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A New Total Synthesis of 2-Pupukeanone[1]

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Abstract: *An efficient total synthesis of 2-pupukeanone is reported which involves a 5-exo-trig allyl radical cyclization as the key step to construct the isotwistane skeleton.*
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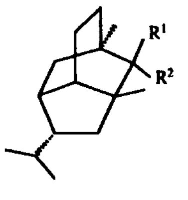
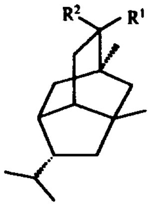
Scheuer et.al.,[2,3] reported the isolation of 2-isocyanopupukeanane 1 and 9-isocyanopupukeanane 2, the two defense allomones, from the nudibranch *Phyllidia varicosa* and also from its prey, a sponge, *Hymeniacidon sp.* Owing to their unique molecular structure, these two tricyclic sesquiterpenes with a new rearranged isoprenoid skeleton offer an interesting challenge to synthetic chemists, as they possess (i) a novel tricyclo$[4.3.1.0^{3,7}]$decane skeleton (ii) four contiguous asymmetric carbons and (iii) an isopropyl group in a thermodynamically unfavourable position. Total synthesis of 2-isocyanopupukeanane 1, 9-isocyanopupukeanane 2 and of their degradation products 2-pupukeananone 3[4] and 9-pupukeanone 4[5] have been reported. Herein, we describe a new total synthesis of 2-pupukeanone 3 by a novel strategy which involves a 5-*exo-trig* allyl radical cyclization[6] as the key step to construct the five membered ring of the desired isotwistane.



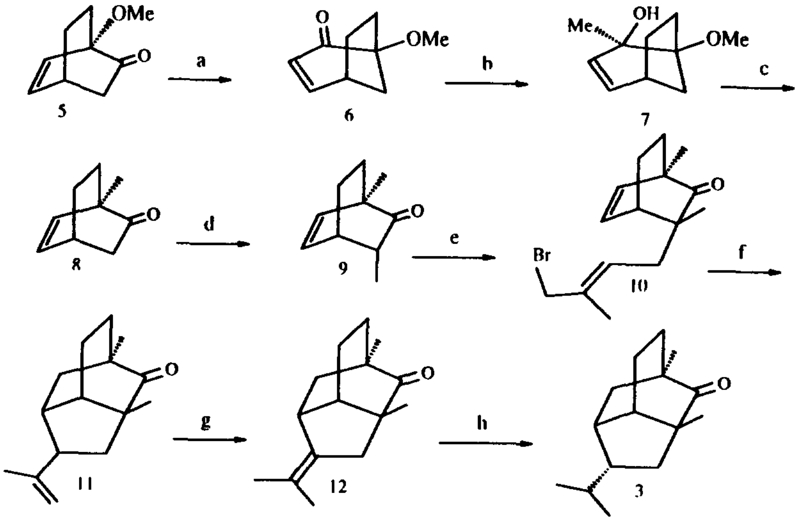
1: R^1 = NC, R^2 = H
3: R^1 & R^2 = O



2: R^1 = NC, R^2 = H
4: R^1 & R^2 = O

Thus, the ketone 5, obtained from anisole by the known method[7], upon treatment with PTS[8] in refluxing benzene, underwent a smooth rearrangement to give the enone 6 which was converted into the tertiary alcohol 7 on treatment with MeLi. The tertiary alcohol 7 was rearranged to the ketone 8[9] under acidic condition. Monoalkylation of 8 was accomplished with LDA/MeI to afford the ketone 9 which was further alkylated with 1,4-dibromo-2-methylbut-2-ene[10] to yield a bromide 10[9] with high degree of stereo- and regioselectivity. The bromide 10 smoothly underwent a 5-*exo-trig* allyl radical cyclization[11] to give predominantly the isotwistane derivative 11. Treatment of 11 with PTS/benzene afforded the olefin 12[9] which was hydrogenated[4] to give 2-pupukeanone 3. The spectral data of 3 was found to be identical with that reported.[4]

In conclusion, we report an efficient synthesis of 2-pupukeanone 3 by involving an intramolecular 5-*exo-trig* allyl radical cyclization as the key step to construct the highly strained isotwistane skeleton.



Reagents & Conditions: (a) PTS, benzene, reflux, 2h, 60%; (b) MeLi, Ether, 0°C, 85%; (c) $HClO_4$, CH_2Cl_2, 30min., 80%; (d) LDA, MeI, THF, -78°C, 90%; (e) LDA, THF, 1,4-dibromo-2-methylbut-2-ene, HMPA, -78°C, 70%; (f) AIBN, TBTH, benzene, reflux, 2h, 60%; (g) PTS, benzene, reflux, 30min, 90%; (h) H_2/Pt-C, MeOH, 90%.

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9. All the new compounds exhibited satisfactory spectral and analytical data. Selected spectral data
   For **8**: IR (neat): ν_{max} 3005, 2930, 1720 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$): δ 6.47 (1H, dd, J 8 & 6.6 Hz), 5.67 (1H, dd, J 6.9 & 1.8 Hz), 2.95 (1H, m), 2.05 (2H, d J 2Hz) 1.2-2.2 (4H, m), 1.22 (3H, s): ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 212.6 (s), 136.3 (d), 133.3 (d), 48.5 (s), 40.0 (t), 31.8 (d), 29.9 (t), 25.7 (t), 17.3 (q). For **10**: IR (neat): ν_{max} 3010, 2930, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.46 (1H, dd, J 8 & 6.5 Hz), 5.79 (1H, dd, J 6.9 & 1.8 Hz), 5.62 (1H, t, J 7.1 Hz), 3.98 (2H, s), 2.6 (1H, m), 1.73 (3H, s), 1.4-2.2 (6H, m), 1.20 (3H, s), 1.05 (3H, s). For **12**: IR (neat): ν_{max} 3010, 2930, 1720 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$): δ 2.91 (1H, dd J 8.7 & 5.3 Hz), 1.61 (3H, s), 1.52 (3H, s), 1.17 (3H, s), 0.9-2.5 (9H, m)
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