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Enantiospecific First Total Synthesis of (–)-4-Thiocyanatoneopupukeanane[1]

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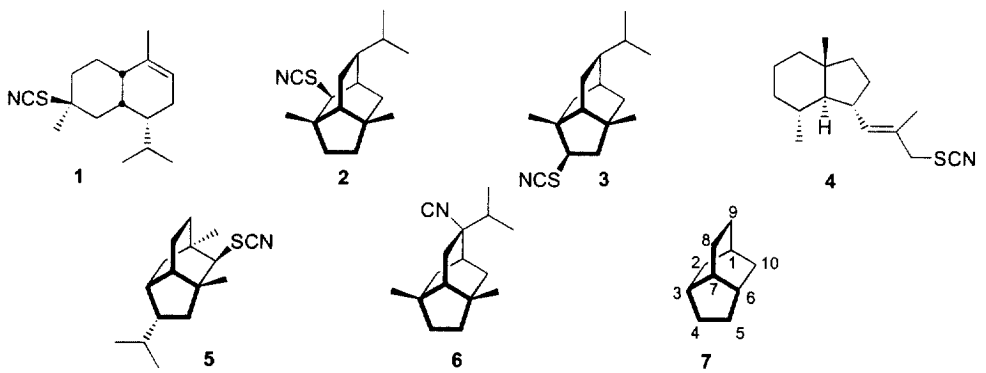
Abstract: The first total synthesis of (-)-4-thiocyanatoneopupukeanane starting from (*R*)-carvone has been achieved, establishing the relative as well as absolute structure of the natural product.

The isothiocyanate and isonitrile functionalities are present in a number of natural products, particularly marine sesquiterpenoids, whereas, the thiocyanate functionality is extremely rare in natural products.[2] Very few terpenoids have been reported to contain the thiocyanate group. In 1989, the research groups of Faulkner and Clardy reported[3] the isolation of the first one, 4-thiocyanato-9-cadinene **1** from the Palauan sponge *Trachyopsis aplysinoides*. In 1991 the research groups of Scheuer and Higa reported[4] the isolation of two sesquiterpene thiocyanates, 2-thiocyanatoneopupukeanane **2** from the sponge *Phycopsis terpnis* (from Okinawa) and 4-thiocyanatoneopupukeanane **3** from an unidentified species from Pohnpei. Subsequently, Fusetani *et al.* reported[5] the isolation of cavernothiocyanate **4** from the marine sponge *Acanthella* cf. *cavernosa* and Faulkner *et al.* isolated[6] 2-thiocyanatopupukeanane **5** from *A. aplysinoides* along with the C-2 epimer of **2**. The thiocyanates **2** and **3** belong to a novel class of sesquiterpenes, neopupukeananes, whose first member[7] 9-isocyanoneopupukeanane **6**, was isolated from the sponge *Ciocalypta* sp. by Scheuer and co-workers, during their biosynthetic experiments directed toward discovering the origin of the isonitrile group in marine sponges. A characteristic of the structure of the neopupukeanane sesquiterpenes is the presence of a unique 9-isopropyl-3,6-dimethyltricyclo[4.3.1.$0^{3,7}$]decane carbon framework (isotwistane **7**) incorporating two quaternary carbon atoms plus the presence of the thiocyanate and isonitrile functionalities, making them challenging synthetic targets.[8] Herein we describe the first enantiospecific total synthesis of the natural enantiomer of (–)-4-thiocyanatoneopupukeanane **3**, establishing the relative as well as the absolute stereochemistry of the natural product.



It was anticipated that intramolecular cyclopropanation[9] of the diazo ketone derived from a bicyclo[2.2.2]-octenecarboxylic acid, *e.g.* **8**, followed by regiospecific cyclopropane ring cleavage would generate the isotwistane framework **9**, Scheme 1. The synthetic sequence starting from (*R*)-carvone **10** is depicted in Schemes 2 and 3.

