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Enantiospecific total synthesis of both enantiomers of 2-thiocyanatoneopupukeanane from (*R*)-carvone

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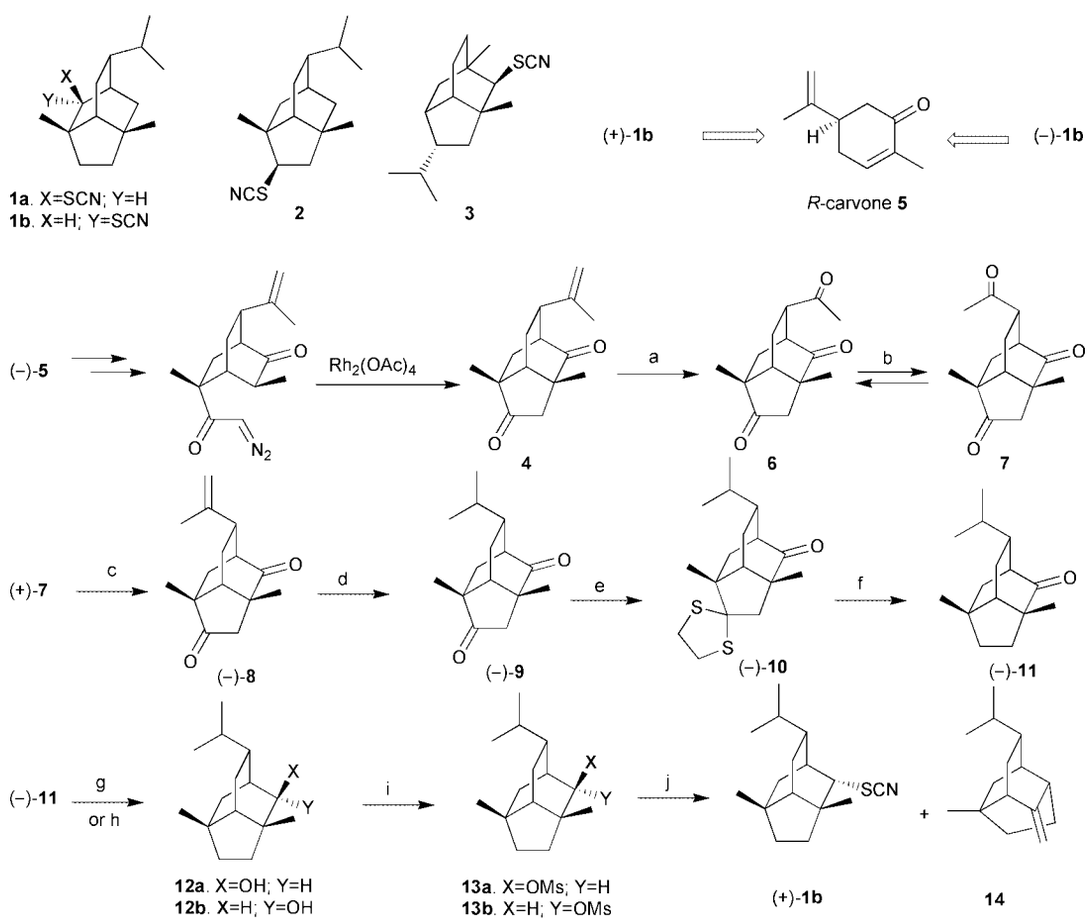
Enantiospecific synthesis of both enantiomers of the marine sesquiterpene 2-thiocyanatoneopupukeanane starting from (*R*)-carvone, employing an intramolecular rhodium carbenoid C–H insertion reaction as the key step, is described.

