2$Cl$_2$, DMAP, 0-5°C. l)PPTS, MeOH, 40-45°C. m)2.5% NaOMe in MeOH, r.t.-40°C, 81% in 3 steps. n)(COCl)$_2$, DMSO, CH$_2$Cl$_2$, -78°C then Et$_3$N, -20°C, 92%. o)*i*-PrMgI, CuCN, Et$_2$O, -78-0°C, 75%.

9a with LiB(*s*-Bu)$_3$H, on the other hand, afforded a lactone (±)-**13**, conversion of which to (±)-**14** was then attempted. Thus, **13** was treated with (*i*-Bu)$_2$AlH followed by Et$_3$SiH in the presence of BF$_3$•Et$_2$O.[11] Unfortunately, the desired **14** was accompanied with a number of by-products, and the yield of **14** was only ~10%. We then reduced **13** with NaBH$_4$ in THF-MeOH[12] to give a triol (±)-**15a**, but its selective mesylation to give (±)-**15b**, the precursor of **14**, was unsuccessful. A successful step to the solution of this problem of the stereoselective reduction was the protection of the OH group of **9a** by treatment with ethyl vinyl ether and PPTS. The resulting (±)-**9b** could be reduced with NaBH$_4$ in the presence of CeCl$_3$ to give a mixture of (±)-**16a** (71% yield) and (±)-**17** (15% yield), which was readily separable by SiO$_2$ chromatography. Assignment of the structure of (±)-**16a** to the major product was based on (i) its less polar nature than (±)-**17** owing to the axial orientation of the OH group of **16a**, and (ii) the intramolecular hydrogen bonding between the OH group and the CO$_2$Me group as manifested by a sharp OH absorption and $\nu_{C=O}$ at 1710 cm^{-1}. The isomer (±)-**17** showed $\nu_{C=O}$ at 1725 cm^{-1}. Thus, stereoselectivity of the reduction could be reversed merely by protecting the OH group of **9a** to give **9b**. The undesired β-alcohol **17** gave back **9b** upon Swern oxidation in 92% yield, and could be recycled.

The next task was to convert (±)-**16a** to (±)-**14**, the tricyclic intermediate with a tetrahedrofuran ring. After protecting the OH group of **16a** as EE ether to give **16b** (77% yield), it was reduced with LAH to give an alcohol **18a** in 71% yield. Treatment of **18a** with MsCl in the presence of DMAP gave the corresponding mesylate (±)-**18b**. Deprotection of the EE protective groups of **18b** was achieved with PPTS in MeOH to give (±)-**18c**. Cyclization of **18c** to the tricyclic intermediate (±)-**14** proceeded smoothly by treatment with NaOMe in MeOH. The overall yield of **14** from **18a** was 81%. The alcohol **14** was oxidized under the Swern condition to give an α,β-unsaturated ketone (±)-**19** in 92% yield.

The key intermediate (±)-**20** (=**B**) was obtained from **19** by the conjugate addition of *i*-PrMgI in the presence of CuCN in Et$_2$O. As expected, the major product obtained in 75% yield was the desired β-adduct (±)-**20**, generated by the axial attack of the reagent. The yield of the isomeric α-adduct was less than 5%. The structure of the major and crystalline product was unambiguously proved to be (±)-**20** by an X-ray crystallographic analysis. The structure was solved by SHEL XS 86 with the final agreement values of R=0.042 and R_W=0.065. The ORTEP computer drawing of (±)-**20** is shown in Fig.3.[13]

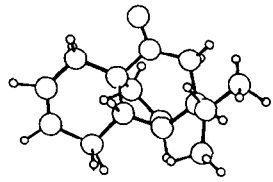


Fig. 3. The molecular structure of (±)-**20**.

Synthesis of the Racemate of PA 22-VII

With the tricyclic key intermediate (±)-**20** in hand, the next stage of our work was the modification of the cyclohexene ring of **20** to give the racemate of PA 22-VII [(±)-**5**] *via* ketol **A** [=(±)-**27a**]. Methylenation of **A** followerd by dehydration would give the diene system of (±)-**5** (Fig.4).

The first phase of our conversion was therefore preparation of **A** from **20**. For the ease of manipulation in the course of this conversion, the CO group of **20** was reduced with Li/NH$_3$-THF in the presence of *t*-BuOH to give (±)-**21a** in 91% yield, which was treated with *t*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine/CH$_2$Cl$_2$ to give (±)-**21b**. Reaction of **21b** with C$_5$H$_5$N•HBr$_3$ quantitatively afforded a dibromide, to which was assigned the structure (±)-**22**, considering the diaxial addition mechanism. Treatment of **22** with DBU gave a diene (±)-**23** contaminated with a small amount of an unknown inpurity.

Introduction of the oxygen functions to the diene **23** was achieved by the slow addition of the singlet oxygen to **23** in the presence of methylene blue as a photo-sensitizer under the irradiation with a tungsten lamp to give an

