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A Highly Flexible Route to Tricyclo[4.3.1.$0^{3,7}$]-, and Tricyclo[4.3.0.$0^{4,10}$]decanes A Short Synthesis of Pupukean-2-one

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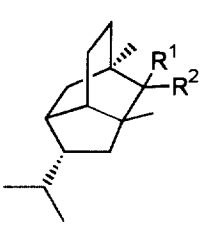
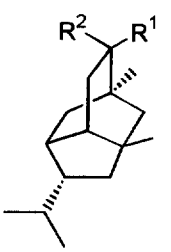
Abstract: *An efficient strategy for the construction of tricyclo[4.3.1.$0^{3,7}$]-, and tricyclo[4.3.0.$0^{4,10}$]decanes is described which involves a novel one-pot tandem acid-catalyzed rearrangement followed by an ene cyclization as key step and is exemplified by the total synthesis of pupukean-2-one* **3**.

A large number of sesquiterpenes possess the tricyclo[4.3.1.$0^{3,7}$]decane (isotwistane) and the tricyclo-[4.3.0.$0^{4,10}$]decane carbon frameworks. The isotwistanes are exemplified by the natural marine defense allomones, 2-isocyanopupukeanane **1** and 9-isocyanopupukeanane **2**, isolated[1,2] from the nudibranch, *Phyllidia varicosa L 1801*. In view of their structural complexity, having the isotwistane moiety with two quaternary carbons, 6-chiral centres and the unfavourable endo orientation of the isopropyl group, the pupukeananes 1 & 2 and their degradation products **3** and **4**, have been attractive synthetic targets.[3,4,5] Recently we reported[6] a short and facile approach to (±) pupukean-2-one **3** by employing a novel 5-*exo-trig*-allyl radical cyclization for constructing the tricyclo[4.3.1.$0^{3,7}$]decane moiety. During the preparation of an intermediate for the synthesis of **3**, we observed a novel rearrangement[7] involving tandem 5-*exo-trig* allyl & 3-*exo-trig* radical cyclizations leading to **5**, having the tricyclo[4.3.0.$0^{4,10}$]decane ring system. We now report a highly flexible approach towards tricyclo[4.3.1.$0^{3,7}$]-, and tricyclo[4.3.0.$0^{4,10}$]decanes involving a one pot-tandem acid-catalyzed rearrangement and an ene cyclization which is exemplified by a formal total synthesis of (±) pupukean-2-one **3**.



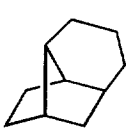
1: R^1 = NC, R^2 = H

3: R^1 & R^2 = O



2: R^1 = NC, R^2 = H

4: R^1 & R^2 = O



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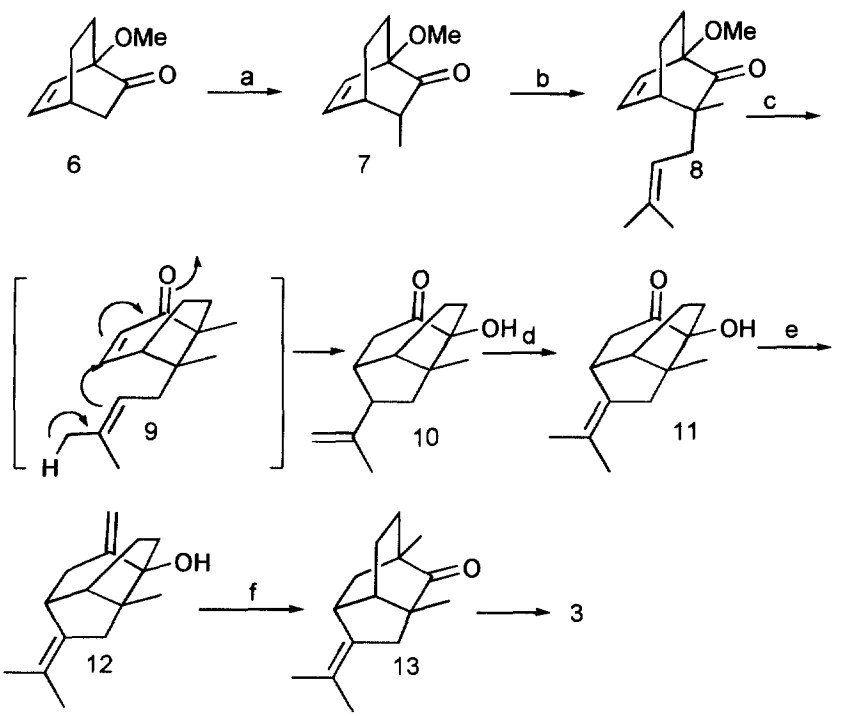
Alkylation of the ketone[8] **6**, readily obtained from 1-methoxycyclohexa-1,4-diene, with LDA/MeI afforded[9] exclusively the *endo* ketone **7** which on treatment with LDA and 1-bromo-3-methylbut-2-ene afforded the product[9] **8** in good yield. Treatment of **8** with perchloric acid (70%) in methylene chloride furnished the tricyclic ketone **10** which was isomerized to the hydroxy ketone **11** with *para* toluenesulphonic acid in refluxing benzene. The structures of the hydroxy-ketones **10** and **11** were deduced from their spectral data[10] and finally their conversion into the known ketone **13**. Thus the Wittig reaction of **11** with methyltriphenylphosphonium iodide & KO^{t}Bu afforded the alkene[10] **12** which smoothly rearranged with on treatment with $BF_3.Et_2O$ in dichloromethane to the known ketone[10] **13**.

