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Enantiospecific synthesis of tricyclo[5.2.1.0^{4,8}]decanes via acid catalysed rearrangement of isotwistanes

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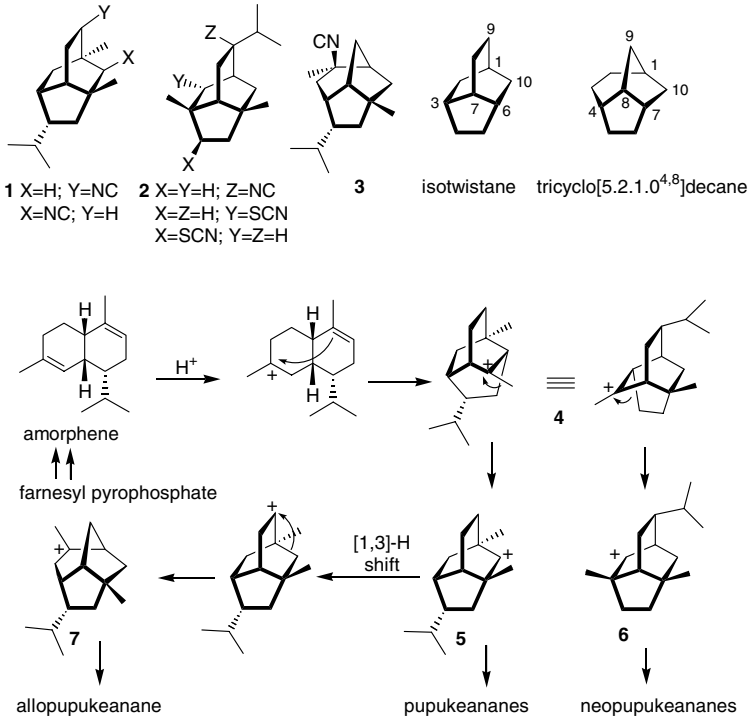
Abstract—An acid catalysed rearrangement was employed for the enantiospecific conversion of isotwistanol to tricyclo[5.2.1.0^{4,8}]-decanes, which provided support for the proposed biosynthesis of allopupukeananes from pupukeananes. The strategy has been further extended to the enantiospecific synthesis of a homobrexane.

The pupukeananes constitute a novel family of marine sesquiterpenes. These are subdivided into three classes according to their carbon skeletons as represented by pupukeananes[1] **1**, neopupukeananes[2] **2** and allopupuk-



Scheme 1.

Keywords: Molecular rearrangement; Isotwistanes; Pupukeananes; Allopupukeanane.
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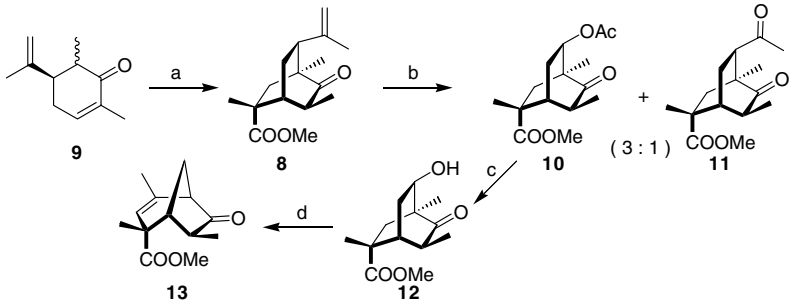


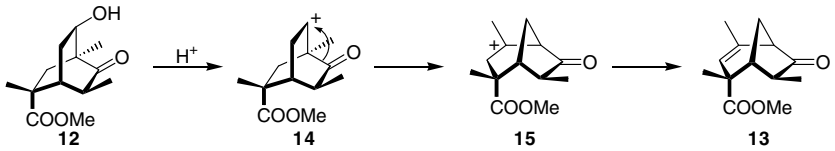
Scheme 2. Reagents, conditions and yields: (a) LiHMDS, hexane, CH_2=C(Me)COOMe, −10 °C→rt, 4 h, 70%; (b) O_3/O_2, CH_2Cl_2–MeOH (9:1), −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 5 h, 81%; (c) K_2CO_3, MeOH, rt, 10 h, 90%; (d) PTSA, C_6H_6, reflux, 3 h, 65%.