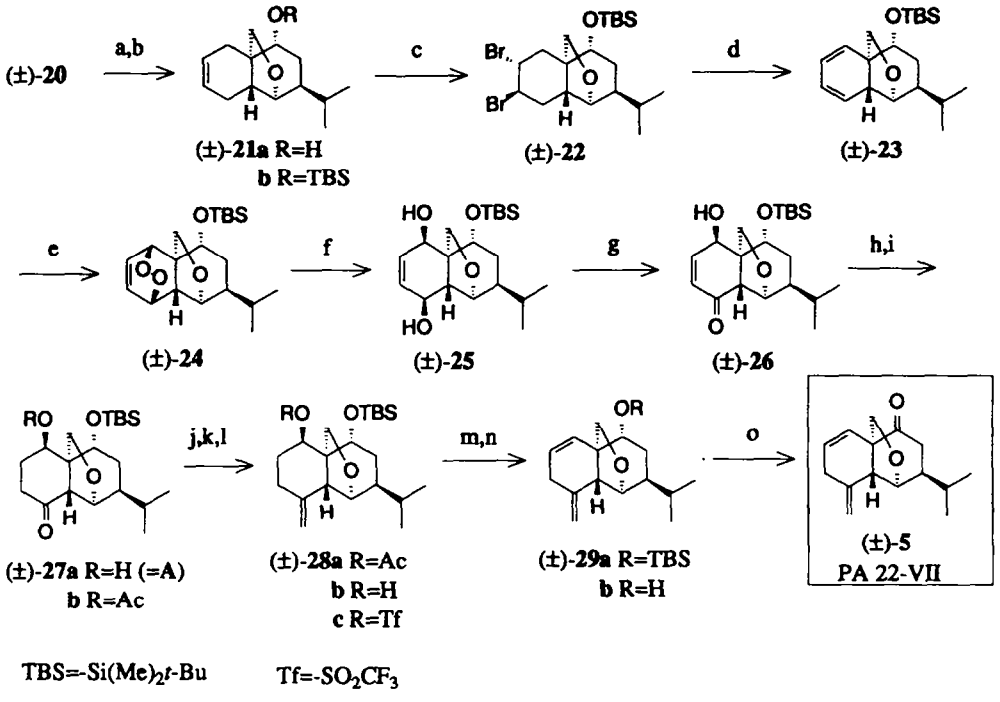


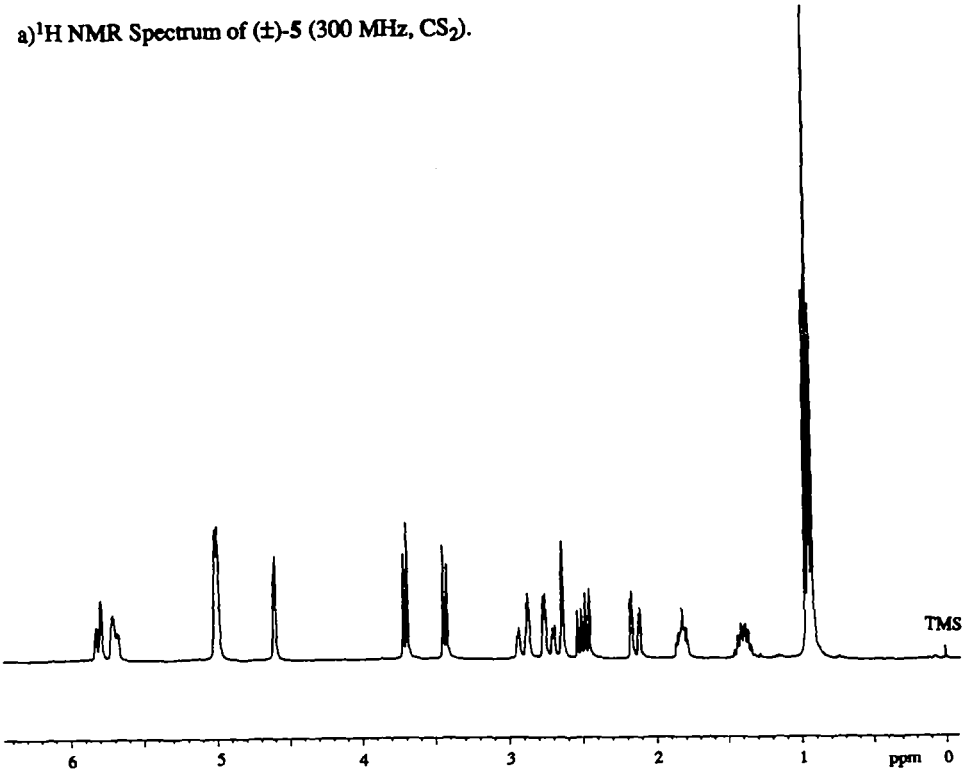
Fig.4. Synthesis of (±)-5 (PA 22-VII).

Reagents: a)Li, NH_3, THF, *t*-BuOH, -78-0°C, 91%. b)TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0-5°C, quant. c)$C_5H_5N{\cdot}HBr_3$, THF, r.t., quant. d)DBU, An, HMPA, 40-45°C. e)O_2, hv, Methylene blue, MeOH, 5-10°C. f)$LiAlH_4$, THF, 0-5°C, 15% in 3 steps. g)MnO_2, $CHCl_3$, r.t., 83%. h)H_2, 10% Pd/C, EtOH, r.t., 99%. i)Ac_2O, Py, CH_2Cl_2, DMAP, r.t., 98%. j)Ph_3PMeBr, *n*-BuLi, DME, 0°C-r.t., 56%. k)MeLi, Et_2O, 0-5°C, 94%. l)TfCl, DMAP, CH_2Cl_2, 0°C-r.t. m)DBU, PhH, 70°C, 78% in 2 steps. n)$(n\text{-}Bu)_4NF$, THF, r.t., quant. o)PDC, CH_2Cl_2, MS 3A, r.t., 81%.

endo-peroxide (±)-**24**. The structure of **24** was given to this product on the assumption that oxygen attacked the less-hindered β-side of the molecule. Reduction of **24** with LAH furnished a diol (±)-**25**. The overall yield of (±)-**25** was only 15% from the dibromide (±)-**22**. The diol (±)-**25** was selectively oxidized with MnO_2 to give a hydroxy ketone (±)-**26**. Attempts to isomerize the *endo*-peroxide (±)-**24** directly into (±)-**26** resulted in failure. The structure of (±)-**26** was confirmed by the ^1H NMR analysis of the corresponding acetate. Its CHOAc proton exhibited no coupling with the proton at the angular position (see Experimental). Hydrogenation of (±)-**26** over Pd-C gave (±)-**27a** (=A) in 99% yield.

The next task was the conversion of the CO group of (±)-**27a** to the methylene group. The Wittig reaction of (±)-**27a** with $Ph_3P{=}CH_2$ in THF gave the desired product (±)-**28b** in ≤30% yield. Neither the use of $TMSCH_2CeCl_2$[14] nor that of $Cp_2TiCH_2{\cdot}ZnI_2$[15] was successful to give the desired olefin **28b**. After protection of the OH group of (±)-**27a** as an acetate (±)-**27b**, however, the Wittig reaction of **27b** with $Ph_3P{=}CH_2$ in DME was a little bit more efficient to give (±)-**28a** in 56% yield. Deprotection of (±)-**28a** was achieved by treatment with MeLi to give (±)-**28b** in 94% yield.

a)^{1}H NMR Spectrum of (±)-5 (300 MHz, CS_2).



b)MS of (±)-5.

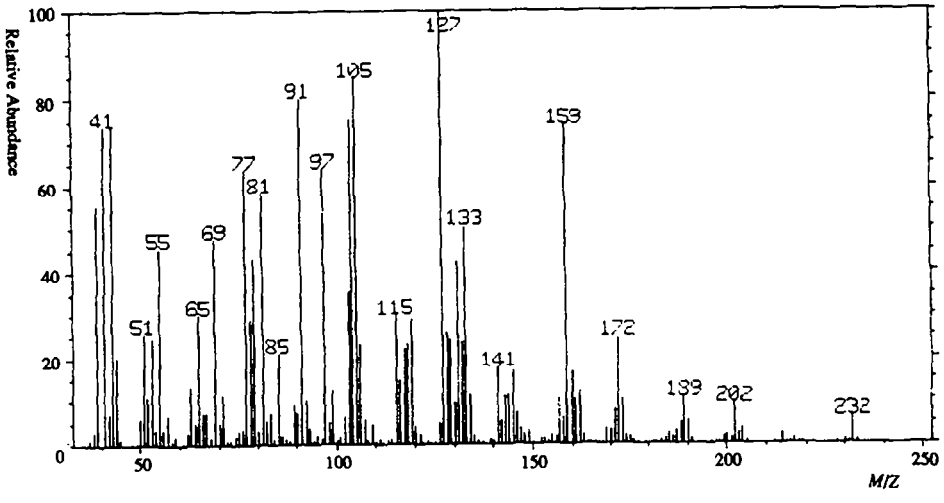


Fig.5. ^{1}H NMR Spectrum (a) and MS (b) of (±)-5 (PA22-VII).

