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The first total synthesis of (±)-2-thiocyanato*neo*pupukeanane based on a pinacol-type rearrangement

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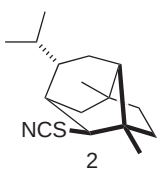
Abstract—The racemic mixture of 2-thiocyanato*neo*pupukeanane, a marine sesquiterpene-thiocyanate with a tricylo[4.3.1.0^{3,7}]decane skeleton, was prepared through a pinacol-type rearrangement of a bicyclo[2.2.2]oct-5-en-2-ol giving a bicyclo[3.2.1]oct-6-en-2-one derivative and an aldol reaction leading to the *neo*pupukeanane framework.

(−)-2-Thiocyanato*neo*pupukeanane **1**, the sesquiterpene with a unique carbon skeleton and a uncommon functional group, have been isolated from sponges, Phycopsis *terpnis* from Okinawa and in an unidentified species from Pohnpei, by Scheuer's and Higa's groups.[1] These special circumstances make the natural product one of challenging synthetic targets. The first total synthesis of (−)-4-thiocyanato*neo*pupukeanene **2**, the coexisting natural product with **1**,[1] has been reported very recently (Fig. 1).[2]

Recently we have reported the pinacol-type rearrangement of a 1-methoxybicyclo[2.2.2]oct-5-en-2-ol as a useful method to prepare the bicyclo[3.2.1]oct-6-en-2-one.[3] A tricyclo[4.3.1.0^{3,7}]decane skeleton would be derived from a bicyclo[3.2.1]oct-6-en-2-one having a suitable substituent at the 8-*endo* position.[4] We wish to report herein a synthesis of **1** in accordance with the plan listed in Scheme 1.

Treatment of the lithium enolate of the ketone **3** with 3-iodopropene at −78°C in THF in the presence of HMPA followed by warming to room temperature gave the *endo*-allylated ketone **4** in 74% yield along with the bis-allylated ketone in 11% yield.† In order to prepare the *endo*-allylated ketone **5**, the stereoisomer of **4**, the lithium enolate was generated from **4** and then treated with ethyl malonate[5] in THF at −95 to −90°C. The resultant was a 3.7 to 1 mixture of **5** and **4**, which were inseparable by means of flash chromatography. Thus the mixture was treated with methylmagnesium bromide in THF at −78°C, and the desired alcohol **6** was



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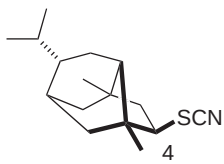

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Figure 1.

Keywords: aldol reactions; bicyclic aliphatic compounds; marine metabolites; rearrangements; terpenes; terpenoids.
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† All new compounds reported here exhibit satisfactory spectral characteristics including HRMS.

