Total Synthesis of (±)-2-Isocyanoallopupukeanane

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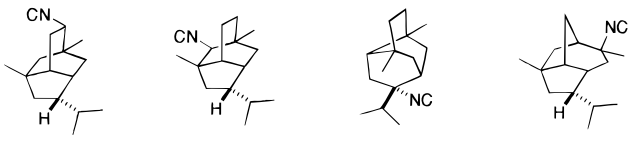
2-Isocyanoallopupukeanane (**4**) has been obtained in racemic form from methyl 2-*exo*-methylbicyclo-[2.2.1]hept-5-ene-2-*endo*-carboxylate via dibromocarbene addition, S_N2' displacement, chain extension, and elaboration of the unsaturated ketone **12c** which underwent an intramolecular hetero-Diels−Alder reaction to afford **13** containing all the skeletal carbon atoms. The dihydropyran unit was cleaved by ozonolysis to give the tricarbocyclic intermediate which required seven more steps to complete the synthesis.

The isocyanopupukeananes constitute a novel class of marine sesquiterpenes which are further subdivided into three types, according to their tricyclic skeletons. The initial observation that the nudibranch *Phyllidia varicosa* acquired defense substances from sponges of the *Ciocalypta* sp. led to subsequent isolation of 9-isocyanopupukeanane (**1**).[1] The Pupukea site of O'ahu, Hawaii, where the sponges were collected, forms the basis for the naming of the metabolites. In other words, 1,3-dimethyl-5-isopropyltricyclo[4.3.1.$0^{3,7}$]decane is now known as pupukeanane. 2-Isocyanopupukeanane (**2**) also possesses the same skeleton.[2] The subsequently found isomers 9-isocyanoneopupukeanane (**3**)[3] and 2-isocyanoallopupukeanane (**4**)[4] are biogenetically related to the isocyanopupukeananes by rearrangement pathways.



1 **2** **3** **4**

Because of the novel skeleton, **1** and **2** attracted much attention from synthetic chemists.[5] However, no report on the synthesis of **3** and **4** has been forthcoming prior to our dissemination.[6] Here we wish to give a full account of a synthetic effort which culminated in the access to racemic **4**.

Our initial plan is outlined in Scheme 1. Essentially, we decided to exploit an intramolecular ene reaction[7] for the construction of the third ring from a bridged bicyclo-[3.2.1]octane derivative which simultaneously allowed for the establishment of the isopropyl pendant in the desired configuration. Thus, our approach would be significantly different from the many routes to the isopupukeananes which featured hydrogenation as the key operation.

Our point of departure was ester **5** which was obtained by methylation[8] of the Diels−Alder adduct of cyclopentadiene and methyl acrylate. After **5** was submitted to a phase-transfer reaction with chloroform−50% KOH in the presence of $BnNEt_3Cl$ for 2 days at room temperature, lactone **6a** was isolated in 62.4% yield on acidic workup. This ring expansion transformation closely followed the preparation of a tricyclic intermediate for 8(*S*),14-cedranediol.[9] At this stage we attempted to either hydroborate the double bond of **6a** with borane in THF or epoxidize it with MCPBA, but both reactions failed. Therefore a convenient entry into the bicyclo[3.2.1]-octenone system was thwarted.

The next step of an alternative elaboration involved an S_N2' displacement using methylmagnesium iodide in the presence of CuI−dimethyl sulfide. A 93% yield of the acid **7a** was obtained. Chain elongation was then carried out by way of LAH reduction (→ **8a**, 90%), tosylation (→ **9a**, 98%), NaCN displacement (→ **10a**, 95.7%), DIBAL-H reduction (→ **11a**, 82%), and Wittig reaction with isopropylidenetriphenylphosphorane (→ **12a**, 80%). This highly efficient reaction sequence furnished the key intermediate for testing our concept (Scheme 2).

