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An enantiospecific synthesis of (−)-2-pupukeanone via a rhodium carbenoid C–H insertion reaction†

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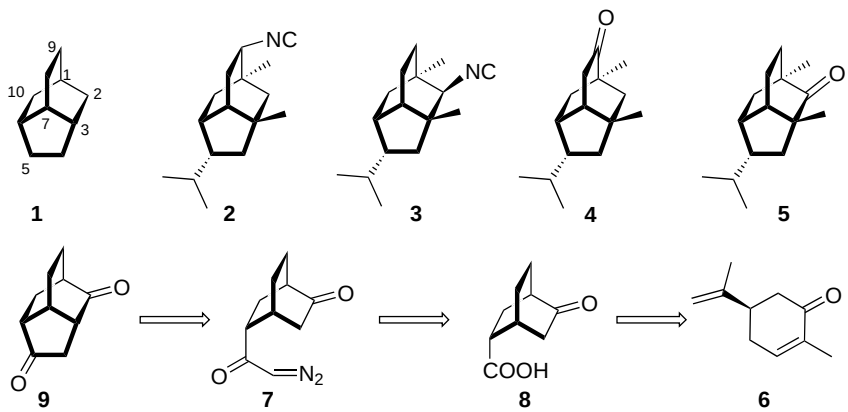
Abstract—An enantiospecific synthesis of (−)-2-pupukeanone, starting from (*R*)-carvone employing a Michael–Michael reaction and an intramolecular rhodium carbenoid C–H insertion reaction as the key steps for the generation of the isotwistane framework, is described.

The nudibranch *Phyllidia varicosa* Lamarck, 1801 secretes, as part of its defence mechanism, two volatile substances that are lethal to fish and crustaceans. Scheuer and co-workers reported the isolation of these two isotwistane (**1**) based sesquiterpenes 9- and 2-isocyanopupukeananes **2** and **3** from the skin extracts of *P. varicosa* and also from its prey, a sponge *Ciocalypta* sp., and the structures were elucidated based on degradative and single-crystal X-ray diffraction studies.[1] The presence of an interesting isotwistane carbon framework made these pupukeananes **2** and **3**, and the corresponding ketones **4** and **5** interesting and challenging synthetic targets. Since the first report on the synthesis of (±)-2-isocyanopupukeanane **3** by Corey et al., several reports have appeared on the synthesis of racemic 2-pupukeanone (±)-**5**.[2] In contrast, there is only one approach reported in the literature for the synthesis of (+)-2-pupukeanone **5** which employs a radical cyclisation reaction as the key step.[3] In continuation of our interest in the enantiospecific synthesis of sesquiterpenes starting from the readily available monoterpene (*R*)-carvone **6**,[3,4] herein, we report an enantiospecific synthesis of (−)-2-pupukeanone **5** employing an intramolecular rhodium carbenoid C–H insertion as the key reaction.

It was anticipated that intramolecular rhodium carbenoid C–H insertion of the diazo ketone **7**, derived from the carboxylic acid **8**, could generate the isotwistanedione **9**.[5] A Michael–Michael reaction of a cyclohexenone with acrylate could be exploited for the generation of the carboxylic acid **8**, and a suitable derivative of (*R*)-carvone **6** could be used as a chiral starting material for the enantiospecific generation of a chiral analogue of the carboxylic acid **8**.

The synthetic sequence starting from (*R*)-carvone **6** is depicted in Schemes 1 and 2. Thus, (*R*)-carvone **6** was transformed into 6-methylcarvone **10**, which on



1 **2** **3** **4** **5**

9 **7** **8** **6**

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† Chiral synthons from carvone Part 47. For Part 46, see: Ref. 4a.