Dehydration of (±)-**28b** was possible by using the Burgess reagent ($MeOCON^-SO_2N^+Et_3$),[16] but the result was not so reproducible, giving 10~79% yield of (±)-**29a**. The following alternative route was found to be more reproducible and efficient. The alcohol (±)-**28b** was first converted to the corresponding triflate (±)-**28c**, which was treated with DBU to give (±)-**29a** in 78% overall yield. Desilylation of (±)-**29a** with $(n\text{-}Bu)_4NF$ to give (±)-**29b** was followed by its PDC oxidation[17] to give (±)-**5**, m.p.118.0-118.5°C, in 81% yield from (±)-**29a**. Fig.5 shows the ^1H NMR and mass spectra of our synthetic (±)-**5**. They are identical with the published spectra of Persoons's PA 22-VII.

In conclusion, our unambiguous synthesis of (±)-**5** established the structure of PA 22-VII as **5** in accord with the suggestions made by Macdonald *et al.*[4] and Shizuri *et al.*[5] As far as PA 22-VII was concerned, the studies by Persoons on the minor component of the American cockroach pheromone was correct. We also confirmed that (±)-**5** is biologically inactive.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured as films for oils and KBr disks for solids on a Jasco A-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Jeol JNM FX-100 spectrometer, at 300 MHz on a Bruker AC-300 spectrometer or at 400 MHz on a Jeol JNM GX-400 spectrometer. ^{13}C NMR spectrum was recorded with TMS as an internal standard at 75 MHz on a Bruker AC-300 spectrometer. Merck Kieselgel 60 Art 7734 was used for SiO_2 column chromatography.

(4R,4aS*,8aR*)-4,4a,5,8-Tetrahydro-4-hydroxy-4a-methoxycarbonyl-1(8aH)-naphthalenone* **9a**

(±)-**8** was prepared from 1,3-butadiene and 2-methoxycarbonyl *p*-bezoquinone according to the reported procedure.[10] To a soln of (±)-**8** (*cis:trans*=1:1.2, 105.0 g, 0.477 mol) in dry THF (2.0 l) was added portionwise $LiAl(Ot\text{-}Bu)_3H$ (125.0 g, 0.492 mol) at 0-5°C with vigorous stirring. After stirring for 2 h at the same temp, dil HCl was added to the mixture until the soln turned neutral. This was filtered through Celite and the filter cake was washed with THF. The filtrate and washings were combined and concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ soln, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1.1 kg). Elution with *n*-hexane-EtOAc-MeOH (20:10:1) gave oily **11** (5.8 g, 5%), crystalline **10** (8.3 g, 7%) and oily **9a** (ca. 60 g). Crystallization from benzene-*n*-hexane gave crystalline **9a** (41.7 g, 39%). An analytical sample was recrystallized from $(i\text{-}Pr)_2O$ to give pure **9a** as leaflets, m.p. 89.0-90.0°C; IR vmax (KBr) 3520 (s), 3460 (s), 3230 (s), 3060 (w), 1720 (s), 1690 (s), 1670 (s), 1660 (m), 1640 (w), 1085 (m), 1050 (m), 730 (w), 685 (m) cm^{-1}; ^1H NMR δ (100 MHz, C_5D_5N) 2.18-2.96 (m, 3H), 3.15-3.95 (m, 2H), 3.55 (s, 3H), 4.95 (br.s, 1H), 5.76 (m, 2H), 6.28 (dd, 1H, *J*=3.0, 10.5 Hz), 6.91 (dd, 1H, 2.5, *J*=10.5 Hz). (Found: C, 65.03; H, 6.36. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%)

Acetate of **9a**

^1H NMR δ (400 MHz, $CDCl_3$) 2.15 (s, 3H), 2.21 (dm, 1H, *J*=20.0 Hz), 2.52 (dm, 1H, *J*=20.0 Hz), 2.69 (dd, 1H, *J*=5.5, 10.5 Hz), 2.90 (dd, 1H, *J*=5.5, 16.0 Hz), 3.66 (s, 3H), 5.66 (dm, 1H, *J*=10.2 Hz), 5.69 (dm, 1H, *J*=10.2 Hz), 5.88 (dd, 1H, *J*=2.0, 2.5 Hz, AcOC<u>H</u>), 6.16 (dd, 1H, *J*=2.5, 10.4 Hz, C<u>H</u>=CHC=O), 6.45 (dd, 1H, *J*=2.0, 10.4 Hz, CH=C<u>H</u>C=O).

(4R,4aS*,8aR*)-4-(1-Ethoxy)ethoxy-4,4a,5,8-tetrahydro-4a-methoxycarbonyl-1(8aH)-naphthalenone* **9b**

To a soln of **9a** (41.7 g, 0.188 mol) in dry CH_2Cl_2 (300 ml) were added pyridinium *p*-toluenesulfonate (1 g, 0.004 mol) and ethyl vinyl ether (25.2 g, 0.349 mol) at room temp with stirring. After stirring for 6 h at room temp, the CH_2Cl_2 soln was washed with water and sat $NaHCO_3$ soln, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [300 g, *n*-hexane-EtOAc (4:1-3:1)] to give **9b** (57.0 g, quant.) as a colorless oil, $n_D^{21.0}$ 1.4959; IR vmax (film) 3040 (w), 2990 (w), 1720 (s), 1685 (s), 1650 (w), 1210 (s), 1060 (s), 810 (m), 720 (m), 675 (m), cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 1.21 and 1.23 (each t, total 3H, *J*=7.5 Hz), 1.36 and 1.37 (each d, total 3H, *J*=5.5 Hz), 1.98-2.72 (4H, m), 3.13 (d, 1H, *J*=15.0 Hz), 3.61 (s, 3H), 3.63 and 3.64 (each dq, total 2H, *J*=7.5, 10.5 Hz), 4.54 and 4.57 (each dd, total 1H, *J*=2.5, 2.5 Hz), 4.89 (q, 1H, *J*=5.5 Hz), 5.68 (s, 2H), 6.09 (ddd, 1H, *J*=2.5, 2.5, 10.5 Hz), 6.63 (ddd, 1H, *J*=2.0, 2.5, 10.5 Hz). (Found: C, 65.22; H, 7.53. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53%)

(1S,4R*,4aS*,8aR*)-4-(1-Ethoxy)ethoxy-1,4,4a,5,8,8a-hexahydro-1-hydroxy-4a-methoxycarbonylnaphthalene* **16a** *and its (1R*)-isomer* **17**

To a soln of **9b** (46.0 g, 0.156 mol) in THF (800 ml) was added $CeCl_3 \cdot 7H_2O$ (69.6 g, 0.188 mol) at room temp with stirring. To this was added portionwise $NaBH_4$ (6.64 g, 0.175 mol) at 0-5°C with stirring. After stirring for 1 h at the same temp, to the soln was added dropwise AcOH (20 ml, 0.457 mol) at 0-5°C with stirring. Then, this was poured into ice-$NaHCO_3$ soln-Et_2O, and extracted with Et_2O. The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (630 g). Elution with *n*-hexane-EtOAc (4:1) gave **16a** (32.9 g, 71%) as a colorless oil, and further elution with the same solvents (1:1) gave **17** (7.1 g, 15%) as a colorless oil. **16a**:$n_D^{20.5}$ 1.4891; IR vmax (film) 3490 (sh.s), 3050 (m), 3000 (s), 1710 (s), 1655 (w), 1220 (s), 1135 (s), 1075 (s), 720 (m), 670 (m) cm^{-1}; ^1H NMR δ

