Enantiospecific total synthesis of (+)-2-pupukeanone

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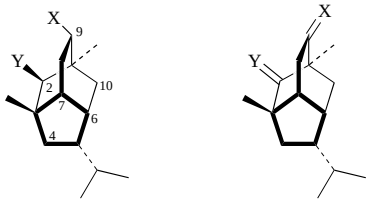
COMMUNICATION

The first total synthesis of chiral 2-pupukeanone (+)-4, starting from *R*-carvone (−)-7 employing a 5-*exo-trig* radical cyclisation as the key reaction for the construction of the tricyclic isotwistane carbon framework, is described.

The nudibranch *Phyllidia varicosa* Lamarck, 1801 secretes, as a part of its defense mechanism, two volatile substances with distinctive odours, which are lethal to fish and crustaceans. In 1975 and 1979, Scheuer and co-workers reported the isolation of these compounds, 9- and 2-isocyanopupukeananes (**1** and **2**) from this nudibranch, and also from its prey, a sponge, *Hymeniacidon* sp. The structures of these tricyclic marine sesquiterpenes **1** and **2**, containing a novel tricyclo[4.3.1.0^{3,7}]decane (isotwistane) framework and an isonitrile functionality, were elucidated based on degradative and single crystal X-ray diffraction studies.[1] The presence of an unusual carbon framework, with two quaternary carbon atoms and an isopropyl group in a thermodynamically unfavourable *endo* position made isocyanopupukeananes **1** and **2**, and the corresponding ketones 9- and 2-pupukeanones (**3** and **4**) interesting and chal-

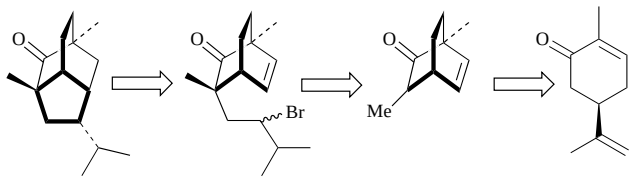


1 X = NC; Y = H
2 X = H; Y = NC

3 X = O; Y = H_2
4 X = H_2; Y = O

lenging synthetic targets, and several approaches have been reported for the synthesis of racemic pupukeananes.[2,3] Recently, we reported a short approach to (±)-2-pupukeanone employing a tandem intermolecular addition of tri-*n*-butyltin radical to a terminal acetylene followed by a 5-*exo-trig* vinyl radical cyclisation as the key strategy.[4] In continuation, herein we report the first enantiospecific total synthesis of chiral 2-pupukeanone [(+)-**4**] starting from the readily available monoterpene, *R*-carvone [(−)-**7**], employing a 5-*exo-trig* radical cyclisation as the key reaction.

