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TOTAL SYNTHESIS OF (±)-2-ISOCYANOPUPUKEANANE

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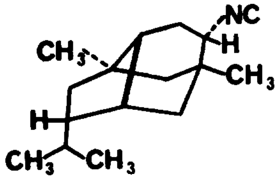
Summary: The first total synthesis of (±)-2-isocyanopupukeanane, a sesquiterpenoid of marine origin, has been completed following a strategy in which a common intermediate serves both for this synthesis and that of an isomeric, naturally occurring allomone, 9-isocyanopupukeanane.

The sponge Hymeniacidon sp. produces and supplies to the nudibranch Phyllidia varicosa a pair of sesquiterpenoid isocyanides which are used by both species for defensive purposes.[1,2] These are the 9- and 2-isocyano derivatives of a novel tricyclic parent pupukeanane (**1**[1] and **2**[2] , respectively). We have recently disclosed a synthesis of **1** designed so that both **1** and **2** can be elaborated from a common intermediate, the readily available lactone **3**.[3,4] In this letter, we describe the successful conversion of the lactone **3** to 2-isocyanopupukeanane (**2**) and also its 2-epimer.[5] The synthesis involves a number of interesting selective functional group transformations.

Reduction of the lactone **3** by lithium aluminum hydride in tetrahydrofuran (THF) at 0° for 1 hr produced the diol **4**[3] quantitatively. Oxidation of this diol with Cr (VI) reagents led mainly to the lactone **3**, indicating that oxidation of the primary alcohol function occurs selectively as the first step. With pyridinium chlorochromate (PCC)[6] in methylene chloride, for example, the conversion of **4** to **3** was essentially quantitative. However, the reverse selectivity could be achieved by the use of N-bromosuccinimide. Thus, exposure of the diol **4** to 1.5 equiv of N-bromosuccinimide in 10% aqueous dimethoxyethane at 25° for 1 hr afforded after removal of dimethoxyethane in vacuo and extractive work-up the hydroxy ketone **5** (> 98% yield), infrared max 3400, 1710 cm.$^{-1}$ (CHCl$_3$), R_f 0.48 on silica gel plates[8] using petroleum ether (PE) - ether (E), 1 : 1.

Further oxidation of the keto alcohol **5** using PCC[6] in methylene chloride yielded (90%) the keto aldehyde **6**, infrared max 1720, 1710 cm.$^{-1}$ (CHCl$_3$), R_f 0.34 (PE - E, 1:1). Treatment of **6** with 15 equiv of potassium carbonate in methanol for 2 hr at 25° produced in 98 % yield the crystalline internal aldol product **7**, mp 167-168° (from CH_3OH), infrared max 3620, 3450, 1740 $cm.^{-1}$ ($CHCl_3$), pmr max 3.30 ppm (s, H at C(1')) , 2.25 ppm (dd, J=4, 2 Hz, 2 H at C (8)), R_f 0.28 (PE - E, 1 : 1). The hydroxy ketone **7** was converted quantitatively to the hydroxy thioketal **8** using excess ethanedithiol with boron trifluoride etherate as catalyst at 25° for 30 min ; found for **8**, mp 109-109.5°, infrared max 3610, 3450 $cm.^{-1}$ ($CHCl_3$), R_f 0.26 (PE - E, 5 : 1). Desulfurization of **8** using Raney nickel (W - 2) washed free of ethanol with dimethoxyethane and in dimethoxyethane as solvent at 25° for 10 min and reflux for 30 min gave the alcohol **9**, infrared max 3610, 3450 $cm.^{-1}$ R_f 0.28 (PE - E, 5 : 1) (89% yield). Oxidation of **9** with PCC in methylene chloride (25°, 1 hr) afforded in 90% yield the ketone **10**, infrared max 1710 $cm.^{-1}$ R_f 0.45 (PE - E, 5 : 1). Oximation of **10** was effected using 7.5 equiv of hydroxylamine hydrochloride in pyridine at 95 - 100° for 15 hr and the oxime **11**, R_f 0.43 (PE - E, 4 : 1) so obtained (88% yield) was reduced using the Pt-Rh Nishimura catalyst in acetic acid at 100 atm and 25° for 65 hr to give a mixture of epimeric amines (**12**) which was directly formylated by reaction with formic-acetic anhydride in pyridine at -15 to + 5° for 1.5 hr to produce a mixture of epimeric formamides (**13**), R_f 0.31 and 0.43 (hexane - ethyl acetate 1 : 1) in approximately equal amounts. After chromatographic purification each of the isomeric formamides **13** was dehydrated by treatment with a small excess of methanesulfonyl chloride in pyridine at 25° for 1 hr to provide in each case the corresponding isocyanide (> 98% yield). The more polar formamide **13** afforded a product chromatographically and spectroscopically identical with naturally derived 2-isocyanopupukeanane (**2**)[10] , infrared max 2150 $cm.^{-1}$ ($CHCl_3$), R_f 0.40 (benzene - hexane 1 : 1). The less polar formamide **13** gave epi - 2 - isocyanopupukeanane (**14**), infrared max 2150 $cm.^{-1}$ ($CHCl_3$), R_f 0.48 (benzene - hexane , 1 : 1).

