An intramolecular rhodium carbenoid C–H insertion approach to chiral isotwistanes. Synthesis of (−)-neopupukean-4,10-dione and (−)-neopupukean-10-one

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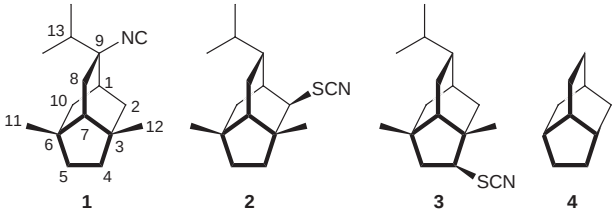
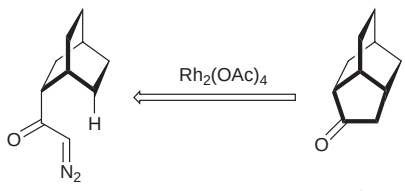
The first synthesis of a chiral neopupukeanane starting, from (*R*)-carvone and employing a double Michael reaction and a regioselective intramolecular rhodium carbenoid C–H insertion reaction as key steps, is described.

Recently, Scheuer and co-workers, during their biosynthetic experiments directed towards discovering the origin of the isocyano group in marine sponges, isolated[1] a new rearranged tricyclic sesquiterpene, 9-isocyanoneopupukeanane **1**, from the sponge *Ciocalypta* sp. whose relative stereostructure was established with the help of extensive 2D NMR spectroscopy. Subsequently, the research groups of Scheuer and Higa reported[2] the isolation of two thiocyanato derivatives of this new class of sesquiterpenes, 2-thiocyanatoneopupukeanane **2** from the sponge *Phycopsis terpnis* from Okinawa and 4-thiocyanatoneopupukeanane **3** from an unidentified species from Pohnpei. A characteristic of the structures of these neopupukeananes is the presence of a unique 9-isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decane carbon framework incorporating two quaternary carbon atoms besides the presence of the isocyano and thiocyanato functionalities, making them challenging synthetic targets. In continuation of our interest in the synthesis of chiral pupukeanones from (*R*)-carvone,[3] we herein report the first total synthesis of a chiral neopupukeanane[4] employing a regioselective intramolecular rhodium carbenoid C–H insertion reaction[5] as the key step for the generation of the isotwistane **4** carbon framework.



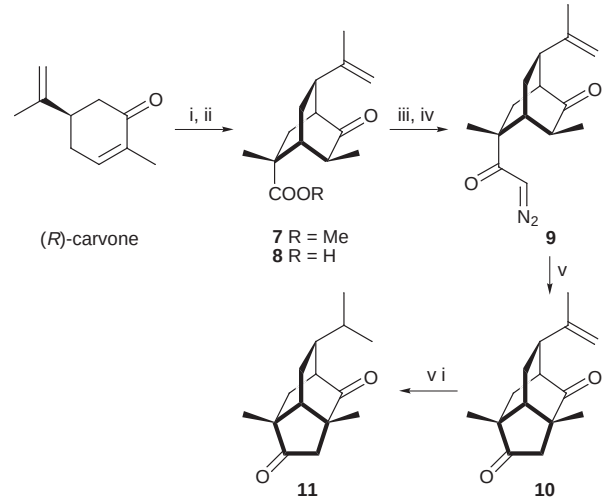
1 **2** **3** **4**

It was envisaged that the rhodium catalysed decomposition of the bicyclic diazo ketone **5** will generate the isotwistane **6** (Scheme 1) in a regioselective manner *via* the preferential formation of a five-membered ring by the insertion of the intermediate rhodium carbenoid into the only available C–H bond. A double Michael reaction on carvone[6] was chosen for the generation of an appropriate bicyclic precursor of an analogue of the diazo ketone **5**, which could be suitable for