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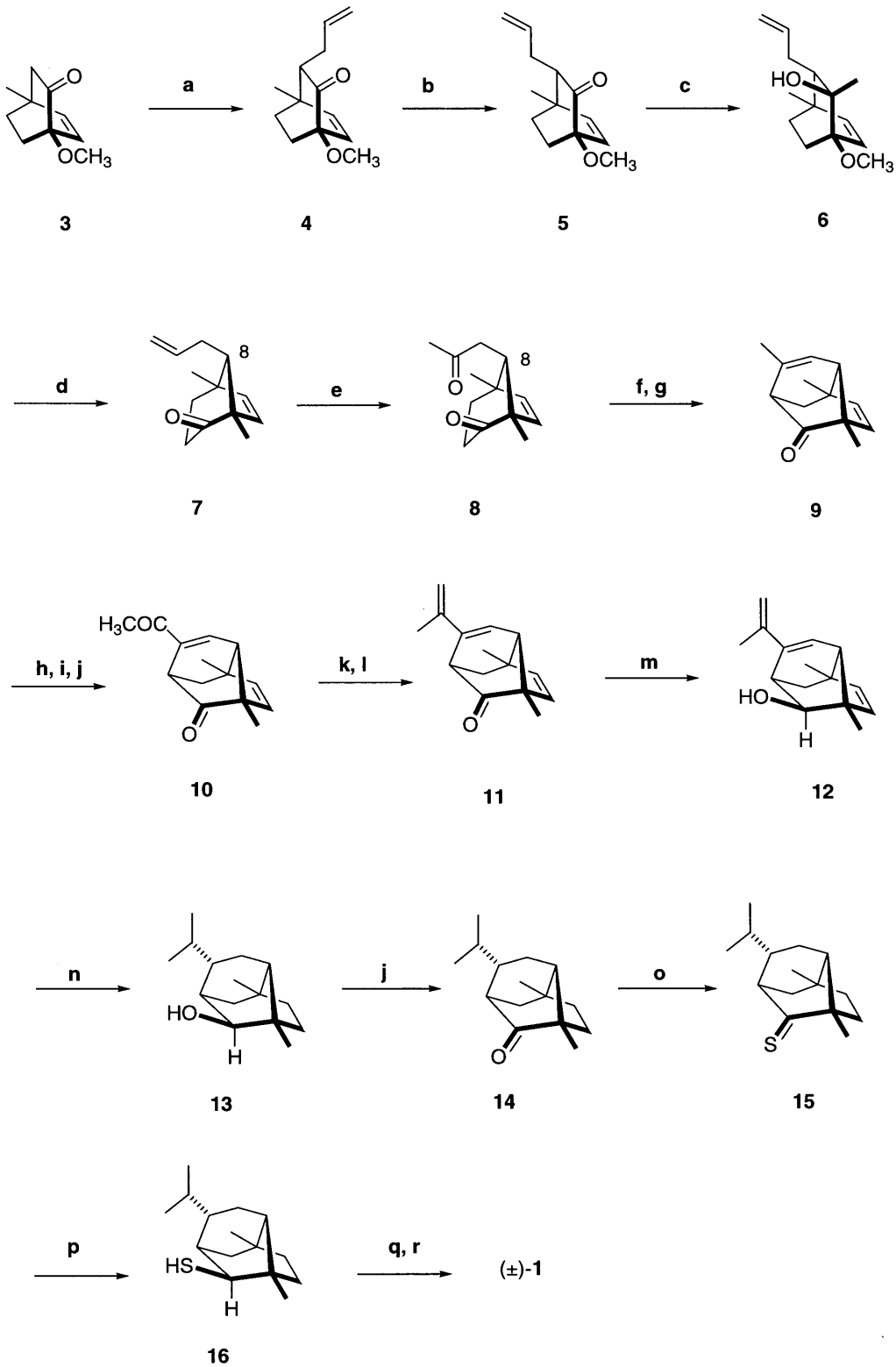

Scheme 1. Total synthesis of (±)-2-thiocyanato*neo*pupukeanane based on the pinacol rearrangement followed by the aldol reaction: (a) LDA, HMPA, THF, then $ICH_2CH{=}CH_2$, −78°C; (b) LDA, THF, then $ICH_2(COOEt)_2$, −95 to −90°C; (c) MeMgBr, THF, −78°C; (d) TsOH, benzene, reflux; (e) $PdCl_2$, CuCl, O_2, DMF, H_2O; (f) KOH, MeOH; (g) TsOH, toluene, reflux; (h) SeO_2, xylene, reflux; (i) MeLi, THF, −100°C; (j) TPAP, NMO, MeCN, 0°C; (k) Me_3SiCH_2Li, THF, −78°C; (l) KH, THF; (m) $LiAlH_4$, THF, −100°C; (n) H_2, 10% Pd-C, AcOEt; (o) (p-$MeOC_6H_4PS_2)_2$, toluene, reflux; (p) $LiAlH_4$, ether; (q) SO_2Cl_2, Et_3N, CCl_4, 0°C (r) Me_3SiCN, CH_3CN.

isolated in 73% yield from **4**. The pinacol-type rearrangement of **6** proceeded to give **7**, one of the key synthetic intermediates for **1**, in 96% yield by treatment with 0.3 equiv. of TsOH in boiling toluene for 1.5 h.