Partial pmr data for **2** and **14** ($CDCl_3$ solution, 80 MHz) are as follows; for **2** : ppm 3.06 (1 H, br s, CHNC), 1.18 (3 H, s, CH_3), 0.94 (3 H, s, CH_3), and 0.84 (6 H, d, J=7 Hz, 2 CH_3) ; for **14** : ppm 3.15 (1 H, br s, CHNC), 1.10 (3 H, s, CH_3), 0.92 (3 H, s, CH_3), and 0.82 (6 H, d, J=7 Hz, 2 CH_3).[11]



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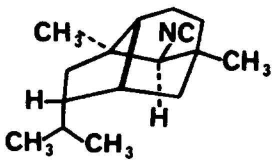

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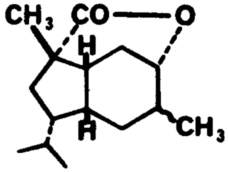

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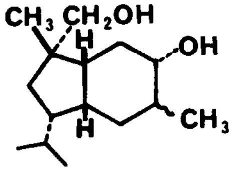

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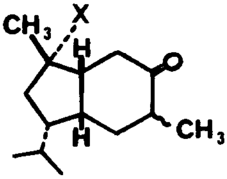
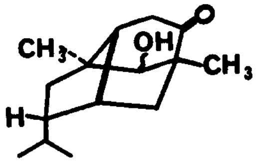


5, X = CH$_2$OH
6, X = CHO



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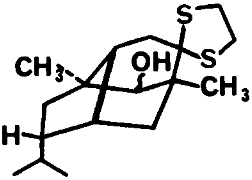

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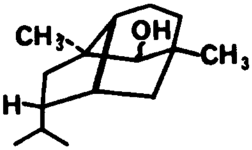

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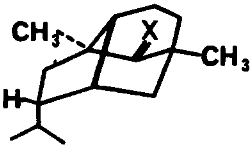
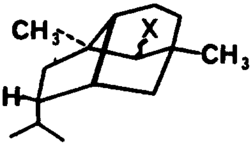
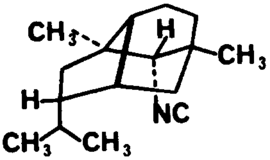


10, X = O
11, X = NOH



12, X = NH$_2$
13, X = NHCHO



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1. B. J. Burreson, P. J. Scheuer, J. Finer, and J. Clardy, J. Am. Chem. Soc., **97**, 4763 (1975).

2. Prof. P. J. Scheuer, personal communication.

3. E. J. Corey, M. Lehforouz and M. Ishiguro, J. Am. Chem. Soc., **101**, 1608 (1979).

4. For another synthesis of **1**, see H. Yamamoto and H. L. Sham, ibid., **101**, 1609 (1979).

5. The structure and stereochemistry of the isomeric congenor of **1** have recently been shown to be as indicated in **2** by an x-ray crystallographic study.[2] In accordance with this finding, formula **2** in ref. 3 requires modification to the 2-epimeric structure.

6. E. J. Corey and J. W. Suggs, Tetrahedron Letters, 2647 (1975).

7. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained using chromatographically purified and homogeneous samples of each synthetic intermediate.

8. All thin layer chromatographic data were obtained using silica gel plates.

9. S. Nishimura, Bull. Chem. Soc. Jpn., **33**, 566 (1960); **34**, 32 (1961).

10. Kindly provided by Profs. P. J. Scheuer and Hisashi Yamamoto.

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