eananes[3] **3**. Pupukeananes and neopupukeananes contain an isotwistane carbon framework, whereas allopupukeanane contains a tricyclo[5.2.1.$0^{4,8}$]decane framework. The pupukeananes probably share a common biogenesis (Scheme 1).[2,3] It was postulated that a twistane carbonium ion **4**, formed by the cyclisation of amorphene, rearranges to the allopupukeanane and neopupukeanane carbonium ions **5** and **6**, and the pupukeanane cation **5** further rearranges to allopupukeanane cation **7**. Herein, we describe rearrangement of isotwistanes to tricyclo[5.2.1.$0^{4,8}$]decanes thus providing partial support for the biogenetic conversion of pupukeananes to allopupukeananes.

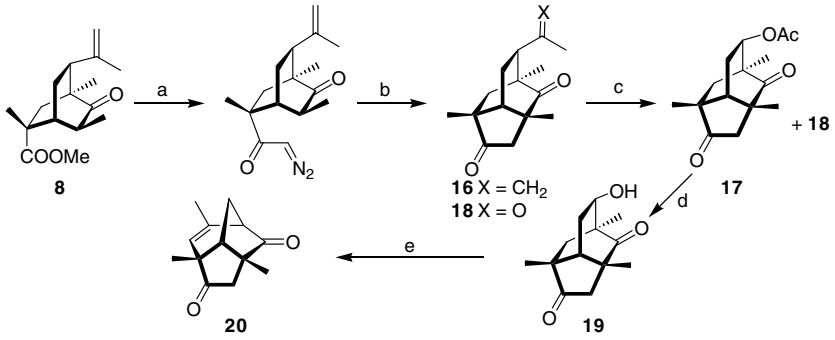
(1)

It seemed obvious that the transformation of pupukeananes to allopupukeananes could involve the rearrangement of the bicyclo[2.2.2]octane moiety present in the isotwistane to a bicyclo[3.2.1]octane (Eq. 1). Hence to begin with, as a model study, the rearrangement of a bicyclo[2.2.2]octane to a bicyclo[3.2.1]octane was investigated (Scheme 2).[4] By choosing an isopropenyl group as a masked hydroxy group, the bicyclic keto-ester **8** was chosen as the starting material, which was readily obtained in 70% yield, by double Michael reaction of 6-methylcarvone **9** with methyl methacrylate.[5] For the degradation of the isopropenyl group, a Criegee rearrangement[6] was employed. Thus, ozonolysis of the isopropenyl group in the bicyclic keto ester **8** in methanol-methylene chloride at −70 °C followed by treatment of the intermediate methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in refluxing benzene furnished a 3:1 mixture of the acetate **10** and diketo ester **11**, in 81% yield, which were separated by column chromatography on silica gel. Hydrolysis of acetate **10** followed by reaction of the resultant hydroxy ester **12** with *p*-toluenesulfonic acid (PTSA) in refluxing benzene furnished the bicyclo[3.2.1]octene-carboxylate **13** in 65% yield in a highly regioselective manner, the structure being established using spectral data.[†]