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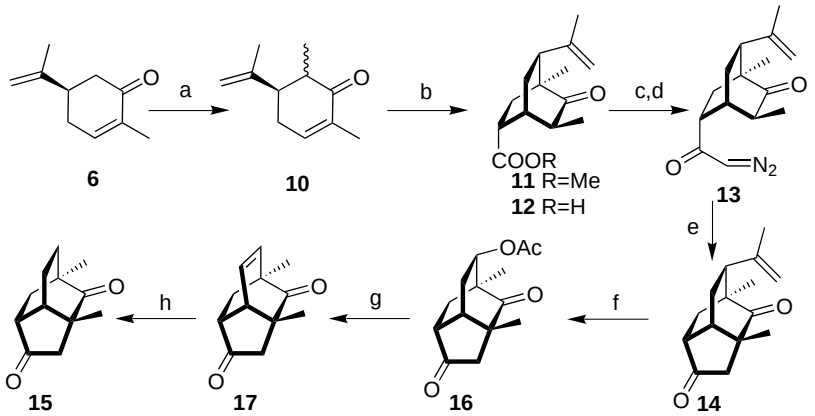
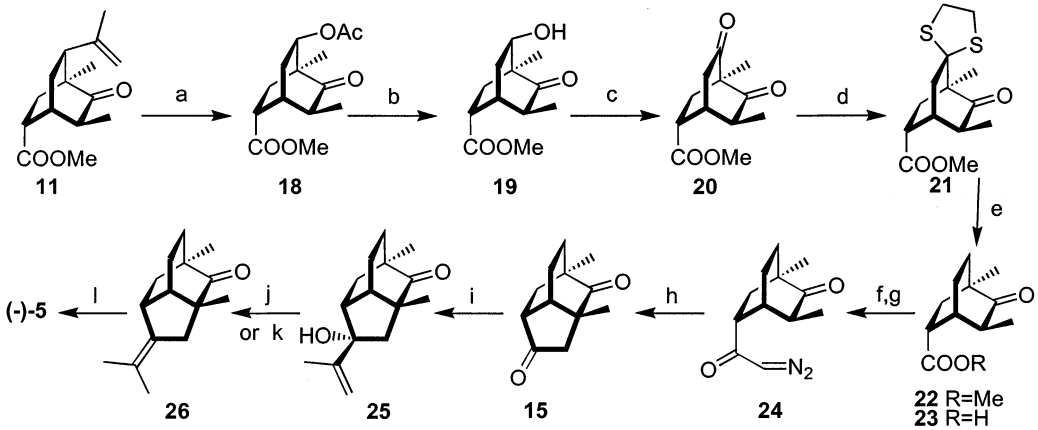


Scheme 1. *Reagents, conditions and yields*: (a) LDA, MeI, THF, 0°C→rt, 10 h, 98%; (b) LiHMDS, hexane, CH_2=CHCOOMe, 0°C→rt, 3 h, 70%; (c) 5% NaOH in MeOH–H_2O (1:1), reflux, 8 h, 93%; (d) i. $(COCl)_2$, C_6H_6, rt, 2 h; ii. CH_2N_2, Et_2O, 0°C, 2 h, 95%; (e) $Rh_2(tfa)_4$, CH_2Cl_2, reflux, 4 h, 56%; (f) i. O_3/O_2, CH_2Cl_2–MeOH (5:1), −78°C; ii. Ac_2O, Et_3N, DMAP, C_6H_6, reflux, 5 h, 48%; (g) FVP, 500°C/0.05 mm; (h) H_2, 1 atm, 10% Pd–C, EtOH, 8 h, 15% (two steps).

Michael–Michael reaction with LiHMDS and methyl acrylate furnished the keto ester **11** in a highly regio- and stereoselective manner.[6] Hydrolysis of the ester **11** generated the acid **12** (102–103°C), which was converted into the diazo ketone **13** via the corresponding acid chloride. Reaction of the diazo ketone **13** with rhodium acetate in refluxing methylene chloride furnished the isotwistanedione **14** in only 11% yield. However, changing the catalyst[5] to the more reactive rhodium trifluoroacetate generated the dione **14**‡ in 53% yield (from the acid **12**). Next, attention was turned towards the degradation of the isopropenyl group, via ozonolysis and Criegee rearrangement,[7] for the generation of the dione **15**, an intermediate in Chang's synthesis of 2-pupukeanone. Accordingly, ozonolysis of the dione **14** in a 1:5 mixture of methanol–methylene chloride followed by treatment of the resultant methoxyhydroperoxide with acetic anhydride, triethylamine and DMAP in refluxing benzene furnished the acetate **16** in 48% yield along with varying amounts of the normal ozonolysis product. Flash vacuum pyrolysis of the acetate **16** at 500°C (0.05 mm) followed by hydrogenation of the resultant olefin **17**‡ using 10% Pd/C as the catalyst generated the dione **15** in 15% yield (from **16**). Since the yield of the dione **15** is low, the strategy was altered, and the degradation of the isopropenyl group was carried out prior to the construction of the isotwistane framework (Scheme 2). Consequently, ozonolysis followed by Criegee rearrangement of the keto ester **11** generated the acetate **18**‡ in 55% yield along with 20% of the normal ozonolysis product. Hydrolysis of the acetate with potassium carbonate in methanol followed by oxidation of the resultant alcohol **19** with a mixture of PCC and silica gel in methylene chloride transformed the acetate **18** into the diketo ester **20**. Thioketalisation of the diketo ester **20** with ethanedithiol and a catalytic amount of $BF_3{\cdot}Et_2O$ in benzene regioselectively furnished the thioketal **21** in 82% yield, which on desulfurisation with Raney nickel in refluxing ethanol generated the keto ester **22**‡ in 79% yield. Hydrolysis of the ester moiety in **22** generated the acid **23**, which was transformed into the diazo ketone **24**. Rhodium trifluoroacetate catalysed intramolecular C–H insertion reaction of the diazo ketone **24** furnished