(100 MHz, $CDCl_3$) 1.19 and 1.21 (each t, total 3H, *J*=7.5 Hz), 1.30 and 1.32 (each d, total 3H, *J*=5.5 Hz), 1.80-2.65 (m, 4H), 3.11 (dm, 1H, *J*=16.0 Hz), 3.40-3.77 (m, 2H), 3.69 and 3.70 (each s, total 3H), 4.07 and 4.10 (each dd, total 1H, *J*=2.5, 2.5 Hz), 4.22 and 4.33 (each d, total 1H, *J*=4.0 Hz), 4.82 and 4.85 (each q, 1H, *J*=5.5 Hz), 5.52-5.85 (m, 3H), 6.01 (dm, 1H, *J*=10.0 Hz). (Found: C, 64.89; H, 8.18. Calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16%). **17**: $n_D^{20.5}$ 1.4899; IR vmax (film) 3440 (s), 3040 (m), 2990 (m), 1725 (s), 1655 (w), 1205 (s), 1100 (s), 730 (m) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 1.18 and 1.20 (each t, total 3H, *J*=7.5 Hz), 1.29 and 1.30 (each d, total 3H, *J*=5.5 Hz), 1.72-2.13 (m, 3H), 2.51 (m, 1H), 3.07 (dm, 1H, *J*=15.0 Hz), 3.38-3.85 (m, 2H), 3.65 (s, 3H), 4.18 and 4.20 (each t, total 1H, *J*=2.0 Hz), 4.36 (m, 1H), 4.81 and 4.82 (each q, total 1H, *J*=5.5 Hz). (Found: C, 64.92; H, 8.23. Calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16%)

Oxidation of **17** *to* **9b**

To a stirred soln of $(COCl)_2$ (9.26 ml, 108 mmol) in dry CH_2Cl_2 (150 ml) was added dropwise a soln of DMSO (15.3 ml, 216 mmol) in dry CH_2Cl_2 (50 ml) at -78°C. After stirring for 60 min at the same temp, to this was added dropwise a soln of **17** (15.9 g, 54.0 mmol) in dry CH_2Cl_2 (100 ml) at -78°C with stirring. The stirring at the same temp for 1.5 h was followed by the addition of Et_3N (33.1 ml, 238 mmol) and the temp was raised to -20°C over 60 min. Then, the soln was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [250 g, *n*-hexane-EtOAc (4:1-2:1)] to give **9b** (14.6 g, 92%) as a colorless oil.

(1S,4R*,4aR*,8aR*)-1,4-Bis-(1-ethoxy)ethoxy-1,4,4a,5,8,8a-hexahydro-4a-methoxycarbonylnaphthalene* **16b**

To a stirred soln of **16a** (31.4 g, 0.106 mol) in dry CH_2Cl_2 (240 ml) were added pyridinium *p*-toluenesulfonate (1 g, 0.004 mol) and ethyl vinyl ether (18.9 g, 0.261 mol) at room temp. After stirring for 10 h, the CH_2Cl_2 soln was washed with water and sat $NaHCO_3$ soln, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [540 g, *n*-hexane-EtOAc (5:1-4:1)] to give **16b** (30.2 g, 77%) as a colorless oil, $n_D^{23.0}$ 1.4777; IR vmax (film) 3050 (m), 3000 (s), 1730 (s), 1665 (w), 1225 (s), 1130 (s), 1060 (s), 720 (w), 680 (m) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 1.17, 1.18, 1.20 and 1.28 (each t, total 6H, *J*=7.5 Hz), 1.25, 1.33 and 1.34 (each d, total 6H, *J*=5.5 Hz), 1.73-2.27 (m, 3H), 2.74 (d, 1H, *J*=16.0 Hz), 3.36-3.79 (m, 4H), 3.58 and 3.59 (each s, total 3H), 3.85 and 3.92 (each dd, total 1H, *J*=3.5, 3.5 Hz), 4.00 and 4.01 (each dd, total 1H, *J*=3.0, 3.0 Hz), 4.67, 4.80 and 4.83 (each q, total 2H, *J*=5.5 Hz), 5.55-6.12 (m, 4H). (Found: C, 65.14; H, 8.73. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75%)

(1S,4R*,4aR*,8aR*)-1,4-Bis-(1-ethoxy)ethoxy-1,4,4a,5,8,8a-hexahydro-4a-hydroxymethylnaphthalene* **18a**

To a stirred suspension of $LiAlH_4$ (3.00 g, 79.1 mmol) in dry Et_2O (300 ml) was added dropwise a soln of **16b** (29.4 g, 79.8 mmol) in dry Et_2O (170 ml) at 0-5°C. It was stirred for 1 h at the same temp and for 30 min at room temp. It was then quenched by the successive addition of water (3 ml), 15% NaOH soln (3 ml) and water (9 ml) with ice-cooling. After the addition, the mixture was stirred for 30 min at room temp. It was filtered through Celite and the filter cake was washed with THF. The filtrate and washings were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [560 g, *n*-hexane-EtOAc (4:1)] to give **18a** (23.6 g, 87%) as a colorless oil, $n_D^{23.0}$ 1.4817; IR vmax (film) 3570 (s), 3050 (m), 3000 (s), 1660 (w), 1130 (s), 1050 (s), 710 (w), 680 (m) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 1.20 and 1.21 (each t, total 6H, *J*=7.5 Hz), 1.35 (d, 6H, *J*=5.5 Hz), 1.60-2.29 (m, 5H), 3.08-3.83 (m, 6H), 3.98 and 4.09 (each s, total 2H), 4.68, 4.76 and 4.84 (each q, total 2H, *J*=5.5 Hz), 5.63 (d, 1H, *J*=10.0 Hz), 5.70 (d, 1H, *J*=10.0 Hz), 5.85 (d, 1H, *J*=9.0 Hz), 5.90 (d, 1H, *J*=9.0 Hz). (Found: C, 66.66; H, 9.31. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47%)

(1S,2R*,7R*,8R*)-11-Oxatricyclo[5,3,2,0^{2,7}]-4,9-dodecadien-8-ol* **14**

Methanesulfonyl chloride (39.3 g, 343 mmol) and 4-(*N,N*-dimethylamino)pyridine (4.67 g, 3.82 mmol) were added at 0-5°C to a stirred soln of **18a** (13.0 g, 38.2 mmol) in dry CH_2Cl_2 (100 ml) and dry pyridine (40 ml). After stirring for 10 h at 0-5°C, this was poured into ice-water and extracted with EtOAc. The extract was washed with water, sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **18b**. This was immediately employed in the next step without further purification.

