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A biogenetically patterned enantiospecific synthesis of allopupukeanones

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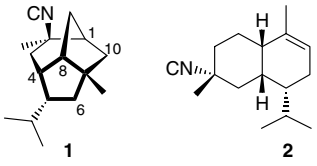
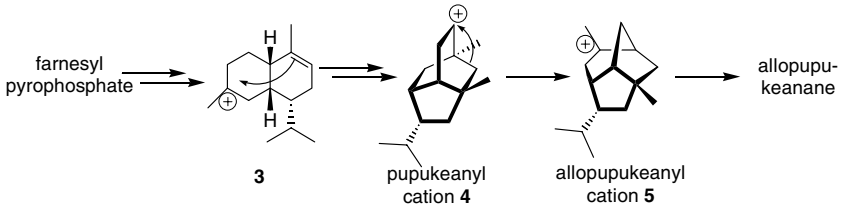
Abstract—The first enantiospecific synthesis of allopupukeanones has been accomplished starting from 6-methylcarvone. A biogenetically patterned rearrangement of a pupukeanane to allopupukeanane was employed as the key step.

Nudibranchs are well known for various types of secondary metabolites in their mucous secretions as a part of self-defence. They have therefore been the focus of many marine natural product studies.[1,2] Members of the genus *Phyllidia* have gained the reputation of being especially pungent due to the presence of sesquiterpene isonitriles. In this context, the research group of Fusetani investigated *P. pustulosa* collected from Hachijo-Jima island. Bioassay-guided investigations led to the isolation of two new sesquiterpene isonitriles, 2-isocyanoallopupukeanane **1** and 4α-isocyano-9-amorphene **2**, whose structures were deduced by extensive 2D NMR spectral analysis.[3] 2-Isocyanoallopupukeanane **1** has shown ichthyotoxicity towards the killifish *Oryzias latipes*. Biogenetically, the origin of pupukeananes[4] and allopupukeananes[7] can be explained by a common pathway via cyclisation and rearrangement of the bicyclic sesquiterpenes, cadinanes.[2,3] As depicted in Scheme 1, cyclisation and rearrangement of the carbocation **3**, derived from amorphene (a cadinane), generates the pupukeanyl cation **4**, which undergoes a 1,2-alkyl shift generating the allopupukean-2-yl carbocation **5**.



1 **2**

The presence of an interesting tricyclo[5.2.1.$0^{4,8}$]decane carbon framework incorporating two quaternary carbon atoms, six stereogenic carbon atoms and an isonitrile functionality make 2-isocyanoallopupukeanane **1** an attractive and challenging synthetic target.[4] Herein, we describe the first enantiospecific synthesis of allopupukeanones, employing a biogenetically patterned conversion of a pupukeanane to an allopupukeanane as the key step. The retrosynthetic analysis is depicted in Scheme 2. By utilising an isopropenyl moiety as a masked hydroxy group and the biogenetically patterned conversion of an isotwistane into a tricyclo[5.2.1.$0^{4,8}$]-decane,[5] isotwistane dione **6** was conceived as the key intermediate, which could be obtained from 6-methylcarvone **7**.



Scheme 1.