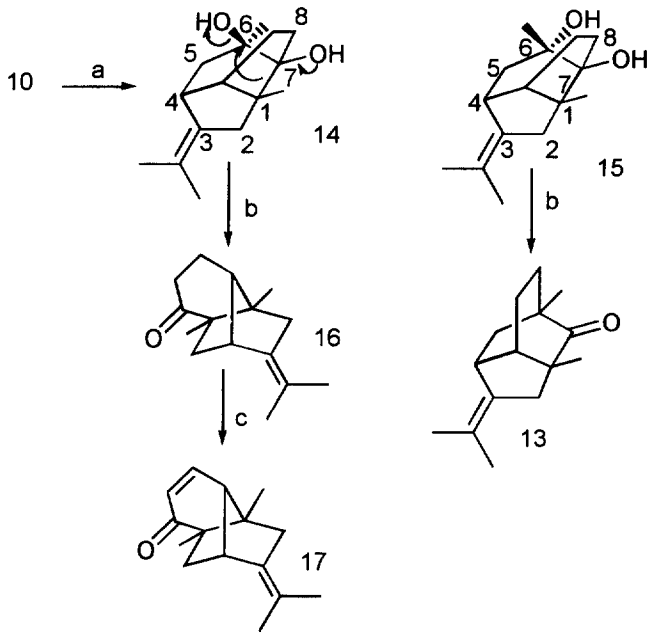


Reagents & Conditions: a) LDA, MeI, THF, -78^{0}C, 92%; b) LDA, THF, 1-bromo-3-methyl-2-butene, HMPA, -78°C, 80%. c) $HClO_4$, CH_2Cl_2, 0.5hr, 60%;d) pTsOH, benzene, reflux, 45mts 90%. e) Ph_3PCH_3I, KO^{t}Bu, benzene, reflux, 84%. f) $BF_3.OEt_2$, CH_2Cl_2, 78%.

The formation of **10** from **8** presumably involves (i) acid catalyzed rearrangement of **8**, having a bicyclo[2.2.2]octene system to the hydroxy-enone **9**, possessing the [3.2.1]octene framework and (ii) an intra-molecular *ene* reaction of **9** to afford the hydroxy-ketone **10.** Since the compound **13** has been converted[9] into (±)-pupukean-2-one, this method constituted a formal total synthesis of **3**.

Reaction of the hydroxy ketone **10** with methyl lithium afforded a (4:1) mixture of the *exo*- & *endo*-diols **14** and **15** respectively which were separated by chromatography. Treatment of the *exo*-diol **14** with

perchloric acid (70%) in dichloromethane afforded the ketone[10] **16** having the tricyclo[4.3.0.$0^{4,10}$]decane frame work while the *endo*-diol **15** rearranged to the known ketone **13** in good yield. Treatment of the ketone **16** with LDA and phenylselenyl bromide followed by oxidative elimination afforded the unsaturated ketone[10] **17** which clearly established the presence of the methylene groups at the α-and β-positions to the keto group in the compound **16.** The formation of **16** from **14** clearly indicates the migration of the C_1-C_7 bond while the C_7-C_8 bond migrated from **15** to **13** during the acid catalysed rearrangement



Reagents & Conditions: a) MeLi. ether, 0^0C, 89%; b) $HClO_4$, CH_2Cl_2, 30 mts, 80%; c) LDA, PhSeBr, THF, -78^0C, H_2O_2, R.T, 1h, 74%.

In conclusion we report an efficient strategy for the construction of tricyclo[4.3.1.$0^{3,7}$]-,and tricyclo-[4.3.0.$0^{4,10}$]decanes using a novel one-pot acid-catalyzed rearrangement followed by an ene cyclization of a bicyclo[2.2.2]octene derivative as exemplified by a formal synthesis of pupukean-2-one. This methodology is being pursued for the synthesis of some naturally occurring tricyclic sesquiterpenes.

