

Stereoselective Synthesis of 2-Isocyanoallopupukeanane

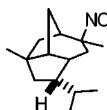
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ABSTRACT



A stereoselective synthesis of 2-isocyanoallopupukeanane (**3**) in ca. 5% overall yield features an intramolecular Diels–Alder reaction to establish a bridged cyclopentane ring to the existing bicyclo[3.2.1]octane unit.

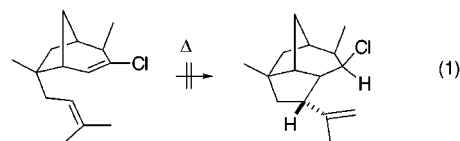
The pupukeananes constitute a novel family of marine sesquiterpenoids. These isonitriles are subdivided into three classes according to their carbon skeletons as represented by the isocyanopupukeananes [e.g., 2-isocyanopupukeanane (**1a**)¹ and 9-isocyanopupukeanane (**1b**)²], 9-isocyanoneopupukeanane (**2**),³ and 2-isocyanoallopupukeanane (**3**),⁴ respectively (Figure 1). Some, if not all, of these substances are implicated in delicate and interesting ecological interactions between sponges and nudibranch mollusks. The mollusks acquire such sponge metabolites as defense weapons against predators.

The novel structures of the isocyanopupukeananes have attracted much attention from synthetic chemists. Thus, synthetic approaches to both **1a** and **1b** were reported in 1979, and formal syntheses of the latter which terminated at 9-pupukeanone have also appeared in the literature.⁵ On the other hand, to our best knowledge, 2-isocyanoallopupukeanane **3**, which possesses a different skeleton, had not

yet been synthesized. We now wish to disclose our efforts in this direction.

Our synthesis started from the Diels–Alder adduct of cyclopentadiene and methyl acrylate. Methylation gave predominantly endo ester **4** (endo:exo 13:1) which was converted to lactone **5** by a phase transfer reaction⁶ (CHBr₃, KOH, Bu₃N; KOH; H⁺) in 56% yield. Reaction of **5** with MeMgI/CuI–Me₂S at –40 °C apparently proceeded via an S_N2' pathway, leading to acid **6** (81%). Next, we commenced a homologation reaction sequence: (1) LAH reduction, to **7a**, 98%; (2) tosylation, to **7b**, 98%; (3) cyanide displacement, to **8**, 99%; (4) DIBAL reduction, to **9**, 95%; (5) Wittig reaction, to **10**, 77%.

Initially with the chloro analogue of **10**, we attempted an intramolecular ene reaction (eq 1) but failed to generate the



desired tricycle.⁷ Actually, it was our inability to induce Cl/Li exchange that caused us to investigate the bromo series. The conversion of **10** to enone **11** by treatment with *t*-BuLi and then with *N*-methoxy-*N*-methylacetamide⁸ was ac-

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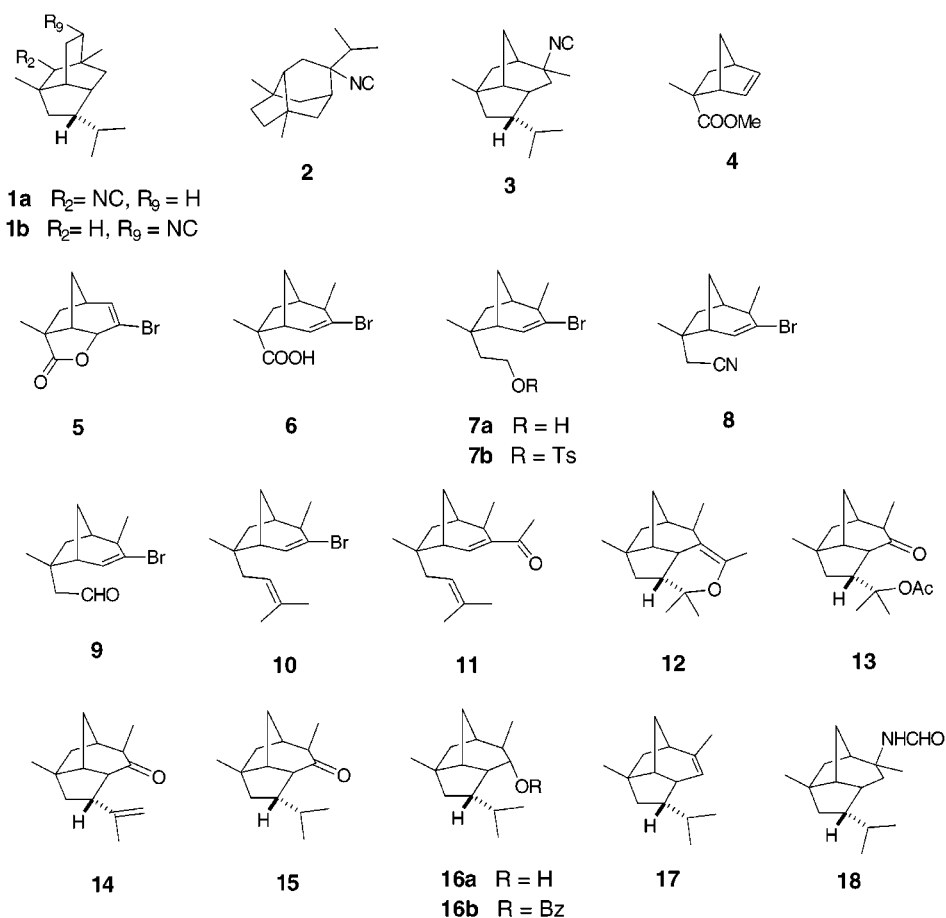


Figure 1.

completed in 54% yield. Unfortunately, the Lewis acid-catalyzed intramolecular ene reaction of this substrate was still ineffective. On the other hand, heating **11** in a sealed tube at 225 °C for 2 days afforded Diels–Alder cycloadduct **12** (86%). Molecular mechanics calculations indicated this product to be more stable than its stereoisomer in which the two methine hydrogen on the dihydropyran moiety are trans. Of course the conclusion of our synthesis confirmed the assignment.

Tetracyclic ether **12** was ozonized to give keto acetate **13** (89%). Pyrolysis of **13** furnished **14** (410 °C; 99%) which was hydrogenated (H_2 , PtO_2/MeOH ; 99%). The resulting ketone **15** was reduced with LAH (\rightarrow **16a**, 82%), benzoylated (\rightarrow **16b**, 96%), and passed through a Pyrex glass column maintained at 410 °C (\rightarrow **17**, 97%). The two final steps to

conclude the synthesis were a modified Ritter reaction⁹ (NaCN , H_2SO_4 , HOAc) to give **18** (70%) and dehydration with TsCl in pyridine at 0 °C under N_2 (90%).

Our synthesis of 2-isocyanoallopupukeanane **3** in ca. 5% overall yield consists of 19 steps from cyclopentadiene. The final product exhibits spectral characteristics consistent with those of the natural product, and various intermediates show proper analytical and spectral properties.

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Supporting Information Available: ^{13}C NMR spectra of compounds prepared. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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