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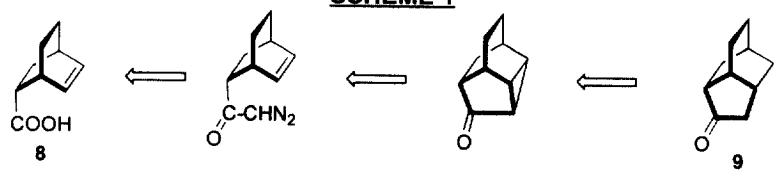
PII: S0040-4039(98)02522-2

SCHEME 1



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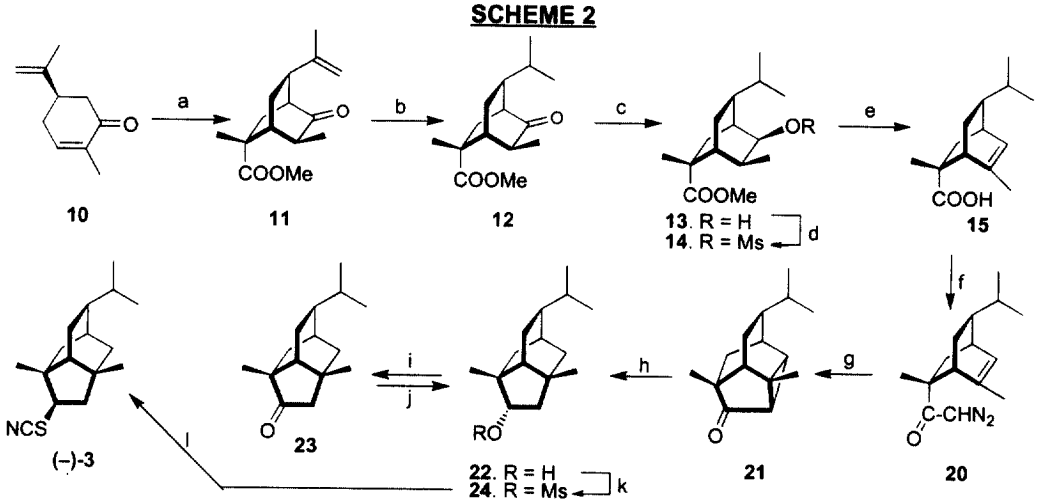
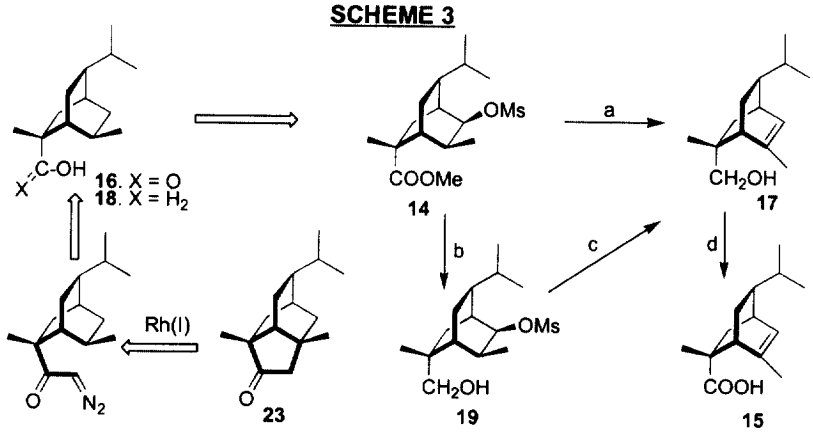


***Reagents, conditions and yields**: (a) LiHMDS, H_2C=C(Me)COOMe, hexane-Et_2O (9:1), -78 °C to rt, 60%; (b) H_2, 1 atm, 10% Pt-C, EtOH, 4 h, 98%; (c) $NaBH_4$, THF, reflux, 48 h, 80%; (d) MsCl, pyridine, DMAP (catalytic), 72 h, 65%; (e) EtONa, EtOH, reflux, 10 h, 53%; (f) i. $(COCl)_2$, C_6H_6, rt, 2 h; ii. CH_2N_2, Et_2O, 0 °C to rt, 2 h, 85% (2 steps); (g) Anhyd. $CuSO_4$, c-C_6H_{12}, reflux (tungsten lamp), 4 h, 56%; (h) Li, liq. NH_3, 0.5 h, 82%; (i) PCC, silica gel, CH_2Cl_2, 3 h, 92%; (j) $NaBH_4$, MeOH, 0.5 h, rt, 87%; (k) MsCl, pyridine, DMAP (catalytic), 24 h, 80%; (l) KSCN, acetone, 80 °C, sealed tube, 5 days, 40% (60% conversion).*