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10. All the new compounds exhibited satisfactory spectral and analytical data. Selected spectral data for:

8: IR (neat): γ_{max} 3020, 2940, 1720 and 1640 cm^{-1}: ^1H NMR (90MHz, $CDCl_3$) δ 0.85-2.18 (6H, m), 1.08 (3H, s, Me), 1.59 (3H, s, Me), 1.73 (3H, s, Me), 2.61 (1H, m, bridgehead proton), 3.52(3H, s, OMe), 5.12(1H, t, J 7.1Hz, olefinic H), 6.17(1H, dd, J 6.7 and 1.7 Hz, olefinic H) and 6.45 (1H, dd, J 8.2 and 6.7 Hz, olefinic H)., ^{13}C NMR(22.5 MHz, $CDCl_3$): δ 17.6(q), 21.0 (q), 21.1(q), 25.7 (t), 26.2 (t),36.5(t), 39.5 (d), 47.0 (s), 52.8 (q), 84.2 (s), 118.7 (d), 127.4 (d), 134.6 (s), 136.5 (d) and 213.1 (s); M^+, 234.

(HRMS Calc. for $C_{15}H_{22}O_2$, 234.1620; Found 234.1616)

11: IR ($CHCl_3$): γ_{max} 3460, 2910 and 1700 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): 1.24(3H, s, Me), 1.53(3H, s, Me), 1.63(3H, s, Me), 1.7-2.5(9H, m), 3.03(1H m, bridgehead H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7, 18.1, 20.6, 20.7, 32.3, 38.1, 41.1, 42.3, 44.9, 53.7, 74.4, 123.6, 136.1, 221.0; M^+, 220.

(HRMS, Calc. for $C_{14}H_{20}O_2$, 220.1453; Found 220.1452)

12: IR (neat): γ_{max} 3350 and 1420 cm^{-1}: ^1H NMR (90MHz,$CDCl_3$): δ 1.10(3H, s, Me), 1.58(3H, s, Me), 1.64(3H, s , Me), 1.7- 2.8(10H, m), 4.54 (1H, t, J 2.5Hz, olefinic H), 4.80(1H, t, J 2.5Hz, olefinic H): ^{13}C NMR(22.5 MHz, $CDCl_3$): δ 19.7, 20.2, 20.5, 21.1, 35.1, 37.2, 37.9, 45.5, 52.6, 52.8, 84.5, 103.4, 120.2, 138.3, 152.4; M^+, 218. (HRMS, Calc. for $C_{15}H_{22}O$, 218.1672; Found 218.1673)

13: IR (neat):γ_{max} 2920 and 1712 cm^{-1}: ^1H NMR (400MHz, $CDCl_3$): δ 0.89(3H, s, Me), 1.17(3H, s, Me), 0.9-2.4(9H, m), 1.52(3H, s, Me), 1.62(3H, s, Me), 2.9(1H, m, bridgehead H): ^{13}C NMR(75 MHz, $CDCl_3$): δ 17.0, 18.7, 20.4, 20.6, 20.7, 32.7, 38.4, 40.6, 42.2, 42.6, 45.4, 53.7, 122.7, 137.4, 222.5; M^+, 218.

(HRMS, Calc. for $C_{15}H_{22}O$, 218. 1672; Found 218.1670)

16: IR ($CHCl_3$): γ_{max} 2900 and 1700 cm^{-1}: ^1H NMR (300MHz, $CDCl_3$) : δ 0.95(3H, s, Me), 1.01(3H, s, Me), 1.51(3H, s, Me), 1.58(3H, s, Me), 2.61(1H, dd, J 3.6 &4.5 Hz, C_{10} H), 2.93(1H, m, C_4 H), 1.6-2.4(8H, m): ^{13}C NMR(75 MHz $CDCl_3$): δ 13.7, 20.1, 20.4, 21.0, 23.0, 36.1, 37.3, 42.1, 44.9, 53.1, 54.4,59.8, 122.2, 136.6, 213.9; M^+, 218. (HRMS, Calc. for $C_{15}H_{22}O$, 218.1673; Found 218.1675)

17: IR (neat): γ_{max} 2920 and 1660 cm^{-1}: ^1H NMR (90MHz, $CDCl_3$) : δ 0.9 (3H, s, Me), 1.07 (3H, s, Me), 1.56 (3H, s, Me), 1.61 (3H, s, Me), 1.65–2.7 (5H, m), 2.98(1H,m), 6.3(1H, d, J 11.5Hz, olefinic H),7.3(1H, dd, J 11.5 & 10.2 Hz, olefinic H); M^+, 216.