Keywords: Allopupukeananes; Pupukeananes; Molecular rearrangement.
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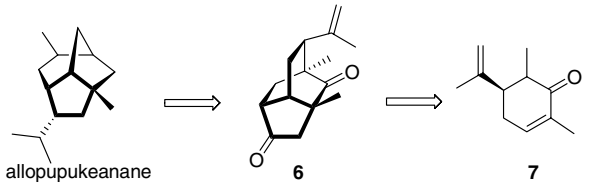
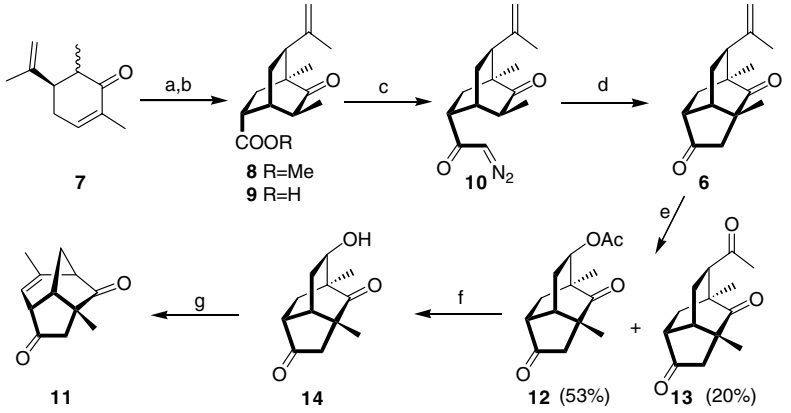
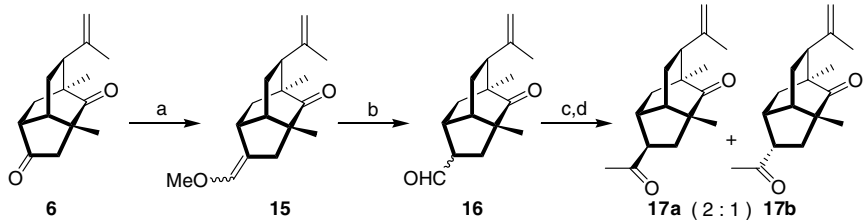


Scheme 2.

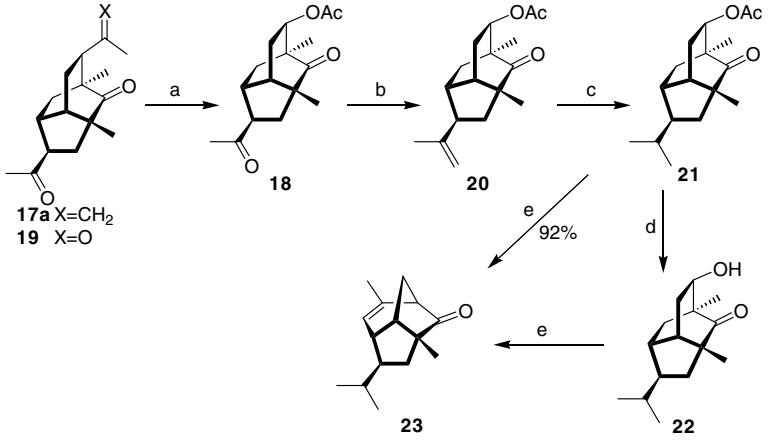
The synthetic sequence was initiated with the construction of the isotwistane dione **6** employing the methodology developed earlier in our laboratory (Scheme 3).[6] Thus, reaction of 6-methylcarvone **7** with lithium hexamethyldisilazide (LiHMDS) followed by treatment of the resultant kinetic dienolate with 1.1 equiv of methyl acrylate furnished bicyclo[2.2.2]octanecarboxylate **8** via intermolecular Michael addition followed by intramolecular Michael addition, which on base catalysed hydrolysis furnished the acid **9**. Reaction of the acid **9** with oxalyl chloride followed by treatment of the resultant acid chloride with diazomethane generated the diazoketone **10**. Reaction of the diazoketone **10** with a catalytic amount of rhodium trifluoroacetate in refluxing methylene chloride furnished isotwistane dione **6**, in 50% yield, via regiospecific C–H insertion of the intermediate rhodium carbenoid.



Scheme 3. Reagents, conditions and yields: (a) LiHMDS, hexane, CH_2=CHCOOMe, −10 °C → rt, 3 h, 75%; (b) NaOH, MeOH, reflux, 8 h, 93%; (c) (i) $(COCl)_2$, C_6H_6, rt, 2 h; (ii) CH_2N_2, Et_2O, 0 °C → rt, 3 h; 90%; (d) $Rh_2(tfa)_4$, CH_2Cl_2, reflux, 4 h, 50%; (e) O_3/O_2, CH_2Cl_2–MeOH (9:1), −70 °C; Ac_2O, Et_3N, DMAP, C_6H_6, reflux, 6 h, 73%; (f) K_2CO_3, MeOH, rt, 10 h, 85%; (g) PTSA, C_6H_6, reflux, 3 h, 74%.