SCHEME 3



***Reagents, conditions and yields**: (a) LAH, THF, reflux, 8 h, 81%; (b) LAH, THF, rt, 3 h, 30% (in addition 50% of 17 was also formed); (c) n-BuLi, THF-hexanes, rt, 58%; (d) i. PCC, anhyd. NaOAc, CH_2Cl_2, 4 h, 76%; ii. Jones reagent, acetone, 1.25 h, 100%.*

The requisite bicyclo[2.2.2]octane system was assembled using a double Michael reaction.[10] Thus, reaction of (*R*)-carvone **10** with lithium hexamethyldisilazide and methyl methacrylate furnished the bicyclic keto-ester **11** in a regio- and stereoselective manner, which on catalytic hydrogenation furnished the keto-ester **12**. Regioselective reduction of the keto-ester **12** with sodium borohydride followed by mesylation (MsCl, py, DMAP) of the resulting alcohol **13** furnished the mesylate **14**.[11] Sodium ethoxide mediated elimination of the mesylate in **14** in refluxing ethanol led to the simultaneous hydrolysis of the ester resulting in the formation of the ene-acid **15**.[11]

Methodology was explored to construct the isotwistane framework *via* the rhodium carbenoid C-H insertion of the diazo ketone derived from the acid **16**, Scheme 3. However, attempted reductive removal of the mesyloxy group in **14** with LAH in refluxing THF resulted in the formation of the ene alcohol **17**,[11] contrary to the expected alcohol **18**.[12] Formation of the ene-alcohol **17** can be explained by the initial reduction of the ester followed by intramolecular alkoxide mediated elimination of the mesylate. This was further established by carrying out the reaction in two distinct steps. Thus, reduction of the ester group in **14** with LAH at rt furnished the hydroxy mesylate **19** which on treatment with one equivalent of n-butyllithium in THF furnished the ene-alcohol **17**. Two step oxidation of **17** furnished the ene-acid **15** confirming the structure of the alcohol **17**.

The sequence was continued with the ene-acid **15** (Scheme 2). Reaction of the acid **15** with oxalyl chloride and treatment of the resulting acid chloride with an excess of ethereal diazomethane furnished the diazo ketone **20**. Anhydrous copper sulfate catalysed decomposition of the diazo ketone **20** in refluxing cyclohexane (using a tungsten lamp) led to the formation of the tetracyclic ketone **21**[11] *via* stereospecific insertion of the intermediate keto-carbenoid. Regiospecific cyclopropane ring cleavage[13] employing lithium in liquid ammonia transformed the tetracyclic ketone **21** into the *endo* alcohol **22**.[11] Oxidation of the alcohol **22** furnished 4-neopupukeanone **23**, m.p. 66-68 °C, which on reduction with sodium borohydride furnished the alcohol **22** establishing the *endo* stereochemistry of the alcohol in **22**. Finally, reaction of the alcohol **22** with methansulfonyl chloride in pyridine in the presence of a catalytic amount of DMAP furnished the mesylate **24**, which on treatment with potassium thiocyanate in acetone furnished 4-thiocyanatoneopupukeanane **3**, $[\alpha]_D^{26}$: –118 (c 1.1, $CHCl_3$) {lit.[4] –120 (c 1.44, $CHCl_3$)}. The synthetic sample of (–)-**3** exhibited the IR, ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra identical to those of the natural sample,[4] establishing the relative structure as well as the absolute configuration of the natural product.