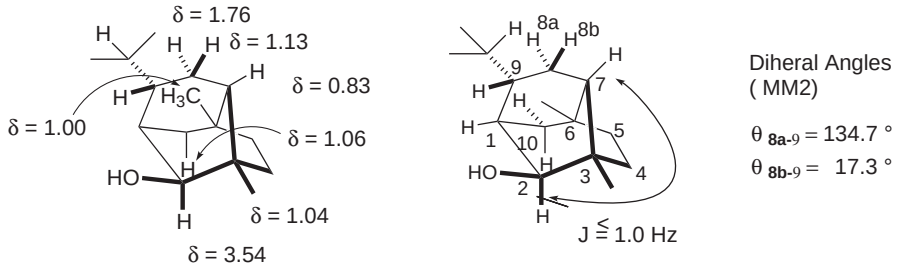

Figure 2.

The terminal olefin of **7** was transformed into the methyl ketone of **8** in 93% yield by Wacker oxidation, treated with palladium chloride, copper (I) chloride, and oxygen in aqueous DMF.[6] The intramolecular aldol condensation of **8** by treatment with KOH (4 equiv.) in methanol at room temperature for 1 h followed by dehydration of the resulting keto-alcohols using TsOH (0.5 equiv.) in the refluxing toluene solution gave the tricyclic dienone **9** in 68% yield from **8**.

Transformation of the olefinic methyl group of **9** into the isopropenyl group of **11** was carried out as follows. Selenium (IV) oxide oxidation of the olefinic methyl group of **9** by refluxing in xylene overnight gave the α,β-unsaturated aldehyde in 80% yield. Methyllithium added exclusively to the aldehyde group at −100°C in ether to give the hydroxyketone in 96% yield. TPAP oxidation[7] of the hydroxyketone using acetonitrile for the solvent gave the diketone **10** in 70% yield. To prepare the isopropenyl group of **11** from the acetyl group by Peterson reaction,[8] **10** was treated with (trimethylsilylmethyl)lithium.[9] The resulting alcohol was isolated in 70% yield from the recovery (23%) by silica-gel chromatography, and then treated with potassium hydride in THF giving **11** in 78% yield.

Reduction of **11** by $LiAlH_4$ at −100°C in THF gave the alcohol **12** and the stereoisomeric alcohol in 85% and 5% yields, respectively. Catalytic hydrogenation of **12** using 10% Pd-C gave the alcohol **13** in 65% yield and the ketone **14** in 33% yield.‡ The stereo-structure of **13** was confirmed on the basis of ^{1}H MNR date: $^4J_{2,7} \leqq 1.0$ Hz, a W-shape coupling; NOEDS between 6-CH_3 and H-8; (a), 1.0%; NOEDS between 3-CH_3 and H-8; (b), 2.0%; $^3J_{8a,9} = 6.8$ Hz (*trans*, supported by MM2 calculation); and $^3J_{8b,9} = 10.4$ Hz (*cis*) (Fig. 2).

The formation of the ketone **14** from **12** seems to be the results of the dehydrogenation of the latter by the palladium catalyst. TPAP oxidation of **13** was carried out in acetonitrile giving **14** in 90% yield.§

The thiocyanate was derived from the ketone **14.** The reaction with Lawesson's reagent[10] in boiling toluene gave the thioketone **15** in 84% yield. Reduction of **15** by $LiAlH_4$ gave a mixture of **16** and the stereoisomeric thiol in 95% yield. This mixture was treated with sulfuryl chloride in CCl_4 at 0°C for 1.5 h. The resulting crude mixture of the sulfenyl chloride was treated with TMSCN in acetonitrile at 20°C for 1 h.[11] The mixture of the products were separated by silica-gel column chromatography followed by repeated HPLC (SiO_2) giving the thiocyanate less than 10% yield. The spectroscopic characteristics of the separated thiocyanate were identical with those of 2-thiocyanato*neo*pupukeanane.[1]

In conclusion, the practical value of the pinacol-type rearrangement of a bicyclo[2.2.2]oct-5-en-2-ol giving a bicyclo[3.2.1]oct-6-en-2-one derivative was elucidated by the first total synthesis of 2-thiocyanato*neo*pupukeanane.

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‡ Catalytic hydrogenation of the stereoisomeric alcohol of **12** gave a 1:1 mixture of the configurational isomer containing an isoproply group.

§ Several attempts to prepare (±)-**1** from **13** and its stereoisomer were unsuccessful. The C-2 hydroxyl groups of them, inactive in substitution reactions and the conversion of to activated leaving groups, seem to be more sterically hindered than the C-4 hydroxyl group of the precursor of **2**.[2]

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