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A Short, Vinyl Radical Cyclisation Approach to (±)-2-Pupukeanone

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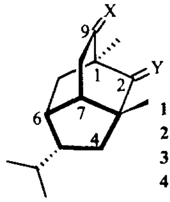
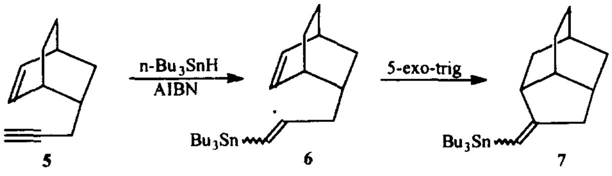
Abstract: Addition of tri-n-butyltin radical to a 5-(prop-2-ynyl)bicyclo[2.2.2]oct-2-ene followed by 5-*exo*-trig cyclisation of the resulting vinyl radical furnishes an isotwistane, providing a short route to the sesquiterpenes, pupukeananes **4** and **2**.

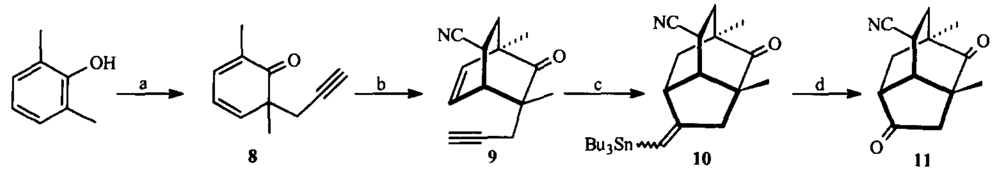
The tricyclic marine sesquiterpenes, 9- and 2-isocyanopupukeananes (**1** and **2**) containing a unique tricyclo[4.3.1.0^{3,7}]decane (isotwistane) framework, were isolated from the nudibranch *Phyllidia varicosa* Lamarck, 1801 and from its prey, a sponge, *Hymeniacidon sp.* by Scheuer and coworkers.[1] The presence of an unusual carbon framework, with two quaternary carbon atoms and an isopropyl group in a thermodynamically unfavoured *endo* position made isocyanopupukeananes **1** and **2**, and the corresponding ketones 9- and 2-pupukeanones (**3** and **4**) interesting and challenging synthetic targets. In addition to the two earlier syntheses,[2] recently, Chang and Chang[3] reported the synthesis of 2-pupukeanone (**4**), a precursor in Corey's[2a] synthesis of **2**. We envisaged that the intermolecular addition of tri-n-butyltin radical to the terminal acetylene of enyne **5** generates a vinyl radical **6** which can undergo a facile 5-*exo*-trig cyclisation to furnish the isotwistane **7**. Based on this concept, herein, we report a short, formal total synthesis of 2-pupukeanone (**4**).[4]



1. $X=NC,H; Y=H_2$
2. $X=H_2; Y=NC,H$
3. $X=O; Y=H_2$
4. $X=H_2; Y=O$

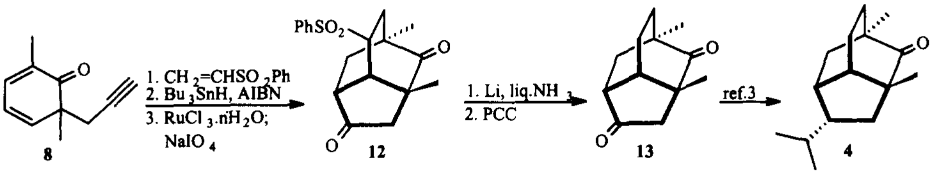


The requisite enyne was assembled employing a Diels-Alder reaction of the dienone **8**. Thus, reaction of sodium 2,6-dimethylphenoxide with propargyl bromide furnished an ≈1:1 mixture of the C-alkylated product, dienone **8** and the O-alkylated product in 90% yield, which on thermal activation with acrylonitrile and purification on a silica gel column furnished the adduct **9**, in 56% yield, creating both the ketone moiety and the two quaternary carbon atoms as present in 2-pupukeanone. The key radical reaction was carried out by refluxing a 0.04 M benzene solution of the enynone **9** with 1.5 equivalents of tri-n-butyltin hydride in the presence of a catalytic amount of AIBN to furnish the isotwistane derivative **10**, which on oxidative cleavage with ruthenium chloride hydrate and sodium periodate[5] in acetonitrile, water and carbon tetrachloride (1:1:1)