In 1991, the research groups of Scheuer and Higa reported the isolation of two sesquiterpene thiocyanates, 2-thiocyanatoneopupukeanane **1a** from the sponge *Phycopsis terpnis* (from Okinawa) and 4-thiocyanatoneopupukeanane **2** from an unidentified species from Pohnpei.[1] Subsequently,[2] Faulkner *et al.* have reported the isolation of 2-thiocyanatopupukeanane **3** from the sponge *Axinyssa aplysinoides* along with 2-thiocyanatoneopupukeanane, which was identical to that reported by Scheuer and Higa, and established its stereostructure as *endo* isomer **1b** on the basis of 2D NMR studies. A characteristic of the structure of these neopupukeananes, whose first member 9-isocyanoneopupukeanane was reported by Scheuer *et al.* from the sponge *Ciocalypta* sp.,[3] is the presence of a unique 9-isopropyl-3,6-dimethyltricyclo[4.3.1.$0^{3,7}$]decane carbon framework (an isotwistane) incorporating two quaternary carbon atoms and the presence of a rare thiocyanate functionality making them challenging synthetic targets. In 1998, we accomplished the first synthesis of a neopupukeanane **4** based on a rhodium carbenoid C–H insertion reaction,[4] and herein, we describe the first enantiospecific total synthesis of both enantiomers of 2-thiocyanatoneopupukeanane **1b** starting from (*R*)-carvone **5**.

The readily available[4] isotwistane dione **4** was chosen as the requisite starting material. It was readily identified that for the generation of 2-thiocyanatoneopupukeanane **1b**, the isopropenyl group in the isotwistane dione **4** needs to be epimerised. As isomerisation to the isopropylidene group and hydrogenation sequence was unsuccessful, we resorted to the conversion of the isopropenyl group into an acetyl group. The synthetic sequence is depicted in Scheme 1. Thus, ozonolysis of



Scheme 1 *Reagents, conditions and yields*: (a) i. O_3–O_2,CH_2Cl_2–MeOH (5:1), −70 °C; ii. Me_2S, rt, 12 h, 95%; (b) DBU, C_6H_6, rt, 4 h 85%, 1:1; (c) Zn, $TiCl_4$, CH_2Br_2, THF, CH_2Cl_2, rt, 4 h, 60% (80% conversion); (d) H_2 (1 atm), 10% Pt/C, EtOH, 4 h, 96%; (e) $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$, C_6H_6, 0 °C to rt, 8 h, 80%; (f) Raney Ni, EtOH, reflux, 12 h, 85%; (g) DIBAL-H, PhMe, −78 °C, 1 h, 95%; (h) Li, liq. NH_3, −78 °C, 0.5 h, 85%; (i) MsCl, Py, DMAP, 10 h; (j) NH_4SCN, $BnNEt_3Cl$, THF, reflux, 4 h, 75% (2 steps), **1b**:**14** 1:4.

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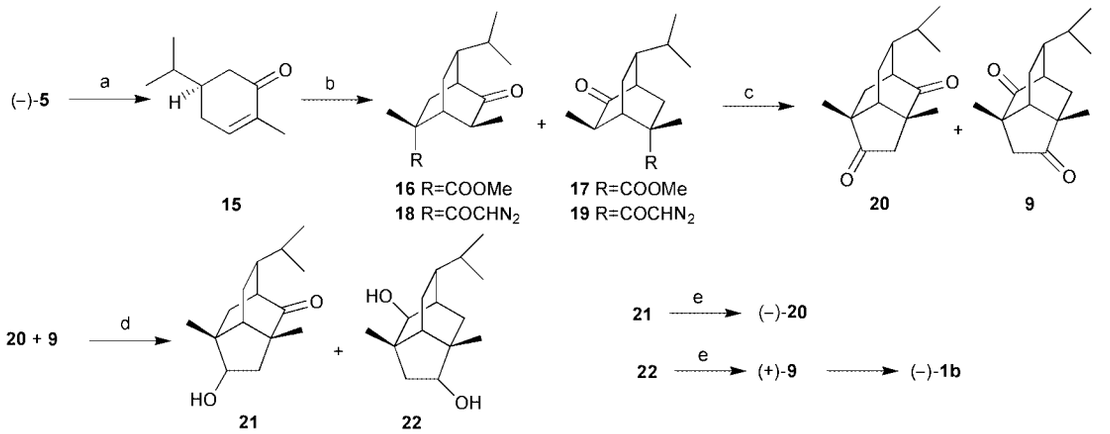