To a soln of crude **18b** in MeOH (100 ml) was added pyridinium *p*-toluenesulfonate (0.8 g, 3.2 mmol) at room temp. After stirring for 2 h at 40-45°C, it was diluted with $CHCl_3$. The organic soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **18c**. Because **18c** was labile, the following reaction was immediately performed.

To a soln of crude **18c** in MeOH (80 ml) was added a 28% soln of NaOMe in MeOH (8 ml, 41.5 mmol) at room temp with stirring. The exothermic reaction took place and the temp raised to 40°C. After stirring for 2 h at the ambient temp, the mixture was diluted with water and concentrated *in vacuo*. The residual soln was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography [100 g, *n*-hexane-EtOAc (3:1-2:1)] to give **14** (5.50 g, 81%) as a colorless oil. This was employed in the next step without further purification

(1S,2R*,7R*)-11-Oxatricyclo[5,3,2,0^{2,7}]-4,9-dodecadien-8-one* **19**

To a stirred soln of $(COCl)_2$ (4.97 ml, 58.0 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise a soln of DMSO (8.24 ml, 116.0 mmol) in dry CH_2Cl_2 (30 ml) at -78°C. After stirring for 30 min at the same temp, to this was added dropwise a soln of **14** (5.17 g, 29.0 mmol) in dry CH_2Cl_2 (50 ml) at -78°C with stirring. The stirring at the same temp for 1 h was followed by the addition of Et_3N (17.8 ml, 127.6 mmol) and the temp was raised to -20°C over 30 min. Then, the soln was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [85 g, *n*-hexane-EtOAc (8:1-3:1)] to give crystalline **19** (4.68 g, 92%). An analytical sample was recrystallized from *n*-hexane-(*i*-Pr)$_2$O to give pure **19** as rods, m.p. 49.0-49.5°C; IR vmax (KBr) 3050 (w), 3040 (m), 1685 (s), 1670 (s), 1655 (m), 1620 (w), 1060 (s), 730 (w), 700 (m), 680 (m) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 1.88-2.63 (m, 5H), 3.56 and 3.92 (each d, each 1H, *J*=9.5 Hz), 4.37 (d, 1H, *J*=6.0 Hz), 5.66 (m, 2H), 6.13 (dd, 1H, *J*=1.0, 10.0 Hz), 7.28 (dd, 1H, 6.0, *J*=10.0 Hz). (Found: C, 75.02; H, 6.84. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%)

(1S,2R*,7R*,10S*)-10-Isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-4-dodecen-8-one* **20**

To a stirred suspension of CuCN (2.28 g, 25.5 mmol) in dry Et_2O (80 ml) was added dropwise a soln of *i*-PrMgI in dry Et_2O [57.0 ml, 51.3 mmol:

which was prepared from Mg (1.65 g, 68.0 mmol) and *i*-PrI (6.79 ml, 68.0 mmol) in dry Et_2O (80 ml)] at 10°C. After stirring for 20 min at 10°C, to this was added a soln of **19** (3.00 g, 17.0 mmol) in dry Et_2O (15 ml) at -78°C with stirring. The temp was raised to 0°C over 4 h with stirring. Then, the mixture was quenched with sat NH_4Cl soln, filtered through Celite and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [110 g, *n*-hexane-EtOAc (20:1)] to give crystalline **20** (2.81 g, 75%). An analytical sample was recrystallized from *n*-pentane-Et_2O to give pure **20** as plates, m.p. 64.0-65.0°C; IR vmax (KBr) 3040 (m), 1705 (s), 1655 (w), 1080 (w), 1050 (m), 725 (w), 700 (m) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 0.92 and 0.96 (each d, each 3H, *J*=6.5 Hz), 1.444 (dqq, 1H, *J*=6.5, 6.5, 9.5 Hz), 1.87 (m, 1H), 1.90 (m, 1H), 2.13-2.31 (m, 4H), 2.35 (ddd, 1H, *J*=1.0, 2.5, 16.5 Hz), 2.71 (dd, 1H, *J*=8.5, 16.5 Hz), 2.71 (m, 1H), 3.81 (d, 1H, *J*=8.5 Hz), 3.87 (d, 1H, *J*=8.5 Hz), 4.20 (d, 1H, *J*=3.0 Hz), 5.66 (m, 2H). (Found: C, 76.25; H, 9.19. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%)

X-ray crystallographic analysis of (±)-**20**.

The crystallographic data of (±)-**20** were given in Table 1. Details of the X-ray analysis will be published separately by Miura and Chikaishi.[13]

$C_{14}H_{20}O_2$	M.W.=220.31
monoclinic	C2
a=22.159 (2) Å	β=99.39 (1)°
b=6.395 (1) Å	V=2488.0 $Å^3$
c=17.196 (2) Å	Z=8
D_X=1.176 gcm^{-3}	F(000)=960
μ(Cu Kα)=5.71 cm^{-1}	

Table 1. Crystallographic data of (±)-**20**.

(1S,2R*,7R*,8R*,10S*)-10-Isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-4-dodecen-8-ol* **21a**

To liquid NH_3 (ca. 50 ml) were added portionwise chips of Li (1.24 g, 179 mmol) at -78°C with stirring. After stirring for 20 min at the same temp, to this was added dropwise a soln of **20** (1.96 g, 8.90 mmol) in dry THF (8 ml) and dry *t*-BuOH (5 ml) at -78°C with stirring. The stirring was continued for 4 h at -78°C and for 16 h at the ambient temp. Then, the mixture was quenched with sat NH_4Cl soln with ice-cooling and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [75 g, *n*-hexane-EtOAc (10:1-3:1)] to give crystalline **21a** (1.79 g, 91%). An analytical sample was recrystallized from *n*-hexane-(*i*-Pr)$_2$O to give pure **21a** as cubes, m.p. 85.5-86.5°C; IR vmax (KBr) 3560 (s), 3060 (m), 1665 (w), 1070 (s), 1045 (s), 705 (m) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 0.86 (d, 3H, *J*=6.5 Hz), 0.98 (d, 3H, *J*=6.5 Hz), 1.32-2.27 (m, 9H), 3.52 (d, 1H, *J*=8.0 Hz), 3.59 (dd, 1H, *J*=6.0, 6.0 Hz), 3.94 (d, 1H, *J*=8.0 Hz), 3.95 (d, 1H, *J*=3.0 Hz), 5.62 (d, 1H, *J*=11.0 Hz), 5.70 (d, 1H, *J*=11.0 Hz). (Found: C, 75.43; H, 10.00. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%)

(1S,2R*,7R*,8R*,10S*)-8-t-Butyldimethylsilyloxy-10-isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-4-dodecene* **21b**