‡ All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the dione **14**: mp 89–90°C. $[\alpha]_D^{24}$ −63.5 (*c* 1.15, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1745, 1719, 1637, 908. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.75 (1H, s), 4.65 (1H, s), 2.67 (1H, d, J=11.0 Hz), 2.55–2.40 (1H, m), 2.44 (1H, d, J=19.2 Hz), 2.25–2.15 (2H, m), 2.10 (1H, d, J=19.2 Hz), 2.02 (1H, dd, J=14.7 and 11.0 Hz), 1.95–1.80 (1H, m), 1.58 (3H, s), 1.35–1.20 (1H, m), 1.34 (3H, s), 0.94 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, DEPT): δ 219.4 (C), 215.0 (C), 146.0 (C), 113.9 (CH_2), 53.3 (CH), 52.5 (C), 48.9 (CH_2), 47.9 (CH), 45.3 (C), 42.5 (CH), 35.9 (CH_2), 23.4 (CH_2), 20.3 (CH_3), 19.0 (CH_3), 18.2 (CH_3). For the diketoacetate **16**: mp 185–186°C. $[\alpha]_D^{25}$ −31.6 (*c* 0.95, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1745, 1726. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.92 (1H, d, J=9.3 Hz), 2.59 (1H, dd, J=10.5 and 5.1 Hz), 2.50–2.30 (2H, m), 2.38 (1H, d, J=18.7 Hz), 2.12 (1H, d, J=18.7 Hz), 2.10–1.95 (1H, m), 2.03 (3H, s), 1.87 (1H, d with fine splitting, J=15.9 Hz), 1.41 (1H, d, J=14.7 Hz), 1.32 (3H, s), 0.98 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 215.4 (C), 215.1 (C), 169.8 (C), 76.0 (CH), 52.4 (C), 49.3 (CH_2), 47.9 (CH), 46.5 (C), 42.6 (CH), 30.7 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 18.2 (CH_3), 16.8 (CH_3). For the diketoolefin **17**: $[\alpha]_D^{23}$ −147.1 (*c* 0.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1748, 1720. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.34 (1H, dd, J=8.1 and 6.6 Hz), 6.05 (1H, d, J=8.1 Hz), 3.05 (1H, t, J=4.8 Hz), 2.57 (1H, dd, J=11.1 and 4.8 Hz), 2.37 (1H, d, J=19.2 Hz), 2.09 (1H, d, J=19.2 Hz), 1.77 (1H, dd, J=12.6 and 10.8 Hz), 1.49 (1H, d, J=13.8 Hz), 1.24 (3H, s), 1.22 (3H, s). For the acetate **18**: mp 102–103°C. $[\alpha]_D^{24}$ −32.7 (*c* 3.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1731. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.89 (1H, dd, J=9.6 and 3.9 Hz), 3.68 (3H, s), 2.74 (1H, ddd, J=11.1, 6.0 and 2.1 Hz), 2.40–2.15 (2H, m), 2.13 (1H, dd, J=14.7 and 6.0 Hz), 1.98 (3H, s), 1.80 (1H, dd, J=14.7 and 11.1 Hz), 1.71 (1H, t of d, J=14.7 and 2.7 Hz), 1.12 (3H, d, J=7.5 Hz), 0.94 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.3 (C), 173.8 (C), 169.8 (C), 75.1 (CH), 52.1 (CH_3), 46.4 (C), 42.4 (CH), 41.6 (CH), 36.8 (CH), 31.1 (CH_2), 30.3 (CH_2), 20.8 (CH_3), 16.3 (CH_3), 13.1 (CH_3). For the ketoester **22**: $[\alpha]_D^{24}$ −48.2 (*c* 5.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1730, 1723. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.66 (3H, s), 2.78 (1H, ddd, J=11.0, 7.0 and 1.8 Hz), 2.32 (1H, q, J=7.3 Hz), 2.20 (1H, br s), 2.04 (1H, ddd, J=14.3, 7.3 and 2.9 Hz), 1.90–1.45 (5H, m), 1.07 (3H, d, J=7.5 Hz), 0.92 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 217.3 (C), 174.7 (C), 51.9 (CH_3), 42.6 (CH), 42.5 (C), 41.9 (CH), 37.5 (CH), 32.7 (CH_2), 31.5 (CH_2), 21.6 (CH_2), 20.1 (CH_3), 13.0 (CH_3).