5 **6**

Scheme 1

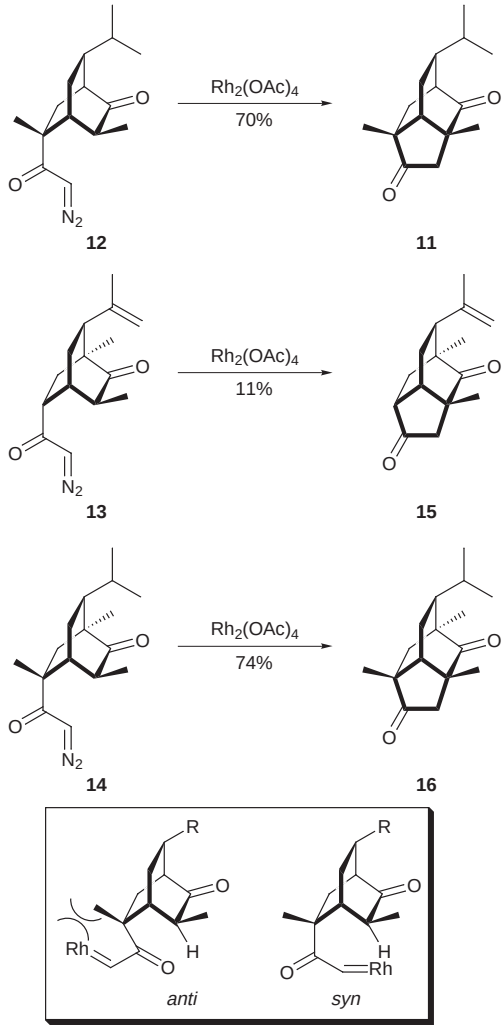


(*R*)-carvone **7** R = Me **8** R = H **9** **11** **10**

Scheme 2 *Reagents and conditions*: i, LiHMDS, $H_2C{=}CMeCO_2Me$, hexane–Et_2O (9 : 1), −78 °C → room temp., 50%; ii, 10% aq. NaOH, MeOH, reflux, 8 h, 92%; iii, $(COCl)_2$, C_6H_6, 2 h; iv, CH_2N_2, Et_2O, 0 °C → room temp., 2 h 90% (2 steps); v, $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, reflux, 2 h, 90%; vi, H_2 (1 atm), 10% Pt/C, EtOH, 4 h, 96%

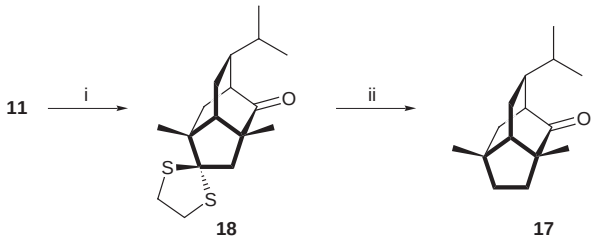
further elaboration into chiral neopupukeananes. Thus, double Michael reaction of (*R*)-carvone with LiHMDS and methyl methacrylate furnished the bicyclic keto ester **7** in a regio- and stereo-selective manner (Scheme 2) which, on base-catalysed hydrolysis, furnished the keto acid **8**. It is worth mentioning that in the keto acid **8**, the stereochemistry of the secondary methyl group at the carbon α to the keto group is *anti* with respect to the acid group, which was perfectly suited for the projected C–H insertion reaction for the generation of the tricyclic system. Reaction of the acid **8** with oxalyl chloride followed by treatment of the resulting acid chloride with an excess of ethereal CH_2N_2 furnished the diazo ketone **9**. Treatment of the diazo ketone **9** with a catalytic amount of rhodium acetate in refluxing CH_2Cl_2 led to the formation of the isotwistane dione **10** containing the complete carbon framework of neopupukeananes, *via* the regioselective C–H insertion of the intermediate keto carbenoid. The structure of neopupukean-13-en-4,10-dione **10** was established from its spectral data.‡ Catalytic hydrogenation in EtOH using 10% Pt/C transformed the dione **10** into neopupukean-4,10-dione **11**.‡ To test the generality of the C–H insertion, the reaction was carried out with three other bicyclic diazo ketones **12**–**14** to generate the isotwistanes **11**,**15** and **16** (Scheme 3). It is interesting to note that the reaction was not so facile when there is no tertiary methyl group at the α′-position of the diazo ketone, *cf.* **13**; perhaps the steric crowding due to the tertiary methyl group forces the rhodium carbenoid to occupy the *syn* orientation.

The difference in the steric crowding of the two ketones in dione **11** was exploited for the conversion of neopupukean-4,10-dione into neopupukean-10-one **17** (or 9-epineopupukean-2-one). Thus, treatment of dione **11** with $HS(CH_2)_2SH$



Scheme 3

(1 equiv.) in the presence of $BF_3{\cdot}OEt_2$ in benzene at room temperature generated the thioketal **18** (Scheme 4), which on desulfurisation with Raney nickel furnished neopupukean-10-one **17**.‡



Scheme 4 *Reagents and conditions*: i, $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, C_6H_6, room temp., 8 h, 82%; ii, Raney Ni, EtOH, reflux, 9 h, 85%

In conclusion, we have developed a rapid methodology for the generation of chiral isotwistanes, containing the neopupukeanane carbon framework, employing a regioselective intramolecular rhodium carbenoid C–H insertion reaction. In addition to being the first synthesis of neopupukeanones, the generation of the chiral compounds, brevity and simplicity are the highlights of the present strategy. Currently, we are investigating the extension of this methodology for the synthesis of other neopupukeananes to establish the absolute stereochemistry of the natural products.