To a stirred soln of **21a** (1.40 g, 6.29 mmol) in dry 2,6-lutidine (3.96 ml, 34.0 mmol) and dry CH_2Cl_2 (5 ml) was added dropwise *t*-butyldimethylsilyl triflate (2.60 ml, 11.3 mmol) at 0-5°C. After stirring for 5 min at the same temp, the mixture was poured into ice-NH_3 soln and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [70 g, *n*-hexane-Et_2O (10:1)] to give **21b** (2.13 g, quantitative) as a colorless oil, $n_D^{19.5}$ 1.4794; IR vmax (film) 3045 (w), 1660 (w), 1250 (m), 1085 (m), 690 (w) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 0.03 (s, 3H), 0.07 (s, 3H), 0.87 (d, 3H, *J*=6.0 Hz), 0.90 (s, 9H), 0.97 (d, 3H, *J*=6.0 Hz), 1.33-2.22 (m, 8H), 3.48 (d, 1H, *J*=8.0 Hz), 3.53 (dd, 1H, *J*=8.5, 8.5 Hz), 3.92 (d, 1H, *J*=3.5 Hz), 3.99 (d, 1H, *J*=8.0 Hz), 5.62 (d, 1H, *J*=12.0 Hz), 5.66 (d, 1H, *J*=12.0 Hz). (Found: C, 70.94; H, 10.70. Calcd for $C_{20}H_{36}O_2Si$: C, 71.37; H, 10.78%)

(1S,2R*,4R*,5R*,7R*,8R*,10S*)-8-t-Butyldimethylsilyloxy-4,5-dibromo-10-isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-dodecane* **22**

To a stirred soln of **21b** (2.65 g, 7.87 mmol) in dry THF (70 ml) was added pyridinium bromide perbromide (3.74 g, 11.7 mmol) at 0°C. After stirring for 2 h at 0°C and for 8 h at room temp, the soln was diluted with 5% $NaHSO_3$ soln and extracted with Et_2O. The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [40 g, *n*-hexane-Et_2O (10:1)] to give crystalline **22** (3.98 g, quantitative). An analytical sample was recrystallized from 99% EtOH to give pure **22** as plates, m.p. 89.5-91.5°C; IR vmax (KBr) 1250 (m), 1090 (s) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 0.04 (s, 3H), 0.09 (s, 3H), 0.87 (d, 3H, *J*=6.0 Hz), 0.90 (s, 9H), 0.96 (s, 3H, *J*=6.0 Hz), 1.40-2.61 (m, 9H), 3.50 (ddd, 1H, *J*=0.5, 6.0, 9.5 Hz), 3.98 (d, 1H, *J*=3.5 Hz), 4.00 (d, 1H, *J*=8.5 Hz), 4.52 (dd, 1H, *J*=0.5, 8.5 Hz), 4.72 (m, 1H), 4.82 (m, 1H). (Found: C, 48.07; H, 7.24. Calcd for $C_{20}H_{36}O_2SiBr_2$: C, 48.39; H, 7.31%)

(1R,2R*,5S*,6S*,7S*,8S*,10R*)-10-t-Butyldimetylsilyloxy-8-isopropyl-11-oxatricyclo[5,3,2,0^{1,6}]-3-dodecene-2,5-diol* **25**

To a soln of **22** (2.70 g, 5.44 mmol) in HMPA (30 ml) and acetone (10 ml) was added DBU (14.6 g, 95.9 mmol) at room temp. This was stirred for 16 h at 40-45°C. Then, it was diluted with water and extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [17 g, *n*-hexane-EtOAc (10:1)] to give crude **23** (0.80 g).

Into a stirred soln of crude **23** (0.75 g) and methylene blue (14 mg, 0.037 mmol) in MeOH (40 ml) was bubbled oxygen through a tube filled with KOH pellets under the irradiation with a tungsten lamp (185 W) at 5-10°C for 12 h. The soln was diluted with water and extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude **24** (0.88 g).

To a stirred soln of crude **24** (0.88 g) in dry THF (15 ml) was added portionwise $LiAlH_4$ (120 mg, 3.16 mmol) at 0-5°C. After stirring for 1 h at 0-5°C and for 1 h at room temp, the mixture was quenched with water (0.12 ml), 15% NaOH (0.12 ml) and water (0.36 ml). It was stirred for 1 h at room temp and filtered through Celite. The filter cake was washed with hot THF-CH_2Cl_2 four times. The combined filtrate and washings were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography [11 g, *n*-hexane-EtOAc (4:1-2:1)] to give crystalline **25** (319 mg, 15% from **22**). An analytical sample was recrystallized from (*i*-Pr)$_2$O to give pure **25** as needles, m.p. 164.0-166.0°C; IR vmax (KBr) 3480 (m), 3320 (s), 3050 (w), 1250 (m), 1090 (s) cm^{-1}; ^1H NMR δ (100 MHz, $CDCl_3$) 0.14 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 0.90 (d, 3H, *J*=6.0 Hz), 0.97 (d, 3H, *J*=6.0 Hz),

1.37-1.98 (m, 4H), 2.39 (d, 1H, *J*=5.0 Hz), 3.23 (dd, 1H, *J*=1.5, 8.5 Hz), 3.90-4.23 (m, 3H), 4.02 (d, 1H, *J*=8.5 Hz), 4.33 (d, 1H, *J*=3.0 Hz), 5.88 (m, 2H). (Found: C, 65.15; H, 9.83. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.84%).

(1S,2R*,6R*,7R*,8R*,10S*)-8-t-Butyldimethylsilyloxy-6-hydroxy-10-isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-4-dodecen-3-one* **26**

A mixture of **25** (286 mg, 0.776 mmol) and MnO_2 (1.32 g, 15.2 mmol) in $CHCl_3$ (15 ml) was stirred for 24 h at room temp. Then, this was filtered through Celite and the filter cake was washed with Et_2O. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by silica gel chromatography [8 g, *n*-hexane-EtOAc (4:1)] to give crystalline **26** (235 mg, 83%). An analytical sample was recrystallized from *n*-hexane-(*i*-Pr)$_2$O to give pure **26** as needles, m.p. 130.5-131.0°C; IR vmax (KBr) 3310 (s), 1680 (s), 1260 (m), 1105 (s), 1065 (m) cm^{-1}; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.14 (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 0.95 (d, 3H, *J*=6.5 Hz), 0.99 (d, 3H, *J*=6.5 Hz), 1.37 (dt, 1H, *J*=6.5, 6.5, 11.0 Hz), 1.70 (ddd, 1H, *J*=6.5, 11.0, 13.5 Hz), 1.98 (dd, 1H, *J*=1.0, 8.5 Hz), 2.17 (br.s, 1H), 2.49 (s, 1H), 3.38 (dd, 1H, *J*=1.0, 8.5 Hz), 4.10 (d, 1H, *J*=8.5 Hz), 4.24 (ddd, 1H, *J*=1.0, 6.0, 11.0 Hz), 4.29 (d, 1H, *J*=6.0 Hz), 4.82 (d, 1H, *J*=4.5 Hz), 6.13 (d, 1H, *J*=10.0 Hz), 6.91 (dd, 1H, *J*=6.0, 10.0 Hz). (Found: C, 65.09; H, 9.21. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35%)

Acetate of **26**

^{1}H NMR δ (300 MHz, $CDCl_3$) 0.98 (d, 3H, *J*=6.5 Hz), 1.00 (d, 3H, *J*=6.5 Hz), 1.40 (dt, 1H, *J*=6.5, 6.5, 10.3 Hz), 1.57 (ddd, 1H, *J*=3.9, 7.0, 10.3 Hz), 1.65 (ddd, 1H, *J*=7.0, 10.5, 13.5 Hz), 1.96 (dd, 1H, *J*=6.0, 13.5 Hz), 2.08 (s, 3H), 2.54 (s, 1H), 3.51 (dd, 1H, *J*=1.0, 8.5 Hz), 4.15 (d, 1H, *J*=8.5 Hz), 4.16 (ddd, 1H, *J*=1.0, 6.0, 10.5 Hz), 4.78 (d, 1H, *J*=3.9 Hz), 5.21 (d, 1H, *J*=5.6 Hz, AcOC<u>H</u>), 6.11 (d, 1H, *J*=10.3 Hz, CH=C<u>H</u>C=O), 7.13 (dd, 1H, *J*=5.6, 10.3 Hz, C<u>H</u>=CHC=O).