Scheme 2. *Reagents, conditions and yields*: (a) i. O_3/O_2, CH_2Cl_2–MeOH (5:1), −78°C; ii. Ac_2O, Et_3N, DMAP, C_6H_6, reflux, 5 h, 55%; (b) K_2CO_3, MeOH, rt, 3 h, 88%; (c) PCC, silica gel, CH_2Cl_2, 3 h, 90%; (d) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$ (catalytic), C_6H_6, 0°C→rt, 4 h, 82%; (e) Raney Ni, EtOH, reflux, 5 h, 79%; (f) 5% NaOH in MeOH–H_2O (1:1), reflux, 8 h, 96%; (g) i. $(COCl)_2$, C_6H_6, rt, 2 h; ii. CH_2N_2, Et_2O, 0°C, 2 h; (h) $Rh_2(tfa)_4$, CH_2Cl_2, reflux, 4 h, 47% (from **23**); (i) CH_2=C(Me)MgBr, anhyd. $CeCl_3$, THF, 0°C→rt, 10 h; (j) i. PPTS, $(CH_2Cl)_2$, reflux, 6 h; ii. H_2, 1 atm, 10% Pd–C, EtOH, 8 h; (k) i. H_2, 1 atm 10% Pd–C, EtOH, 3 h, 90%; ii. *p*-TSA, C_6H_6, reflux, 5 h, 83%. (l) Reference 3.

the isotwistane dione **15** in 47% yield (from the acid **23**), $[\alpha]_D^{23}$ −28.1 (*c* 3.6, $CHCl_3$) {lit.[3] for (+)-**15** $[\alpha]_D^{25}$ +27 (*c* 2, $CHCl_3$)}, which exhibited spectral data (IR, ^1H and ^{13}C NMR) identical to its optical antipode reported earlier.[3] Chang et al. had already reported the conversion of the racemic dione **15** into (±)-2-pupukeanone.[8] Anhydrous cerium chloride catalysed addition of isopropenylmagnesium bromide to the dione **15** generated, regioselectively, the tertiary alcohol **25**. PPTS catalysed dehydration of the alcohol followed by hydrogenation of the resultant diene in ethanol with 10% Pd/C as the catalyst; or alternatively catalytic hydrogenation followed by *p*-TSA catalysed dehydration, transformed the tertiary alcohol **25** into the enone (−)-**26**, $[\alpha]_D^{24}$ −108.7 (*c* 1.5, $CHCl_3$) {lit.[3] for (+)-**26** $[\alpha]_D^{25}$ +102 (*c* 2.3, $CHCl_3$)}, which exhibited spectral data (IR, ^1H and ^{13}C NMR) identical to that of its optical antipode (+)-**26**.[3] Since the enone (+)-**26** has already been converted into (+)-2-pupukeanone **5**,[3] present synthesis of (−)-**26** constitutes a synthesis of (−)-2-pupukeanone **5**.

In conclusion, we have achieved an enantiospecific synthesis of (−)-2-pupukeanone **5** starting from the readily available monoterpene (*R*)-carvone, employing a Michael–Michael reaction and an intramolecular rhodium carbenoid C–H insertion reaction as the key steps for the construction of the isotwistane carbon framework. It is worth noting that the present methodology and the radical cyclisation based methodology reported earlier[3] are complementary to each other, as they generated optical antipodes of 2-pupukeanone starting from (*R*)-carvone. Currently, we are investigating the extension of this strategy for the enantiospecific synthesis of 9-pupukeanone.

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