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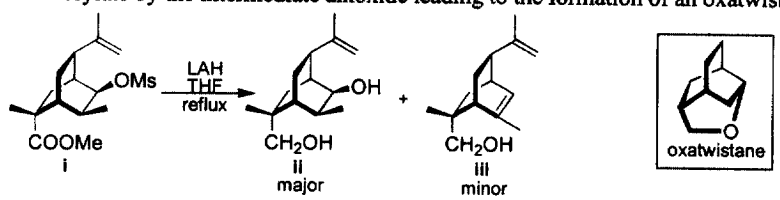
References and Notes

1. Chiral synthons from carvone, part 38. For part 37, see Srikrishna, A.; Dinesh, C.; Anebouselvy, K. *Tetrahedron Lett.* previous paper in this issue.
2. Faulkner, D. J. *Nat. Prod. Rep.* **1991**, *8*, 97.
3. He, H. -Y.; Faulkner, D. J.; Shumsky, J. S.; Hong, K.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 2511.
4. Pham, A. T.; Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Uchida, T.; Tanaka, J. -i.; Higa, T. *Tetrahedron Lett.* **1991**, *32*, 4843.
5. Fusetani, N.; Wolstenholme, H. J.; Shinoda, K.; Asai, N.; Matsunaga, S.; Onuki, H.; Hirota, H. *Tetrahedron Lett.* **1992**, *33*, 6823.
6. He, H.-y.; Salva, J.; Catalos, R. F.; Faulkner, D. J. *J. Org. Chem.* **1992**, *57*, 3191.
7. Karuso, P.; Poiner, A.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 2095.