Scheme 2 *Reagents, conditions and yields*: (a) H_2 (1 atm), $(Ph_3P)_3RhCl$, C_6H_6, 5 d, 100%; (b) LiHMDS, $H_2C{=}C(Me)COOMe$, −78 °C–rt, 55%, **16**:**17** 3:1; (c) i. 5% NaOH, MeOH–H_2O (1:1), reflux, 12 h, 95%; ii. $(COCl)_2$, C_6H_6, rt, 2 h; iii. CH_2N_2, Et_2O, 0 °C, 2 h; iv. $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 2 h, 65%, **20**:**9** 3:1; (d) i. $NaBH_4$, MeOH, 0 °C, 15 min; ii. silica gel chromatography; (e) PCC, silica gel, CH_2Cl_2, rt, 2 h, 95%.

the dione **4** furnished the trione **6**. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU) catalysed isomerisation of the trione **6** furnished a ~1:1 mixture of the triones **6** and **7**,† which were separated by silica gel column chromatography. As the attempted Wittig methylenation of the trione **7** furnished a mixture of the diones **4** and **8**, obviously *via* equilibration of **7** during the Wittig reaction, the methylene group was introduced using Lombardo's procedure.[5] Consequently, reaction of the trione **7** with titanium tetrachloride, methylene bromide and zinc generated the isopropenyl compound **8**, mp 71–72 °C, $[a]_D^{26}$ −34 (*c* 1, $CHCl_3$), in a regiospecific manner, which on hydrogenation using 10% Pt/C as the catalyst furnished neopupukeanane-2,5-dione (−)-**9**.† The less hindered C-5 ketone was deoxygenated *via* its thioketal. Reaction of the dione **9** with ethane-1,2-dithiol in the presence of boron trifluoride–diethyl ether generated the thioketal (−)-**10**, which on treatment with Raney Ni in refluxing ethanol furnished neopupukeanan-2-one (−)-**11**.† Reduction of the ketone **11** using either sodium borohydride or lithium aluminium hydride furnished a mixture of the *exo* and *endo* alcohols **12a,b**. On the other hand, reduction of the ketone **11** using lithium in liquid ammonia conditions furnished exclusively the *endo* isomer **12b**.† Reduction of the ketone **11**, however, using diisobutylaluminium hydride furnished predominantly the *exo* alcohol **12a**† along with minor amounts of the *endo* alcohol. Treatment of the alcohol **12a** with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) furnished the mesylate **13a**, which was found to be unstable. Reaction of the mesylate **13a** with ammonium thiocyanate in the presence of a catalytic amount of benzyltriethylammonium chloride in refluxing THF furnished 2-thiocyanatoneopupukeanane (+)-**1b**, $[a]_D^{23}$ 65 (*c* 0.6, $CHCl_3$), along with the rearranged eliminated compound **14**. The synthetic sample of (+)-**1b**, contaminated with trace amounts of its epimer, was found to be the antipode of the natural 2-thiocyanatoneopupukeanane and exhibited the ^1H and ^{13}C NMR spectral data identical to that of the natural product.[1,2] It is worth noting that the replacement of the mesylate by a thiocyanato group proceeded *via* an S_N1 mechanism. This was established by the reaction of the epimeric mesylate **13b**, obtained from the alcohol **12b**, with ammonium thiocyanate, which also furnished the same mixture of **1b** and **14**.