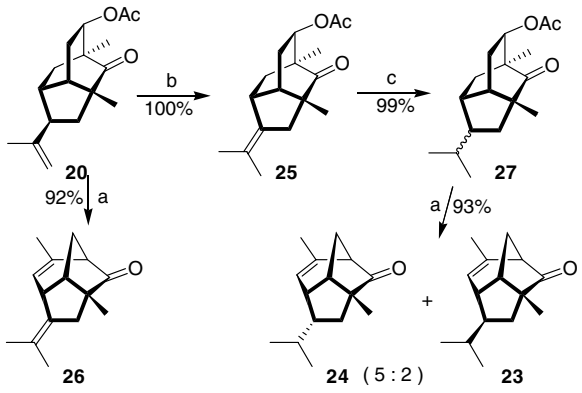
Scheme 4. Reagents, conditions and yields: (a) Ph_3P=CHOMe, THF, reflux, 3 h, 64%; (b) 3 N HCl, THF, rt, 1 h, 86%; (c) MeMgI, Et_2O, 0 °C → rt, 0.5 h, 96%; (d) PCC, silica gel, CH_2Cl_2, rt, 3 h, 95%.



Scheme 5. Reagents, conditions and yields: (a) O_3/O_2, CH_2Cl_2–MeOH (9:1), −70 °C; Ac_2O, Et_3N, C_6H_6, reflux, 5 h, 87% (**18**:**19** 3:1); (b) Ph_3P=CH_2, C_6H_6, rt, 0.5 h, 75%; (c) H_2, 10% Pd–C, hexane, 1 atm, 6 h, 99%; (d) K_2CO_3, MeOH, rt, 10 h, 93%; (e) PTSA, C_6H_6, reflux, 3 h, 92%.

Conversion of isotwistane dione **6** into a tricyclo-[5.2.1.$0^{4,8}$]decenone **11** was first investigated. Thus, ozonolysis of the isopropenyl group in the tricyclic dione **6** in methanol–methylene chloride at −70 °C followed by treatment of the resultant methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished acetate **12**, along with the normal ozonolysis product, trione **13**. Hydrolysis of keto-acetate **12** with potassium carbonate in methanol gave alcohol **14** in 85% yield. Treatment of alcohol **14** with *p*-toluenesulfonic acid (PTSA) in refluxing benzene for three hours furnished cleanly the rearranged product **11** in 74% yield, whose structure was deduced from its spectral data.[†]

Subsequently, extension of the methodology for the synthesis of allopupukeananes was investigated (Schemes 4–6). For further elaboration of isotwistane dione **6**, the generation of an isopropyl group at the C-5 carbon was addressed prior to the degradation of the isopropenyl group. The relative steric crowding of the C-2 ketone when compared to that of the C-5 ketone group was exploited for the selective introduction of a side chain at the C-5 carbon of isotwistane dione **6**.[8] Accordingly, Wittig reaction of the tricyclic dione **6** with methoxymethylenetriphenylphosphorane in refluxing THF for 3 h furnished a 2:1 *E*/*Z* mixture of enol ether **15**, in 64% yield, which on hydrolysis with 3 N hydrochloric acid in 0.02 M THF solution furnished a 2:1 epimeric mixture of the aldehyde **16**. Reaction of aldehyde **16** with methylmagnesium iodide followed by oxidation of the resultant secondary alcohol with pyridinium chlorochromate (PCC) and silica gel in methylene chloride for three hours at room temperature furnished a 2:1 mixture of the epimeric diones **17a**,**b** in 91% yield, which were separated by column chromatography on silica gel. The structures of the two isomers **17a**,**b** were established from their spectral data.



Scheme 6. Reagents, conditions and yields: (a) PTSA, C_6H_6, reflux, 3 h; (b) $RhCl_3{\cdot}nH_2O$, EtOH, reflux, 24 h; (c) H_2, PtO_2, EtOH, 1 atm, 48 h.