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Notes and References

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‡ All the compounds exhibited spectral data consistent with their structures. *Selected data* for **10**: mp 111–113 °C; $[\alpha]_D^{26}$ −45.5 (*c* 1.32, $CHCl_3$); ν_{max}/cm^{-1} 1740, 1710, 1640, 900, 890; δ_H(300 MHz, $CDCl_3$) 4.82 (1 H, s) and 4.79 (1 H, s) (C=CH_2), 2.55–2.50 (2 H, m, H-1 and 9), 2.52 (1 H, d, *J* 18.9, H-5a), 2.21 (1 H, ddd, *J* 14.5, 10.5 and 3.3, H-8a), 2.10 (1 H, d, *J* 18.9, H-5b), 1.94 (1 H, ddd, *J* 14.5, 6.3 and 2.7, H-8b), 1.90 (1 H, br s, H-7), 1.80 (1 H, dd, *J* 14.7 and 4.2, H-2a), 1.76 (3 H, s, olefinic CH_3), 1.59 (1 H, d, *J* 14.7, H-2b), 1.25 (3 H, s) and 1.24 (3 H, s) (2 × *tert*-CH_3); δ_C(75 MHz, $CDCl_3$, DEPT) 218.6 (C=O), 217.6 (C=O), 146.8 (*C*=CH_2), 110.4 (C=*C*H_2), 50.9 (quat. C), 49.0 (CH, C-1), 48.5 (quat. C), 48.1 (CH_2), 46.3 (CH), 45.1 (CH), 35.2 (CH_2), 22.0 (CH_3), 20.7 (CH_2), 19.5 (CH_3), 18.1 (CH_3); *m*/*z* 232 (M^+) (Calc. C, 77.5; H, 8.8. $C_{15}H_{20}O_2$ requires C, 77.55; H 8.7%). For **11**: mp 131–133 °C; $[\alpha]_D^{26}$ −48.9 (*c* 1.48, $CHCl_3$); ν_{max}/cm^{-1} 1740, 1720; δ_H(300 MHz, $CDCl_3$) 2.47 (1 H, d, *J* 19.2, H-5a), 2.48 (1 H, br s), 2.07 (1 H, d, *J* 18.9, H-5b), 2.05–2.20 (1 H, m), 1.86 (1 H, t, *J* 3.3), 1.78 (1 H, dd, *J* 14.7 and 4.5, H-2a), 1.60–1.75 (2 H, m), 1.47 (1 H, d, *J* 15, H-2b), 1.45–1.55 (1 H, m), 1.26 (3 H, s) and 1.20 (3 H, s) (2 × *tert*-CH_3), 0.94 (3 H, d, *J* 6.3) and 0.91 (3 H, d, *J* 6.6) (2 × *sec*-CH_3); δ_C(22.5 MHz, $CDCl_3$) 218.3 (s, C=O), 217.6 (s, C=O), 50.6 (s, quat. C), 49.1, 48.1 (s, quat. C), 47.6, 46.7, 45.0 (d, CH), 34.4 (t, CH_2), 33.9 (t, CH_2), 21.3, 20.5, 19.7, 19.2, 17.8; *m*/*z* 234 (M^+) (Calc. C, 76.98; H, 9.64. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%). For **17**: $[\alpha]_D^{27}$ −84.1 (*c* 1.70, $CHCl_3$); ν_{max}/cm^{-1} 1715; δ_H(300 MHz, $CDCl_3$) 2.32 (1 H, br s), 1.20–2.10 (11 H, m), 1.16 (3 H, s) and 1.11 (3 H, s) (2 × *tert*-CH_3), 0.893 (3 H, d, *J* 6.3) and 0.886 (3 H, d, *J* 6.3) (2 × *sec*-CH_3]; δ_C(75 MHz, $CDCl_3$) 222.4 (C=O), 55.5 (quat. C), 51.8, 46.6, 45.6, 40.2, 39.7, 35.5 (quat. C), 35.2, 34.0, 26.5, 21.9, 20.8, 20.3, 18.6; *m*/*z* 220 (M^+).

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