[†] Yields refer to isolated and chromatographically pure compounds. All compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for methyl (1*R*,2*S*,5*R*,7*S*)-2,4,7-trimethyl-6-oxobicyclo[3.2.1]oct-3-ene-2-carboxylate **13**: $[\alpha]_D^{26}$ +441.3 (*c* 3.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1736; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.55 (1H, t, *J* 1.5 Hz, H-3), 3.70 (3H, s, OCH_3), 2.52 (1H, d, *J* 3.0 Hz, H-5), 2.30 (1H, d, *J* 3.9 Hz, H-1), 2.10–1.85 (3H, m), 1.75 (3H, s, olefinic CH_3), 1.38 (3H, s, *tert*-CH_3), 1.15 (3H, d, *J* 7.5 Hz, *sec*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 212.6 (C, C-6), 175.7 (C, OC=O), 133.8 (C, C-4), 125.6 (CH, C-3), 52.6 (CH_3, OCH_3), 51.9 (CH, C-5), 50.3 (C, C-2), 46.2 (CH), 44.8 (CH), 27.2 (CH_2, C-8), 26.7 (CH_3), 22.7 (CH_3), 16.7 (CH_3). HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154; found: 245.1156. For (1*R*,4*R*,7*R*,8*S*)-2,4,7-trimethyltricyclo[5.2.1.$0^{4,8}$]dec-2-ene-5,10-dione **20**: Mp: 125–127 °C; $[\alpha]_D^{27}$ −109.4 (*c* 9.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1731; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.88 (1H, s, H-3), 2.79 (1H, dd, *J* 4.2 and 1.5 Hz, H-1), 2.59 (1H, d, *J* 19.8 Hz, H-6A), 2.26 (1H, d, *J* 3.9 Hz), 2.16 (1H, dt, *J* 12.0 and 4.5 Hz), 2.01 (1H, d, *J* 19.8 Hz, H-6B), 1.70 (3H, s, olefinic CH_3), 1.66 (1H, d, *J* 12.0 Hz), 1.25 (3H, s), 1.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.6 (C, C-5), 211.4 (C, C-10), 138.4 (C, C-2), 123.3 (CH, C-3), 55.6 (C), 51.5 (CH), 50.8 (CH), 49.0 (C), 44.4 (CH_2), 24.9 (CH_2), 23.0 (CH_3), 22.4 (CH_3), 19.7 (CH_3); Mass: *m*/*z* 204 (M^+, 75%), 161 (40), 148 (18), 133 (80), 119 (32), 107 (100), 106 (57), 105 (50), 91 (90); HRMS: *m*/*z* calcd for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048; found: 227.1058. For (1*R*,4*R*,7*R*,8*S*)-2,4,7-trimethyltricyclo[5.2.1.$0^{4,8}$]dec-2-en-10-one **22**: $[\alpha]_D^{25}$ +585.4 (*c* 3.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1736; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.00 (1H, s, H-3), 2.52 (1H, dd, *J* 3.9 and 1.8 Hz, H-1), 1.90–1.75 (2H, m), 1.69 (3H, d, *J* 1.5 Hz, olefinic CH_3), 1.70–1.50 (5H, m), 1.16 (3H, s), 1.13 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 216.3 (C, C-10), 133.3 (C, C-2), 131.2 (CH, C-3), 54.9 (CH), 54.4 (C), 51.5 (CH), 47.6 (C), 38.2 (CH_2), 36.1 (CH_2), 25.7 (CH_2), 25.5 (CH_3), 22.9 (CH_3), 22.6 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}ONa$ (M+Na): 213.1255; found: 213.1263. For (1*R*,4*R*,7*S*,8*S*)-2,9,9-trimethyltricyclo[5.3.0.$0^{4,8}$]dec-2-ene-5,10-dione **27**: Mp: 106–108 °C. $[\alpha]_D^{24}$ +2147 (*c* 2.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1723, 1737; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.40 (1H, d, *J* 6.3 Hz, H-2), 2.95–2.74 (4H, m), 2.50–2.30 (2H, m), 1.72 (3H, s, olefinic CH_3), 1.29 (3H, s), 1.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 209.9 (C), 207.3 (C), 134.0 (C, C-3), 120.0 (CH, C-2), 58.1 (CH), 51.2 (2C, CH), 48.9 (C), 38.1 (CH_2), 34.8 (CH), 26.6 (CH_3), 24.9 (CH_3), 21.2 (CH_3); Mass: *m*/*z* 204 (M^+, 73%), 161 (26), 148 (41), 134 (28), 133 (70), 119 (72), 105 (66), 92 (51), 91 (100); HRMS: *m*/*z* calcd for $C_{13}H_{17}O_2$ (M+H): 205.1228; found: 205.1230; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%. Found: C, 76.24; H, 7.98%.