(1S,2R*,6R*,7R*,8R*,10S*)-8-t-Butyldimethylsilyloxy-6-hydroxy-10-isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-3-dodecanone* **27a**

A mixture of **26** (220 mg, 0.600 mmol) and 10% Pd/C (25 mg) in 95% EtOH (10 ml) was stirred under H_2 (atmospheric pressure) at room temp for 10 h. This was filtered through Celite and the filter cake was washed with Et_2O. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by silica gel chromatography [5 g, *n*-hexane-EtOAc (1:1)] to give crystalline **27a** (218 mg, 99%). An analytical sample was recrystallized from (*i*-Pr)$_2$O to give pure **27a** as needles, m.p. 151.5-153.0°C; IR vmax (KBr) 3410 (s), 1710 (s), 1245 (m), 1095 (s), 1085 (m) cm^{-1}; ^{1}H NMR δ (100 MHz, $CDCl_3$) 0.14 (s, 6H), 0.85 (d, 3H, *J*=6.5 Hz), 0.92 (s, 9H), 0.96 (d, 3H, *J*=6.5 Hz), 1.38-2.38 (m, 7H), 2.55 (s, 1H), 2.79 (m, 1H), 3.37 (dd, 1H, *J*=1.5, 9.0 Hz), 4.00 (d, 1H, *J*=9.0 Hz), 4.12 (ddd, 1H, *J*=2.5, 2.5, 3.5 Hz), 4.76 (ddd, 1H, *J*=1.5, 6.0, 10.0 Hz), 4.85 (d, 2H, *J*=3.0 Hz). (Found: C, 65.26; H, 9.68. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.84%)

(1S,2R*,6R*,7R*,8R*,10S*)-6-Acetoxy-8-t-butyldimethylsilyloxy-10-isopropyl-11-oxatricyclo[5,3,2,0^{2,7}]-3-dodecanone* **27b**

To a stirred soln of **27a** (181 mg, 0.49 mmol) in dry CH_2Cl_2 (3 ml) were added dry pyridine (0.6 ml, 7.4 mmol), Ac_2O (0.35 ml, 3.7 mmol) and DMAP (11 mg, 0.090 mmol) at room temp. After stirring for 12 h at the same temp, it was diluted with ice-water and extracted with ether. The extract was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [5 g, *n*-hexane-EtOAc (6:1-5:1)] to give crystalline **27b** (196 mg, 98%). An analytical sample was recrystallized from *n*-hexane-(*i*-Pr)$_2$O to give pure **32** as plates, m.p. 111.0-113.5°C; IR vmax (KBr) 1740 (s), 1720 (s), 1240 (s), 1090 (s) cm^{-1}; ^{1}H NMR δ (100 MHz, $CDCl_3$) 0.01 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 0.87 (d, 3H, *J*=6.0 Hz), 0.98 (d, 3H, *J*=6.0 Hz), 1.35-2.62 (m, 8H), 2.16 (s, 3H), 2.54 (s, 1H), 3.45 (dd, 1H, *J*=1.5, 9.0 Hz), 4.06 (d, 1H, *J*=9.0 Hz), 4.13 (ddd, 1H, *J*=1.5, 7.0, 10.0 Hz), 4.88 (d, 1H, *J*=3.0 Hz), 5.15 (dd, 1H, *J*=2.0, 2.0 Hz). (Found: C, 64.55; H, 9.21. Calcd for $C_{22}H_{38}O_5Si$: C, 64.35; H, 9.33%)

(1R,2R*,6R*,7S*,8S*,10R*)-2-Acetoxy-10-t-butyldimethylsilyloxy-8-isopropyl-5-methylene-11-oxatricyclo[5,3,2,0^{1,6}]-dodecane* **28a**

To a suspension of Ph_3PMeBr (3.10 g, 8.68 mmol) in dry DME (20 ml) was added dropwise *n*-BuLi in *n*-hexane (1.57 M, 4.15 ml, 6.52 mmol) at 0-5°C with stirring. This was stirred for 2 h at the same temp and left standing to precipitate the salts. To a stirred soln of **27b** (161 mg, 0.45 mmol) in dry DME (5 ml) was added the ylide described above (17.0 ml, 4.59 mmol) at 0-5°C. After stirring for 4 h at 0-5°C and for 12 h at room temp, the mixture was diluted with ice-water and extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [17 g, *n*-hexane-EtOAc (20:1-10:1)] to give crystalline **28a** (89 mg, 56%), m.p. 63.0-66.0°C; IR vmax (KBr) 3090 (w), 1740 (s), 1645 (w), 1245 (s), 1090 (m), 1040 (m), 890 (w), 770 (m) cm^{-1}; ^{1}H NMR δ (100 MHz, $CDCl_3$) 0.01 (s, 3H), 0.09 (s, 3H), 0.83 (s, 9H), 0.85 (d, 3H, *J*=6.5 Hz), 0.99 (d, 3H, *J*=6.5 Hz), 1.35-2.38 (m, 8H), 2.47 (s, 1H), 2.60 (s, 3H), 3.50 (dd, 1H, *J*=1.5, 8.0 Hz), 3.95 (d, 1H, *J*=8.0 Hz), 4.07 (ddd, 1H, *J*=1.5, 6.5, 9.5 Hz), 4.60 (d, 1H, *J*=3.0 Hz), 4.93 (s, 2H), 5.01 (dd, 1H, *J*=2.5, 2.5 Hz). (Found: C, 67.40; H, 9.83. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87%)

(1R,2R*,6R*,7S*,8S*,10R*)-10-t-Butyldimethylsilyloxy-8-isopropyl-5-methylene-11-oxatricyclo[5,3,2,0^{1,6}]-2-dodecanol* **28b**