For the generation of the natural enantiomer of 2-thiocyanatoneopupukeanane (−)-**1b**, dihydrocarvone **15** was chosen as the starting material (Scheme 2). Wu and co-workers have reported that the reaction of the enone **15** with LiHMDS and methyl methacrylate provides a 3:1 mixture of the bicyclic compounds **16** and **17** *via* the approach of methacrylate from the *anti* and *syn* faces of the isopropyl group, respectively, during a Michael–Michael reaction.[6] As the isomers were not easily separable, the sequence was carried out with a mixture of **16** and **17**. Consequently, the esters **16** and **17** were transformed into the diazo ketones **18** and **19**, *via* a standard sequence, *i.e.* hydrolysis of the ester, formation of the corresponding acid chloride and reaction with ethereal diazomethane. Rhodium acetate catalysed intramolecular C–H insertion of the diazo ketones **18** and **19** in refluxing methylene chloride furnished a ~3:1 mixture of the neopupukeananediones **20** and **9**. Treatment of a mixture of the diones **20** and **9** with sodium borohydride furnished a mixture of the ketol **21** and the diol **22**, which were separated by silica gel column chromatography. Oxidation of the ketol **21** with pyridinium chlorochromate (PCC) and silica gel furnished the dione (−)-**20**, which was found to be identical to the compound obtained by hydrogenation of the dione **4** in all respects. Similarly, oxidation of the diol **22** furnished the dione (+)-**9**, $[a]_D^{23}$ 16.7 (*c* 1, $CHCl_3$), which exhibited IR, ^1H and ^{13}C NMR spectra identical to its enantiomer obtained *via* the dione **4**. Repetition of the same sequence of reactions on (+)-**9** furnished the natural enantiomer of 2-thiocyanatoneopupukeanane (−)-**1b**, *via* 2-neopupukeanone (+)-**11**, $[a]_D^{23}$ 24.4 (*c* 1.3, $CHCl_3$).

In conclusion, we have accomplished the first enantiospecific synthesis of both enantiomers of the marine sesquiterpene 2-thiocyanatoneopupukeanane starting from a single enantiomer of carvone, employing an intramolecular rhodium carbenoid C–H insertion as the key reaction.

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Notes and references

† All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the trione **6**: mp 76–78 °C. $[a]_D^{26}$ −78.3 (*c* 1.15, $CHCl_3$). ν_{max}/cm^{-1} 1735, 1720, 1700. δ_H (300 MHz, $CDCl_3$ + CCl_4) 2.91 (1 H, t of d, *J* 8.1 and 3.0 Hz), 2.60–2.45 (2 H, m), 2.37 (1 H, d, *J* 18.9 Hz), 2.13 (3 H, s, $COCH_3$), 2.02 (1 H, d, *J* 18.9 Hz), 1.95–1.70 (2 H, m), 1.82 (1 H, d, *J* 14.7 Hz), 1.54 (1 H, d, *J* 14.4 Hz), 1.22 (3 H, s), 1.16 (3 H, s). δ_C (75 MHz, $CDCl_3$ + CCl_4) 216.2 (C), 215.2 (C), 205.9 (C), 51.5 (CH), 51.2 (C), 48.8 (CH), 48.3 (C), 47.8 (CH_2), 44.9 (CH), 34.0 (CH_2), 28.0 (CH_3), 19.6 (CH_3), 18.0 (CH_3), 15.5 (CH_2). *m*/*z*: 234 (M^+, 48%). For the trione **7**: mp 102–104 °C. $[a]_D^{25}$ 30.8 (*c* 0.91, $CHCl_3$). ν_{max}/cm^{-1} 1735, 1720, 1700. δ_H (300 MHz, $CDCl_3$ + CCl_4) 2.96 (1 H, dd, *J* 10.8 and 6.9 Hz), 2.59 (1 H, br s), 2.50–2.40 (1 H, m), 2.44 (1 H, d, *J* 18.6 Hz), 2.19 (3 H, s, $COCH_3$), 2.10 (1 H, d, *J* 18.6 Hz), 1.95–1.80 (2 H, m), 1.52 (1 H, d, *J* 15.0 Hz), 1.45 (1 H, d, *J* 15.0 Hz), 1.33 (3 H, s), 1.18 (3 H, s). δ_C (75 MHz, $CDCl_3$ + CCl_4) 216.2 (C), 215.7 (C), 204.9 (C), 50.4 (C), 49.0 (CH), 48.9 (C), 47.7 (CH_2), 47.3 (CH), 44.0 (CH), 28.4 (CH_3), 27.8 (CH_2), 19.0 (CH_3), 18.9 (CH_3), 15.5 (CH_2). *m*/*z*: 234 (M^+, 100%). For the neopupukeananedione **9**: mp 93–95 °C. $[a]_D^{23}$ −15.6 (*c* 1.8, $CHCl_3$). ν_{max}/cm^{-1} 1735, 1710. δ_H (300 MHz, $CDCl_3$ + CCl_4) 2.40 (1 H, d, *J* 18.6 Hz), 2.35–2.30 (1 H, m), 2.20–2.10