Reagents and Conditions: *(a) NaH, C_6H_6, $HC\equiv CCH_2Br$, 50°C, 12 h; (b) $CH_2=CHCN$, C_6H_6, 80°C, 14 h, 56% (based on* ***8****); (c) $^nBu_3SnH$, AIBN, C_6H_6, reflux, 18 h; (d) $RuCl_3.nH_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt, 3 h; 31% from* ***9****.*

furnished the cyanodione **11**, in 31% overall yield. In an analogous manner, Diels-Alder reaction of the dienone **8** with phenyl vinyl sulfone followed by tandem inter- and intramolcular radical addition reaction, and oxidative cleavage furnished the diketosulfone **12**[6] in almost similar yield.[7] Finally, treatment of the diketosulfone **12** with lithium in liquid ammonia and subsequent oxidation with PCC furnished the diketone **13**, in 80% yield, which exhibited ^1H and ^{13}C NMR spectral data[6] identical to that of the authentic sample.[3] Since the diketone **13** has already been converted by Chang and Chang[3] into **4** *via* regiospecific isopropenyl Grignard addition-dehydration-hydrogenation sequence, the present synthesis of the diketone **13** constitutes a formal synthesis of 2-pupukeanone (**4**) and 2-isocyanopupukenane (**2**).



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References and Notes

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2. (a) Corey, E.J.; Ishiguro, M. *Tetrahedron Lett.*, **1979**, 2745. (b) Frater, G.; Wenger, J. *Helv. Chim. Acta*, **1984**, *67*, 1702. (c) Subba Rao, G.S.R.; Kaliappan, K. *Tetrahedron Lett.*, **1997**, *38*, 0000.
3. Chang, N.-C.; Chang, C.-K. *J. Org. Chem.*, **1996**, *61*, 4967.
4. Just before the completion of our synthesis, our colleagues Subba Rao and Kaliappan[2c] have achieved the total synthesis of 2-pupukeanone starting from dihydroanisole-ketene Diels-Alder adduct, using two acid mediated rearrangements and an allyl radical cyclisation reaction as key steps.
5. Nunez, M.T.; Martin, V.S. *J. Org. Chem.*, **1990**, *55*, 1928.
6. Selected spectral data: For the diketosulfone **12**: IR (neat): ν_{max} 1745, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (2 H, d, *J* 7.6 Hz), 7.72 (1 H, t, *J* 7.5 Hz), 7.63 (2 H, t, *J* 7.8 Hz), 3.64 (1 H, ddd, *J* 11.6, 5.2, 2.7 Hz, H-8), 3.23 (1 H, dd, *J* 10.9, 4.3, H-6), 2.59 (1 H, dd, *J* 4.7, 2.7 Hz, H-7), 2.43 (1 H, dd, *J* 14.4, 10.9 Hz, $H\text{-}10_{exo}$), 2.38 (1 H, d, *J* 18.8 Hz, $H\text{-}4_{endo}$), 2.23 (1 H, dd, *J* 14.8, 5.2 Hz, $H\text{-}9_{syn}$), 2.1 (1 H, dd, *J* 18.8, 1.4 Hz, $H\text{-}4_{exo}$), 1.81 (1 H, ddd, *J* 14.8, 11.6, 3.1 Hz, $H\text{-}9_{anti}$), 1.41 (1 H, dd, *J* 14.4, 3.2 Hz, $H\text{-}10_{endo}$), 1.25 (3 H, s) and 1.03 (3 H, s) [2 x CH_3]. Mass: m/z 332 (M^+, 10%), 207 (30), 191 (65), 163 (85), 162 (45), 119 (100). HRMS: Calcd. for $C_{18}H_{20}O_4S$, *M* 332.1082; Found, m/z 332.1096. For the dione **13**: IR (neat): ν_{max} 1750, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.68 (1 H, dd, *J* 10.8, 5.1 Hz), 2.35 (1 H, d, *J* 18.3 Hz), 2.25 (1 H, m), 2.11 (1 H, d, *J* 18.3 Hz), 2.02 (1 H, dd, *J* 14.8, 10.8 Hz), 1.85-2.1 (2 H, m), 1.6-1.75 (2 H, m), 1.4 (1 H, d, *J* 14.8 Hz), 1.31 (3 H, s), 0.96 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.5, 217.5, 52.5, 48.9, 48.75, 43.3, 42.4, 32.6 (2 C), 20.2, 18.7, 16.2. Mass: m/z 192 (M^+).
7. To establish the generality, the sequence was also carried out successfully using methyl acrylate and methyl vinyl ketones as dienophiles.

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