As depicted in Scheme 1, it was anticipated that the radical



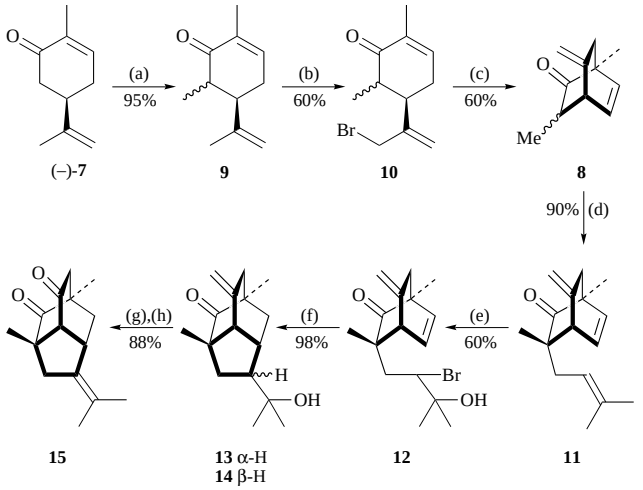
5 **6**

Scheme 1

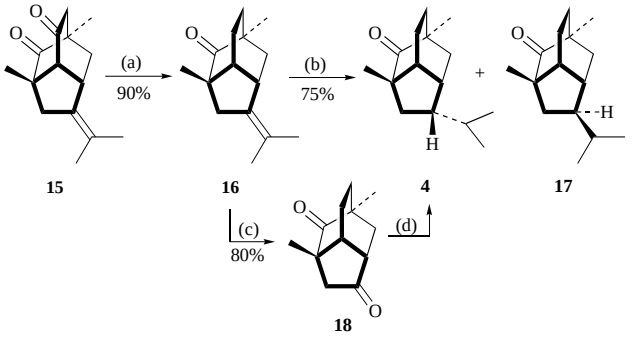
cyclisation of a bromide, *e.g.* **5**, would generate the pupukeanane framework, whereas kinetic alkylation of the bicyclic enone **6** would provide the requisite precursor for the bromide **5**. As 10-bromocarvone is known to produce 1-methylbicyclo[2.2.2]-oct-5-en-2-one derivatives *via* intramolecular alkylation,[5] *R*-carvone was chosen as the starting material for the preparation of the chiral analogue of **6**. The synthetic sequence starting from *R*-carvone is depicted in Schemes 2 and 3. To begin with, carvone **7** was converted into the bicyclo[2.2.2]octenone derivative **8**. Thus, alkylation of *R*-carvone **7** using LDA and methyl iodide[6] furnished a 3:2 (*trans*:*cis*) epimeric mixture of α′-methylcarvone **9**, which on treatment with *N*-bromosuccinimide in the presence of sodium acetate and acetic acid in methylene chloride generated the allyl bromide **10**, in 60% yield.[7,8] Intramolecular alkylation of the allyl bromide **10** using potassium *tert*-butoxide in *tert*-butyl alcohol and THF generated the bicyclo[2.2.2]octenone derivative **8**, in 60% yield. Generation of the enolate using LDA followed by alkylation with dimethylallyl bromide transformed the bicyclic enone **8** into the alkylated product **11**, $[\alpha]_D^{24}$ −304.1 (*c* 1.71, $CHCl_3$). Regioselective conversion of the trisubstituted olefin in **11** into the corresponding bromohydrin (NBS–H_2O–THF)[7] furnished the radical precursor **12**, $[\alpha]_D^{25}$ −254.9 (*c* 1.22, $CHCl_3$), which was found to contain predominantly one epimer. The key radical cyclisation was carried out by refluxing a 0.02 M benzene solution of the bromohydrin **12** and 1.1 equiv. tri-*n*-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) to furnish a 2.5:1 mixture of the isotwistanes **13** and **14**† in near quantitative yield, which were separated by silica gel column chromatography. After constructing the isotwistane framework, attention was turned to the degradation of the C-8 methylene group. Thus, ozonolysis of the *exo*-methylene moiety in **13** and **14** followed by dehydration of the tertiary alcohol furnished the enedione **15**.‡ In the final stage, the remaining two tasks, namely regioselective reductive deoxygenation of the C-8 ketone and hydrogenation of the olefin were addressed (Scheme 3). Thus, modified Wolff–Kishner reduction of the enedione **15**

† All the compounds exhibited spectral data including HRMS consistent with their structures. Selected spectral data (*J* values given in Hz) for the isotwistane **13** (contains a small amount of a rearranged product): mp 106–108 °C, $[\alpha]_D^{27}$ +49.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480, 3050, 1715, 1640, 1370, 1215, 1160, 885; δ_H(200 MHz, $CDCl_3$) 4.97 and 4.87 (each 1 H, br s; C=CH_2), 2.25–2.50 (2 H, m), 2.27 (2 H, br s, H-9), 1.85–2.05 (2 H, m), 1.26–1.56 (3 H, m), 1.203 and 1.16 [each 3 H, s; HO–C(CH_3)$_2$], 1.09 and 0.98 (each 3 H, s; 2 × tertiary-CH_3); δ_C(22.5 MHz, $CDCl_3$) 221.3 (s, C=O), 143.1 (s, *C*=CH_2), 110.6 (t, C=*C*H_2), 72.0 (s, C–OH), 57.9 (d), 55.2 (2 C, s and t), 43.6 (s), 42.2 (d), 40.3, 39.6, 39.1, 28.1 (q), 26.6 (q), 19.5 (q), 18.8 (q). For the isotwistane **14**: mp 80–82 °C; $[\alpha]_D^{25}$ +18.0 (*c* 1.67, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3500, 1710, 1650, 1360, 1130, 1020, 930, 885; δ_H(90 MHz, $CDCl_3$) 4.91 and 4.78 (each 1 H, q, *J* 2; C=CH_2), 1.35–2.65 (9 H, m), 1.25 and 1.12 [each 3 H, s; HO–C(CH_3)$_2$], 1.09 and 0.93 (each 3 H, s; 2 × tertiary CH_3); δ_C(22.5 MHz, $CDCl_3$) 221.9 (C=O), 143.8 (C-8), 110.1 (C=*C*H_2), 71.4 (*C*–OH), 57.6, 54.7, 50.6, 43.0, 41.0, 40.4, 36.2, 31.7, 30.4, 28.7, 23.3, 19.5.