8. For the only report on the synthesis of the neopupukeanane framework (by rhodium carbenoid C-H insertion route) see, Srikrishna, A.; Gharpure, S. J. *Chem. Commun.* **1998**, 1589.
9. (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(b) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; ed. L. S. Hegedus; Pergamon Press, New York, 1995; vol. 12, Chapter 5.1.
10. Zhao, R. -B.; Zhao, Y. -F.; Song, G. -Q.; Wu, Y. -L. *Tetrahedron Lett.* **1990**, *31*, 3559.
11. All the compounds exhibited spectral data consistent with their structures. Melting point, optical rotation, IR and NMR (^{1}H and ^{13}C) spectral data for some of the compounds are as follows: For the mesylate **14**: m.p. 67-69 °C. $[\alpha]_D^{22}$: –45.7 (c 1.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1720, 1350, 1170. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.84 (1 H, dd, *J* 10.5 and 4.2 Hz), 3.68 (3 H, s, $COOCH_3$), 2.96 (3 H, s, OSO_2CH_3), 2.40 (1 H, dd, *J* 14.4 and 2.4 Hz), 2.31 (1 H, brs), 1.10-2.00 (7 H, m), 1.31 (3 H, s, *tert.* CH_3), 1.06 (3 H, d, *J* 7.2 Hz), 0.93 (3 H, d, *J* 6.6 Hz) and 0.88 (3 H, d, *J* 6.3 Hz) [3 x *sec.* CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6 (O-C=O), 81.7 (*C*H-OMs), 52.2 (O-CH_3), 44.9 (*quat.* C), 41.6, 39.5, 37.7, 35.5, 33.5, 33.1, 32.9, 26.1, 22.4, 21.7, 20.9, 13.5. For the methyl ester of the ene acid **15**: $[\alpha]_D^{27}$: +6.1 (c 1.3, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1730, 1200. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (1 H, d, *J* 6.0 Hz), 3.62 (3 H, s, $COOCH_3$), 2.49 (2 H, m), 2.23 (1 H, dd, *J* 13.2 and 4.2 Hz), 1.93 (1 H, ddd, *J* 13.2, 9.2 and 2.7 Hz), 1.72 (3 H, s, olefinic CH_3), 1.27 (3 H, s, *tert.* CH_3), 0.85-1.20 (4 H, m), 0.84 (3 H, d, *J* 6.3 Hz) and 0.78 (3 H, d, *J* 6.6 Hz) [2 x *sec.* CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8 (O-C=O), 142.7 (*C*=CH), 124.4 (C=*C*H), 51.6 (O-*C*H_3), 45.9, 45.3 (*quat.* C), 43.6, 39.6, 33.7, 33.6, 27.2, 25.7, 21.1, 20.4, 20.2. For the enealcohol **17**: $[\alpha]_D^{26}$: +30.6 (c 1.1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3360, 1030. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64 (1 H, d, *J* 6.0 Hz, olefinic H), 3.29 (1 H, d, *J* 10.4 Hz) and 3.09 (1 H, d, *J* 10.4 Hz) [CH_2OH], 2.48 (1 H, m), 2.02 (1 H, brs), 1.97 (1 H, ddd, *J* 16.2, 8.7 and 3.0 Hz), 1.78 (3 H, d, *J* 1.5 Hz, olefinic CH_3), 1.51 (1 H, brs, OH), 1.15-1.45 (3 H, m), 0.95-1.10 (2 H, m), 1.07 (3 H, s, *tert.* CH_3), 0.85 (3 H, d, *J* 6.6 Hz) and 0.78 (3 H, d, *J* 6.6 Hz) [2 x *sec.* CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0 (*C*=CH), 123.0 (C=*C*H), 72.2 (CH_2OH), 45.6, 42.9, 39.4, 37.9 (*quat.* C), 34.0, 33.7, 28.6, 24.1, 21.2, 21.1, 20.4. For the tetracyclic ketone **21**: m.p. 61-63 °C. $[\alpha]_D^{26}$: –17.9 (c 1.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1720. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (1 H, m), 1.65-1.75 (4 H, m), 1.40-1.60 (3 H, m), 1.30 (3 H, s, *tert.* CH_3), 1.15-1.25 (1 H, m), 1.12 (1 H, dd, *J* 13.2 and 2.4 Hz), 0.95 (3 H, d, *J* 6.6 Hz) and 0.94 (3 H, d, *J* 6.9 Hz) [2 x *sec.* CH_3], 0.91 (3 H, s, *tert.* CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 214.4 (C=O), 46.8 (CH), 45.6 (*quat.* C), 43.8 (CH_2), 41.3 (CH), 33.7 (CH), 33.2 (CH), 31.7 (CH), 31.6 (*quat.* C), 25.7 (CH), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_2), 17.8 (CH_3), 15.9 (CH_3). For 4-hydroxyneopupukeanane **22**: m.p. 57-59 °C. $[\alpha]_D^{27}$: –66.1 (c 1.1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3360, 1050, 1020. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (1 H, dd, *J* 9.9 and 6.6 Hz), 2.02 (1 H, dd, *J* 13.8 and 9.9 Hz), 1.91 (1 H, dd, *J* 13.8 and 3.6 Hz), 1.74 (1 H, ddd, *J* 14.4, 10.5 and 4.5 Hz), 1.66 (1 H, brs), 1.6 (1 H, brs, OH), 1.40 (1 H, d, *J* 15.3 Hz), 1.00-1.35 (6 H, m), 1.01 (3 H, s) and 0.96 (3 H, s) [2 x *tert.* CH_3], 0.89 (3 H, d, *J* 6.6 Hz) and 0.83 (3 H, d, *J* 6.6 Hz) [2 x *sec.* CH_3], 0.80-0.90 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 78.8 (CHOH), 50.4 (CH_2), 46.7 (CH), 44.6 (CH), 42.9 (*quat.* C), 39.6 (CH_2), 38.2 (*quat.* C), 34.7 (CH_2), 31.9 (CH), 27.5 (CH), 26.8 (CH_3), 24.5 (CH_3), 23.0 (CH_2), 21.2 (CH_3), 21.0 (CH_3).
12. Surprisingly, the reaction of the mesylate **i** derived from the keto-ester **11**, with LAH in refluxing THF furnished the diol **ii** as major product (possibly *via* hydride attack on sulfur) and the ene-alcohol **iii** was formed as a minor product (25%). It is worth noting that neither **14** nor **i** underwent an intramolecular SN_2 displacement of mesylate by the intermediate alkoxide leading to the formation of an oxatwistane.



13. Srikrishna, A.; Krishnan, K. *J. Org. Chem.* **1993**, *58*, 7751 and references cited therein.