Scheme 3.

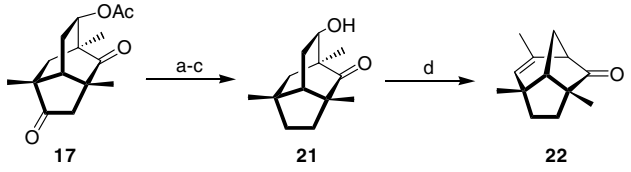


Scheme 4. Reagents, conditions and yields: (a) (i) NaOH, MeOH, reflux, 28 h, 93%; (ii) $(COCl)_2$, C_6H_6, rt, 2 h; (iii) CH_2N_2, Et_2O, 0 °C→rt, 3 h; 90%; (b) $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 40 min, 84%; (c) O_3/O_2, CH_2Cl_2–MeOH (9:1), −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 7 h, 95% (**17**:**18** 3:1); (d) K_2CO_3, MeOH, rt, 6 h, 94%; (e) PTSA, C_6H_6, reflux, 3 h, 92%.

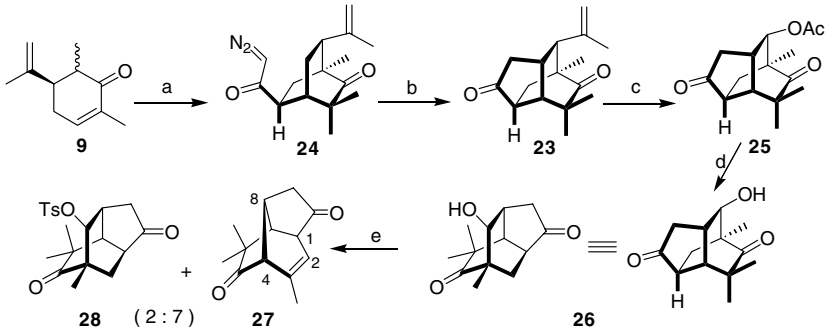
Formation of keto-ester **13** can be readily explained as depicted in Scheme 3. Formation of the secondary carbonium ion **14** followed by an easy migration of the acyl group generates the more stable tertiary carbonium ion **15** in a regioselective manner (alkyl group migration, even though *anti* to the hydroxy group, would lead to an unstable α-ketocarbonium ion), which loses a proton to form **13**.

After successfully demonstrating the rearrangement of a bicyclo[2.2.2]octane **12** to bicyclo[3.2.1]octane **13**, the strategy was extended to the rearrangement of an isotwistane to a tricyclo[5.2.1.$0^{4,8}$]decane. Isotwistanedione **16** was prepared from keto-ester **8** by employing an intramolecular rhodium carbenoid CH insertion reaction as the key step[7] (Scheme 4). Degradation of the isopropenyl group in dione **16** via Criegee rearrangement followed by hydrolysis of the acetate group in **17** generated hydroxy-dione **19**. Rearrangement of hydroxy-dione **19** with PTSA in refluxing benzene exclusively furnished dione[†] **20**, in 92% yield, in a highly regioselective manner, as anticipated, which contains tricyclo[5.2.1.$0^{4,8}$]decane carbon framework of allopupukeanane.

In a similar manner, reductive monodeoxygenation of dione **17** followed by hydrolysis of the acetate generated hydroxy-ketone **21**, which on treatment with PTSA in refluxing benzene generated 2,4,7-trimethyltricyclo[5.2.1.$0^{4,8}$]dec-2-en-10-one[†] **22** (Scheme 5).