‡ For the compound **15**: $[\alpha]_D^{26}$ +82.4 (*c* 3.12, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730, 1710, 1395, 1370, 1295, 1225, 1180, 1160, 1095, 1040, 1005, 980, 825; δ_H(200 MHz, $CDCl_3$) 3.26 (1 H, dd, *J* 9, 5.5, H-6), 2.56 (1 H, d, *J* 5.5, H-7), 2.51 (1 H, half AB q, *J* 16, H-4a), 2.26 (2 H, close AB, H-9), 2.12 (1 H, d with str., *J* 16.0, H-4b), 2.03 (1 H, dd, *J* 13.5, 9, H-10$_{exo}$), 1.63 and 1.57 (each 3 H, s; 2 × olefinic CH_3), 1.42 (1 H, d, *J* 13.5, H-10$_{endo}$), 1.19 and 1.071 (each 3 H, s; 2 × tertiary CH_3); δ_C(22.5 MHz, $CDCl_3$) 217.6 (s, C=O), 211.7 (s, C=O), 136.1 (s), 124.6 (s), 62.2 (d), 54.9 (s), 47.9 (t), 44.9 (s), 42.2 (t), 40.1 (d), 39.1 (t), 21.0 (q), 20.6 (q), 19.4 (q), 19.2 (q).



Scheme 2 *Reagents and conditions*: (a) LDA, THF, −10 °C ⟶ rt, MeI, 9 h; (b) NaOAc, AcOH, NBS, CH_2Cl_2, 0 °C ⟶ rt, 6 h; (c) $K^{+-}OBu^t$, THF, 0 °C ⟶ rt, 3 h; (d) LDA, THF, HMPA, $(CH_3)_2C{=}CH{-}CH_2Br$, −90 °C ⟶ rt, 8 h; (e) NBS (1.1 equiv.), H_2O, THF, −10 °C ⟶ rt, 24 h; (f) AIBN, $Bu^n{}_3SnH$, C_6H_6, reflux, 5 h; (g) (i) O_3–O_2, MeOH, CH_2Cl_2, −90 °C; (ii) Me_2S, −90 °C ⟶ rt, 8 h; (h) TsOH, C_6H_6, reflux, 8 h (rt = room temp.)



Scheme 3 *Reagents and conditions*: (a) (i) $NH_2NH_2{\cdot}H_2O$, $HOCH_2CH_2OH$, diethylene glycol, 180 °C, 2 h; (ii) Na, diethylene glycol, 180 °C, 4 h; (b) PtO_2, H_2, EtOH, 2 d; (c) (i) O_3–O_2, MeOH, CH_2Cl_2, −90 °C; (ii) Me_2S, −90 °C ⟶ rt, 8 h; (d) reference 3*c*

furnished the enone **16** in 90% yield,§ *via* regioselective reduction of the C-8 ketone, leaving the sterically more crowded C-2 ketone intact. Catalytic hydrogenation[3b–d] of the enone **16** furnished a 1.3 : 1 mixture of 2-pupukeanone **4** and its C-5 *exo* epimer **17**, which exhibited a 400 MHz NMR spectrum identical to that reported.[3b] In contrast, ozonolytic cleavage of the enone **16** furnished the dione **18**, $[\alpha]_D^{25}$ 27.0 (*c* 2.0, $CHCl_3$), which exhibited spectral data identical to that of an authentic[3c,4] racemic sample. The racemic dione **18** has been converted into 2-pupukeanone stereoselectively by Chang and co-workers.[3c] Even though the present sequence generates the enantiomer of the natural series, the ready availability of *S*-carvone makes the present strategy applicable for the synthesis of the natural enantiomer also.

§ For the compound **16**: $[\alpha]_D^{26}$ +101.8 (*c* 2.26, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1725, 1710, 1450, 1370, 1100, 1015, 995; δ_H(200 MHz, $CDCl_3$) 2.92 (1 H, dd, *J* 8.5, 3.4, H-6), 2.34 (1 H, d, *J* 16.5), 1.5–2.1 (8 H, m), 1.63 and 1.53 [each 3 H, s; $C{=}C(CH_3)_2$], 1.19 and 0.90 (each 3 H, s; 2 × tertiary CH_3); δ_C(22.5 MHz, $CDCl_3$) 222.5 (s, C=O), 137.5 (s), 122.7 (s), 53.8 (s), 45.5 (d, C-6), 42.6 (t, C-4), 42.3 (s), 40.7 (d), 38.4 (t), 32.8 (t), 20.8 (2 C, t and q), 20.5 (q), 18.7 (q), 17.1 (q).

Acknowledgements

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8 In addition, varying amounts (15–20%) of easily separable 2,6-dimethyl-5-(2-acetoxy-1-bromoisopropyl)cyclohexenone, resulting from the trapping of the intermediate carbonium ion, was also obtained.

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