(1 H, m), 2.04 (1 H, d, *J* 18.6 Hz), 1.82 (1 H, m), 1.70–1.35 (5 H, m), 1.30 (3 H, s), 1.14 (3 H, s), 0.98 (3 H, d, *J* 6.6 Hz), 0.88 (3 H, d, *J* 6.6 Hz). δ_C (75 MHz, $CDCl_3$ + CCl_4) 218.1 (C), 217.6 (C), 50.2 (C), 49.5 (CH), 49.2 (C), 48.0 (CH_2), 44.6 (CH), 41.6 (CH), 30.9 (CH), 27.1 (CH_2), 22.2 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 19.4 (CH_3), 18.9 (CH_3). *m*/*z*: 234 (M^+, 54%). For 2-neopupukeanone **11**: $[a]_D^{23}$ −24.6 (*c* 2.4, $CHCl_3$). ν_{max}/cm^{-1} 1720. δ_H (300 MHz, $CDCl_3$ + CCl_4) 2.25–2.15 (1 H, m), 1.86 (1 H, ddd, *J* 14.4, 10.8 and 4.8 Hz), 1.80–1.15 (10 H, m), 1.12 (6 H, s), 0.92 (3 H, d, *J* 6.6 Hz), 0.84 (3 H, d, *J* 6.6 Hz). δ_C (75 MHz, $CDCl_3$ + CCl_4) 221.4 (C), 54.7 (C), 51.9 (CH), 45.0 (CH), 41.6 (CH), 40.4 (C), 40.2 (CH_2), 35.3 (CH_2), 33.0 (CH_2), 31.1 (CH), 26.5 (CH_3), 22.5 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 19.6 (CH_3). *m*/*z*: 220 (M^+, 11%). For the *exo* alcohol **12a**: ν_{max}/cm^{-1} 3380. δ_H (300 MHz, $CDCl_3$ + CCl_4) 3.51 (1 H, d, *J* 3.7 Hz), 1.75 (1 H, ddd, *J* 14.2, 10.2 and 4.1 Hz), 1.70–1.65 (1 H, m), 1.55–0.80 (11 H, m), 1.03 (3 H, s), 1.00 (3 H, s), 0.93 (3 H, d, *J* 6.3 Hz), 0.82 (3 H, d, *J* 6.3 Hz). δ_C (75 MHz, $CDCl_3$ + CCl_4) 79.0 (CH), 49.6 (CH), 44.5 (C), 41.0 (CH_2), 40.5 (CH_2), 39.7 (C), 36.5 (CH_2), 35.3 (CH), 32.8 (CH), 31.3 (CH), 26.8 (CH_3), 22.3 (CH_2), 21.5 (CH_3), 21.2 (CH_3), 19.5 (CH_3). *m*/*z*: 222 (M^+, 3%). For the *endo* alcohol **12b**: $[a]_D^{24}$ 43.2 (*c* 0.9, $CHCl_3$). ν_{max}/cm^{-1} 3340. δ_H (300 MHz, $CDCl_3$ + CCl_4) 3.36 (1 H, br s), 2.09 (1 H, ddd, *J* 14.0, 9.0 and 5.0 Hz), 1.68 (1 H, ddd, *J* 14.4, 11.0 and 3.5 Hz), 1.55–1.25 (8 H, m), 1.20–0.95 (1 H, m), 1.17 (1 H, ddd, *J* 14.4, 5.7 and 2.7 Hz), 1.06 (3 H, s), 1.00 (3 H, s), 0.92 (3 H, d, *J* 6.6 Hz), 0.82 (3 H, d, *J* 6.3 Hz), 0.95–0.85 (1 H, m). δ_C (75 MHz, $CDCl_3$ + CCl_4) 81.1 (CH), 51.0 (CH), 45.8 (C), 43.2 (CH), 41.4 (CH_2), 39.7 (C), 36.7 (CH), 32.3 (CH_2), 31.7 (CH), 29.5 (CH_2), 26.7 (CH_3), 26.6 (CH_3), 22.4 (CH_2), 21.4 (CH_3), 21.2 (CH_3). *m*/*z*: 222 (M^+, 4%).

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