We were greatly disappointed on finding out that the thermal reaction was totally unpromising. Thus, on heating between 450 °C and 550 °C compound **12a** remained unchanged (eq 1), whereas it became charred when temperature was raised to 650 °C. The reluctance of **12a** to undergo an intramolecular ene reaction led us to consider modification to permit Lewis acid activation.[10] To that end we proceeded to introduce an acetyl group,

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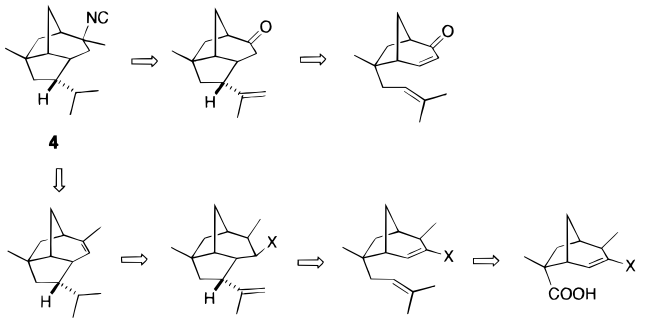
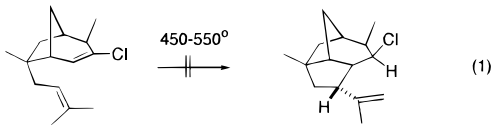
Scheme 1. Retrosynthetic Analysis of 2-Isocyanoallopupukeanane



but the action was unfortunately aborted by our inability to perform a Cl/Li exchange. Therefore we were forced to pursue the bromo series.



In the ring expansion that transformed **5** into **6b** tri-*n*-butylamine was found to be the best of several phase transfer catalysts tested and longer reaction time was required to give a 56% yield of the product. As expected, the series of intermediates behaved in essentially the same manner as the corresponding chloro compounds. Excellent yields were obtained.

With bromodiene **12b** in hand, we introduced the acetyl group by successive treatment with *t*-BuLi and *N*-methoxy-*N*-methylacetamide.[11] A 54% yield of **12c** was realized, and the critical Lewis acid-catalyzed reactions were confronted. At or below room temperature the exposure of **12c** to Et_2AlCl, $ZnBr_2$, $FeCl_3$, and several other Lewis acids did not furnish any tricyclic product, and under more vigorous conditions only decomposition was observed. Finally, reverting to the thermal process solved our problem, although the product was not derived from an ene reaction.

Thus, after heating a toluene solution of **12c** in a sealed tube at 210° for 2 days a compound showing four methyl groups in the ^{1}H-NMR spectrum at high field (>1.2 ppm) and one on a double bond (1.67 ppm) was produced (86% yield). The disappearance of the ketone group was evident from its IR spectrum. More detailed analysis of the NMR spectra readily indicated the product had arisen from an intramolecular hetero-Diels−Alder reaction. While we could not be certain that the two new stereocenters are as indicated in formula **13,** molecular mechanics calculations (Molecular Simulations Inc., Cerius 2 Version 3.7) on **13** and **13a** gave total energies of 38.7817 and 60.7012 kcal/mol, respectively. For confirmation of assignment of **13** we must await the final outcome of the synthesis.

The unexpected generation of **13** [or **13a**] necessitated a change of tactics in its modification in order to reach 2-isocyanoallopupukeanane. Accordingly, **13** was subjected to ozonolytic cleavage to afford the keto acetate **14**. Pyrolysis of **14** led to the unsaturated ketone **15** which was hydrogenated. At this point we considered its derivatization into a tosylhydrazone and use it in a Shapiro reaction. Unfortunately, the tosylhydrazone could not be prepared in the conventional fashion which we attributed to the presence of an *endo*-isopropyl group in **16**, since in that orientation it provided strong steric compression against the addition of tosylhydrazide to the ketone. The emergent hydroxy function would make the congestion intolerable.

Ketone **16** was reduced with LAH and then benzoylated to afford **17b**. The appearance of a multiplet at δ 2.80 in the ^{1}H NMR spectrum of **17b** rather intrigued us therefore a computer simulation (ACD Lab. H NMR dB program) was performed. On receiving the structure the computer yielded a spectrum containing a multiplet at δ 2.65 and it was identified as the signal of the ring junction proton at the β-carbon atom to the benzoyloxy group.