First degradation of the isopropenyl group in the major dione **17a** was addressed via Creigee rearrangement.[7] Ozonolysis of the tricyclic dione **17a** in a mixture of methanol–methylene chloride followed by treatment of the intermediate methoxyhydroperoxide with a mixture of acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished the acetate **18**, along with a varying amount of the normal ozonolysis product, trione **19**. In order to establish the stereochemistry of the acetyl group unambiguously, diketo-acetate **18** was subjected to X-ray diffraction analysis (Fig. 1).[9] Wittig reaction of keto-acetate **18** with methylenetriphenylphosphorane furnished olefin **20**, which on hydrogenation in hexane at one atmospheric pressure of hydrogen (balloon) using 10% palladium on activated charcoal as the catalyst generated keto-acetate **21** in 75% yield, which on hydrolysis gave hydroxyketone **22** in 93% yield. Treatment of the hydroxyketone **22** with 1.5 equiv of PTSA in refluxing benzene for 3 h furnished the 5-epiallopupukean-10-one **23**, in 92% yield, in a highly regioselective manner.[†] Alternatively, it was found that the reaction of keto-acetate **21** with PTSA in refluxing benzene for 8 h also furnished 5-epiallopupukean-10-one **23**, directly.

Next, the synthesis of allopupukean-10-one **24**, starting from the tricyclic dione **17b**, was investigated. However, a comparable sequence led to a mixture of epimers at the C-5 carbon, due to epimerisation of the acetyl group

[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for (1*R*,4*R*,7*R*,8*S*)-2,7-dimethyltricyclo[5.2.1.$0^{4,8}$]dec-2-ene-5, 10-dione **11**: Mp: 116–118 °C; $[\alpha]_D^{25}$: −165.5 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1738; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.20 (1H, d, *J* 3.9 Hz), 3.19 (1H, br s), 2.84 (1H, dd, *J* 4.5 and 1.8 Hz), 2.61 (1H, t, *J* 5.1 Hz), 2.53 (1H, d, *J* 19.2 Hz, H-6A), 2.18 (1H, t of d, *J* 12.0 and 4.2 Hz, H-9A), 1.98 (1H, d, *J* 19.2 Hz, H-6B), 1.81 (3H, s, olefinic CH_3), 1.66 (1H, d, *J* 12.0 Hz, H-9B), 1.27 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 212.0 (C), 211.5 (C), 139.6 (C, C-2), 117.3 (CH, C-3), 54.3 (CH), 51.6 (C, C-7), 51.5 (CH), 44.0 (CH_2), 43.9 (CH), 26.3 (CH_2), 23.3 (CH_3), 22.2 (CH_3); Mass: *m*/*z* 190 (M^+, 70%), 162 (13), 147 (25), 134 (27), 119 (100), 105 (45), 98 (11), 93 (38), 92 (75), 91 (77); HRMS: *m*/*z* Calcd for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0901. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. Found: C, 75.70; H, 7.42%. For (1*R*,4*R*,5*S*,7*R*,8*S*)-5-isopropyl-2,7-dimethyltricyclo[5.2.1.$0^{4,8}$] dec-2-en-10-one (5-*epi*allopupukean-2-en-10-one **23**): $[\alpha]_D^{24}$: +321.8 (*c* 4.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1737; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.16 (1H, br s, H-3), 2.85 (1H, br s), 2.54 (1H, dd, *J* 4.5 and 1.5 Hz), 2.24 (1H, t, *J* 4.8 Hz), 2.00–1.82 (2H, m), 1.70 (3H, s, olefinic CH_3), 1.62 (1H, d, *J* 11.7 Hz), 1.60–1.40 (2H, m), 1.36 (1H, dd, *J* 14.4 and 2.7 Hz), 1.12 (3H, s, *tert* CH_3), 0.92 and 0.91 (6H, 2 × d, *J* 6.3 Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 215.7 (C, C-10), 133.8 (C, C-2), 127.7 (CH, C-3), 54.5 (C), 51.3 (CH), 51.0 (CH), 46.8 (CH), 45.9 (CH), 39.0 (CH_2), 31.6 (CH), 28.0 (CH_2), 22.8 (2C, CH_3), 21.6 (CH_3), 21.1 (CH_3); Mass: *m*/*z* 218 (M^+, 15%), 190 (13), 147 (100), 119 (28), 105 (77); HRMS: *m*/*z* Calcd for $C_{15}H_{23}O$ (M+H): 219.1749. Found: 219.1756. (1*R*,4*R*,5*R*,7*R*,8*S*)-5-Isopropyl-2,7-dimethyltricyclo[5.2.1.$0^{4,8}$]dec-2-en-10-one (allopupukea-2-en-10-one **24**): $[\alpha]_D^{24}$: +325.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1736; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.35 (1H, br s), 2.92 (1H, br s), 2.63 (1H, dd, *J* 4.5 and 1.8 Hz), 2.21 (1H, t, *J* 4.5 Hz), 1.89 (1H, t of d, *J* 11.7 and 4.5 Hz), 1.82–1.51 (4 H, m), 1.70 (3H, s), 1.40–1.25 (1H, m), 1.14 (3H, s), 0.98 (3H, d, *J* 6.6 Hz), 0.83 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 217.7 (C, C-10), 136.1 (C, C-2), 121.9 (CH, C-3), 53.3 (C, C-7), 52.3 (CH), 51.5 (CH), 49.4 (CH), 44.8 (CH), 41.7 (CH_2), 31.2 (CH), 27.7 (CH_2), 22.9 (CH_3), 22.6 (CH_3), 22.0 (CH_3), 21.7 (CH_3); Mass: *m*/*z* 218 (M^+, 27%), 190 (13), 175 (6), 148 (23), 147 (100), 119 (43), 107 (52), 105 (66), 93 (16), 91 (21); HRMS: *m*/*z* Calcd for $C_{15}H_{23}O$ (M+H): 219.1749. Found: 219.1755.