To a stirred soln of **28a** (132 mg, 0.323 mmol) in dry Et_2O (6 ml) was added dropwise a soln of MeLi in Et_2O (1.19 M, 0.75 ml, 0.893 mmol) at 0-5°C. After stirring for 30 min at the same temp, it was quenched with sat NH_4Cl soln, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [10 g, *n*-hexane-EtOAc (8:1-6:1)] to give crystalline **28b** (111 mg, 94%). An analytical sample was recrystallized from *n*-hexane-(*i*-Pr)$_2$O to give pure **28b** as needles, m.p. 161.0-162.0°C; IR vmax (KBr) 3420 (s), 1640 (w), 1245 (m), 1090 (s), 1080 (s), 900 (m), 770 (m) cm^{-1}; ^{1}H NMR δ (100 MHz, $CDCl_3$) 0.12 (s, 3H), 0.13 (s, 3H), 0.85 (d, 3H, *J*=6.0 Hz), 0.90 (s, 9H), 0.97 (d, 3H, *J*=6.0 Hz), 1.36-2.68 (m, 9H), 3.43 (dd, 1H, *J*=1.0, 8.0 Hz), 3.87 (d, 1H, *J*=8.0 Hz), 3.98 (m, 1H), 4.17 (ddd, 1H, *J*=1.0, 7.0, 10.5 Hz), 4.57 (d, 1H, *J*=3.0 Hz), 4.89 (m, 1H). (Found: C, 68.79; H, 10.39. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45%)

(1S,2R*,7R*,8R*,10S*)-8-t-Butyldimethylsilyloxy-10-isopropyl-3-methylene-11-oxatricyclo[5,3,2,0^{2,7}]-5-dodecene* **29a**

To a stirred soln of **28b** (65.0 mg, 0.177 mmol) in dry CH_2Cl_2 (20 ml) were added DMAP (432 mg, 3.54 mmol) and CF_3SO_2Cl (188 μl, 1.77 mmol) at 0-5°C. After stirring for 2 h at room temp, it was diluted with water and extracted with Et_2O. The extract was washed with water and sat $NaHCO_3$ soln, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **28c**. This was employed in the next step without further purifications.

A soln of crude **28c** and DBU (5 ml, 33.4 mmol) in dry benzene (10 ml) was stirred for 12 h at 70°C. Then, it was diluted with water and extracted

with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [10 g, *n*-hexane-Et_2O (20:1)] to give crystalline **29a** (48.4 mg, 78%). This was employed in the next step without further purifications.

(1S,2R*,7R*,8R*,10S*)-10-Isopropyl-3-methylene-11-oxatricyclo[5,3,2,0^{2,7}]-5-dodecen-8-ol* **29b**

To a soln of **29a** (32.5 mg, 0.0932 mmol) in THF (1.5 ml) was added a soln of $(n\text{-}Bu)_4NF$ in THF (1.0 M, 1.5 ml, 1.5 mmol) at room temp. After stirring for 2 h at room temp, it was diluted with EtOAc. The organic soln was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography [5 g, *n*-hexane-EtOAc (4:1-2:1)] to give crystalline **29b** (22.2 mg, quantitative). An analytical sample was recrystallized from $(i\text{-}Pr)_2O$ to give pure **29b** as needles, m.p. 127.0-130.0°C; IR vmax (KBr) 3430 (s), 3050 (m), 1660 (w), 1475 (w), 1080 (m), 1035 (s), 730 (w), 700 (s) cm^{-1}; ^1H NMR δ 0.88 (d, 3H, *J*=6.5 Hz), 0.99 (d, 3H, *J*=6.5 Hz), 1.40-2.10 (m, 4H), 2.30 (s, 1H), 2.76 (dd, 1H, *J*=3.5, 19.0 Hz), 2.94 (dm, 1H, *J*=19.0 Hz), 3.38 (dd, 1H, *J*=0.5, 8.0 Hz), 3.71 (dd, 1H, *J*=5.0, 8.5 Hz), 3.99 (d, 1H, *J*=8.0 Hz), 4.58 (d, 1H, *J*=3.5 Hz), 7.99 (s, 2H), 5.77 (dm, 1H, *J*=10.0 Hz), 5.84 (d, 1H, *J*=10.0 Hz). (Found: C, 76.83; H, 9.32. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.32%)

(1S,2R*,7R*,8R*,10S*)-10-Isopropyl-3-methylene-11-oxatricyclo[5,3,2,0^{2,7}]-5-dodecen-8-one* [(±)-PA 22-VII] **5**

To a stirred mixture of powdered molecular sieves 3A (0.9 g) and PDC (98%, 169 mg, 0.440 mmol) in dry CH_2Cl_2 (4ml) was added a soln of **29b** (24.9 mg, 0.106 mmol) at room temp. After stirring for 3 h at the same temp, the mixture was filterd through florisil. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography [2 g, *n*-hexane-EtOAc (9:1)] to give crystalline **5** (20.0 mg, 81%). An analytical sample was recrystallized from *n*-hexane-EtOAc to give pure **5** as prisms, m.p. 118.0-118.5°C; IR vmax (KBr) 3100 (w), 3060 (m), 2980 (s), 2940 (s), 2910 (s), 2890 (m), 2840 (w), 1710 (s), 1655 (m), 1490 (w), 1470 (w), 1450 (w), 1420 (w), 1390 (w), 1370 (w), 1330 (w), 1310 (w), 1270 (w), 1260 (m), 1240 (w), 1185 (m), 1160 (w), 1130 (w), 1110 (w), 1080 (w), 1045 (s), 995 (w), 975 (m), 945 (w), 930 (m), 910 (m), 895 (m), 875 (m), 830 (w), 805 (w), 780 (w), 750 (w), 720 (m), 690 (w), 665 (w) cm^{-1}; ^1H NMR δ (300 MHz, CS_2) 0.93 (d, 3H, *J*=6.6 Hz), 0.95 (d, 3H, *J*=6.6 Hz), 1.39 (dt, 1H, *J*=6.6, 6.6, 9.3 Hz), 1.82 (dddd, 1H, *J*=2.9, 3.4, 8.6, 9.3 Hz), 2.14 (dd, 1H, *J*=3.4, 16.5 Hz), 2.49 (ddd, 1H, *J*=0.9, 8.6, 16.5 Hz), 2.63 (s, 1H), 2.73 (dd, 1H, *J*=4.6, 19.0 Hz), 2.89 (d, 1H, *J*=19.0 Hz), 3.43 (d, 1H, *J*=7.8 Hz), 3.69 (d, 1H, *J*=7.8 Hz), 4.60 (d, 1H, *J*=2.9 Hz), 4.99 and 5.01 (each s, total 2H), 5.69 (dm, 1H, *J*=10.8 Hz), 5.80 (d, 1H, *J*=10.8 Hz); ^{13}C NMR δ (75 MHz, $CDCl_3$) 20.18, 21.39, 30.29, 33.82, 38.57, 45.99, 47.58, 59.06, 74.52, 77.16, 109.47, 121.60, 128.79, 139.24, 210.83; MS (70 eV) *m/z* (%) 232 (M^+, 6), 202 (9), 189 (11), 172 (25), 159 (74), 145 (17), 141 (18), 133 (50), 127 (100), 105 (85), 104 (75), 97 (64), 91 (80), 81 (58), 79 (43), 77 (64), 69 (48), 55 (46), 43 (74), 41 (74). (Found: C, 77.23; H, 8.70. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%)

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