Next, pyrolytic elimination of benzoic acid from **17b** delivered the tricyclic olefin **18** in 97% yield. As expected for an *syn*-elimination, the double bond was located in the desired position. The remaining operation then required addition of [H/NC] to **19** in the Markovnikov sense. In the event, a Ritter reaction[12] using NaCN and H_2SO_4 in HOAc converted **18** to formamide **19** (70%), and the latter was dehydrated with TsCl in pyridine. The final product exhibits spectral characteristics in total agreement with those of an authentic sample.

In conclusion, we have completed a total synthesis of racemic 2-isocyanoallopupukeanane **4** starting from methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate, based on dibromocarbene addition and intramolecular hetero-Diels−Alder reaction as the key steps in modifying and construction of the ring system.

Experimental Section

General Methods. NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 74 MHz, respectively, for ^{1}H and ^{13}C absorptions. Chemical shifts reported in ppm relative to 0 for TMS. Electron impact mass spectra were measured at 70 eV. Silica gel (70−230 mesh) for chromatography was a Merck product. Melting points, determined with a Laboratory Devices apparatus, were uncorrected.

Methyl 2-*exo*-Methylbicylo[2.2.1]hept-5-ene-2-*endo*-carboxylate (5). *n*-Butyllithium (2.5 M in hexane, 18.9 mL, 47.4 mmol) was added to a solution of diisopropylamine (6.8 mL, 47.4 mmol) in anhydrous THF (94 mL) at −78 °C under N_2, and the mixture was stirred for 20 min. Methyl bicyclo-[2.2.2]hept-5-ene-2-carboxylate (6.0 g, 39.5 mmol) in anhydrous THF (42 mL) was added dropwise to the LDA solution, followed by methyl iodide (2.7 mL, 43.4 mmol) at the end of 1 h. The reaction mixture was stirred for an additional 2 h, warmed to ambient temperature, and poured into ice/water. The resultant mixture was extracted with ether, washed with H_2O, 10% $Na_2S_2O_3$ solution, and brine, and dried over $MgSO_4$. Filtration and removal of the solvent afforded **5** (6.43 g, 98%; *endo* ester:*exo* ester = 12.77:1) as an oil. IR (neat) ν_{max} 1732, 1291, 1283 cm^{-1}; ^{1}H NMR δ 1.39 (3H, s), 1.42−1.44 (1H, m), 1.53 (2H, d, J = 9.0 Hz), 1.88−1.92 (1H, dd, J = 12.0, 2.7 Hz), 2.77 (2H, d, J = 17.1 Hz), 3.58 (3H, s), 5.96−5.99 (1H, m), 6.08−6.11 (1H, m); ^{13}C NMR δ 26.2 (q), 37.7 (t), 42.4 (d), 46.6 (t), 49.8 (s), 50.7 (d), 51.3 (q), 135.1 (d), 137.5 (d), 177.7 (s).

3-Bromo-7-methyl-5-oxatricyclo[5.2.1.0^{4,8}]dec-2-en-6-one (6b). A mixture of ester **5** (6.0 g, 36.2 mmol), tributylamine (0.48 g, 2.6 mmol), benzene (25 mL), and 50% KOH (45.6 g) was stirred vigorously at ambient temperature under argon, while bromoform (20 mL) was added dropwise over a period