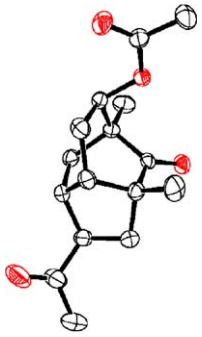


Figure 1. ORTEP diagram of **18**.

during the Wittig reaction. Hence, an alternative strategy via generation of the tetrasubstituted olefin **25** followed by hydrogenation was explored. Reaction of the keto-acetate **20** with PTSA in refluxing benzene for three hours led to isomerization of the double bond as well as the rearrangement of the ring system and generated allopupukeadienone **26** in 92% yield. On the other hand, reaction of keto-acetate **20** with rhodium chloride hydrate[10] in refluxing ethanol isomerised the olefin moiety and furnished the isopropylidene compound **25** in quantitative yield, which on hydrogenation with platinum oxide as the catalyst in ethanol furnished a 5:2 epimeric mixture of ketoacetate **27**. Treatment of the epimeric mixture of **27** with PTSA in refluxing benzene furnished a 5:2 mixture of allopupukeanones **24** and **23**, which were separated by column chromatography on 10% silver nitrate impregnated silica gel. The structures of allopupukean-10-ones **24** and **23** were established from their spectral data.

In summary, the first enantiospecific synthesis of allopupukeananes has been accomplished. A biogenetically patterned conversion of a pupukeanane to allopupukeanane was employed as the key step.

Acknowledgements

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References and notes

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8. Since addition of isopropyl Grignard reagent or the isopropylidene Wittig reaction were unsuccessful, a longer route was employed.
9. Crystal data for **18**: X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.7107$ Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{16}H_{22}O_4$, MW = 278.34, Crystal system: monoclinic, space group: $P2(1)$; cell parameters: $a = 8.219(2)$ Å, $b = 11.331(3)$ Å, $c = 8.314(2)$ Å, $\alpha = 90°$, $\beta = 101.28(4)°$, $\gamma = 90°$, $\rho = 759.2(3)$ Å^3; $Z = 2$; $D_c = 1.218$ g cm^{-3}; $F(000) = 300$, $\mu = 0.086$ mm^{-1}. Total number of l.s. parameters = 185; $R1[I > 2\sigma(I)] = 0.0424$ for 2647. $Rw[I > 2\sigma(I)] = 0.1028$; GOF = 1.048; restrained GOF = 1.048 for all data. ORTEP diagram is depicted in Fig. 1 (for clarity hydrogen atoms were omitted). Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Centre and the depository number is CCDC 275775.
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