Scheme 5. Reagents, conditions and yields: (a) $(CH_2SH)_2$, CH_2Cl_2, I_2 (catalytic), rt, 3 h, 88%; (b) Raney Ni, EtOH, reflux, 5 h, 80%; (c) K_2CO_3, MeOH, rt, 4 h, 97%; (d) PTSA, C_6H_6, reflux, 3 h, 91%.



Scheme 6. Reagents, conditions and yields: (a) (i) LiHMDS, hexane, CH_2=CHCOOMe, −10 °C→rt, 4 h; HMPA, MeI, 5 h; 63%; (ii) NaOH, MeOH, reflux, 28 h, 93%; (iii) $(COCl)_2$, C_6H_6, rt, 2 h; (iv) CH_2N_2, Et_2O, 0 °C→rt, 3 h; 91%; (b) $Rh_2(tfa)_4$, CH_2Cl_2, reflux, 40 min, 68%; (c) O_3/O_2, CH_2Cl_2–MeOH (9:1), −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 6 h, 53%; (d) K_2CO_3, MeOH, rt, 10 h, 89%; (e) PTSA, C_6H_6, reflux, 10 h, 70%.

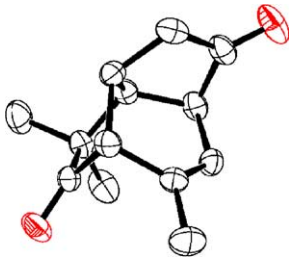


Figure 1. ORTEP diagram of the homobrexane **27**.

After successfully establishing the acid catalysed rearrangement of isotwistanes to tricyclo[5.2.1.0^{4,8}]decanes, the strategy was extended to the enantiospecific synthesis of a tricyclo[5.3.0.0^{4,8}]decane (homobrexane)[8] via acid catalysed rearrangement of an isotwistane (Scheme 6). Isotwistane dione **23** was obtained from 6-methylcarvone **9** via the double Michael reaction followed by alkylation,[9] and an intramolecular rhodium carbenoid CH insertion reaction of diazoketone **24**. Degradation of the isopropenyl group in **23** employing a Criegee rearrangement followed by hydrolysis of the resultant acetate **25** generated hydroxy-dione **26**. Treatment of the hydroxy-dione **26** with PTSA in refluxing benzene furnished a 7:2 mixture of the homobrexane **27** and tosylate **28** in 70% yield, which were separated by column chromatography on silica gel. The structure of homobrexane **27** was established from its spectral data,[†] and confirmed by single crystal X-ray diffraction analysis[10] (Fig. 1).

In summary, we have demonstrated that isotwistanes can be transformed into tricyclo[5.2.1.0^{4,8}]decanes, extending support to the proposed biosynthesis of allopupukeananes from pupukeananes. The strategy has also been extended to the enantiospecific synthesis of a homobrexane from an isotwistane.[11]

Acknowledgements

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10. Crystal data for **27**: X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.7107$ Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{13}H_{16}O_2$, MW = 204.3, Crystal system: orthorhombic, space group: $P2_12_12_1$; cell parameters: $a = 10.078(2)$ Å, $b = 10.149(2)$ Å, $c = 11.078(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $\rho = 1133.0(4)$ Å^3; $Z = 4$; $D_c = 1.20$ g cm^{-3}; $F(0\,0\,0) = 440$, $\mu = 0.079$ mm^{-1}. Total number of l.s. parameters = 139; $R1[I > 2\sigma(I)] = 0.042$ for 2110. $Rw[I > 2\sigma(I)] = 0.099$; GOF = 1.093. ORTEP diagram (for clarity hydrogen atoms were omitted) is depicted in Figure 1. Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Centre and the depository number is CCDC 275774.
11. The strategy has been further extended to the first enantiospecific total synthesis of allopupukeanones, Srikrishna, A.; Satyanarayana, G. *Tetrahedron Lett.* **2005**, *46*, in this issue. DOI:10.1016/j.tetlet.2005.11.009.