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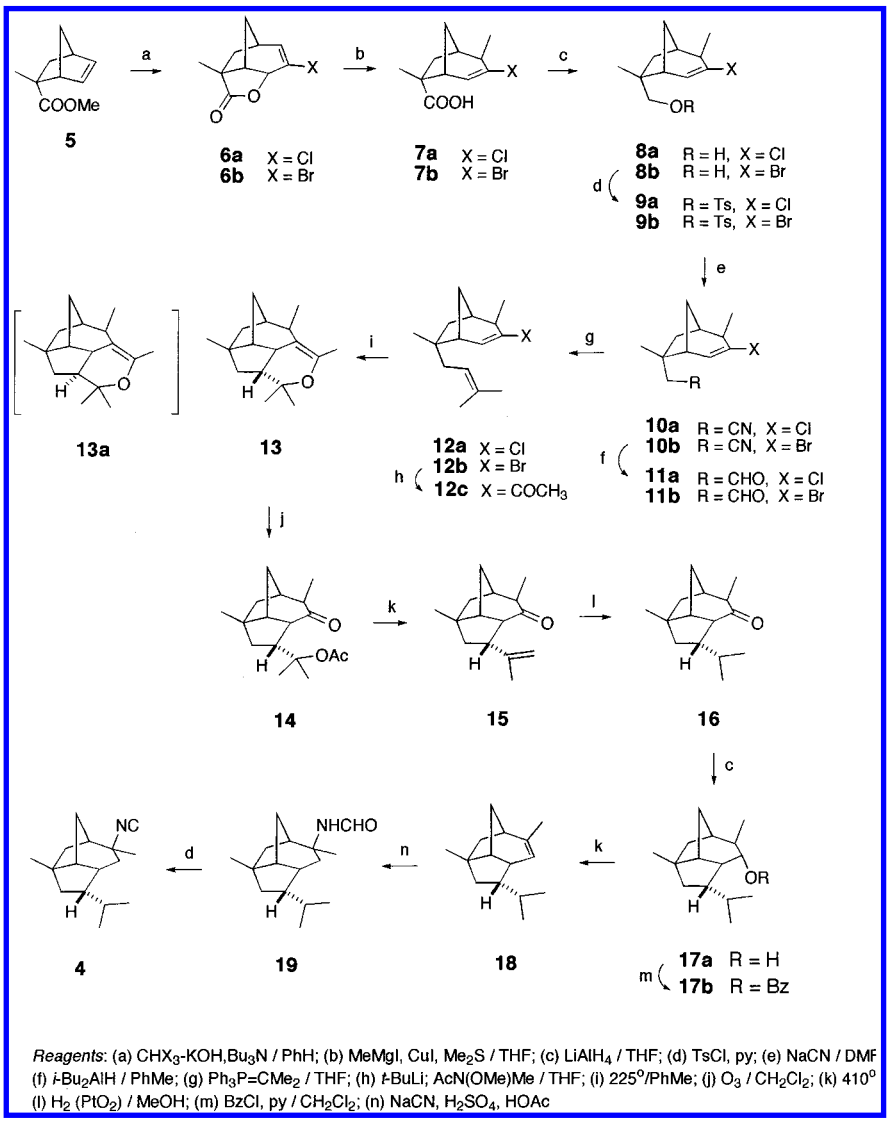
Scheme 2



of 8 h via a syringe pump. After 4 more days, the mixture was acidified with 6 N HCl and extracted with ether. The combined organic extracts were washed with H_2O and concentrated to yield a brown residue, which was heated with 10% KOH (60 mL) and THF (16 mL) under reflux for 12 h. The mixture was cooled to ambient temperature, acidified with 6 N HCl, and extracted with ether. The organic layer was washed with H_2O, aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of solvents and purification of the crude product by chromatography on silica gel (eluent: hexanes−EtOAc 4:1) yielded the lactone **6b** (4.94 g, 56%; mp 113−115°). IR (neat) ν_{max} 1768 cm^{-1}; ^1H NMR δ 1.32 (3H, s), 1.67 (1H, dd, J = 13.5, 6.0 Hz), 1.81−1.95 (2H, m), 2.06 (1H, dd, J = 13.5, 1.5 Hz), 2.68 (1H, q, J = 6.0, 3.0 Hz), 2.77 (1H, m), 5.0 (1H, d, J = 7.5 Hz), 6.64 (1H, d, J = 7.5 Hz); ^{13}C NMR δ 23.7 (q), 36.2 (t), 38.1 (d), 43.8 (t), 46.7 (s), 50.6 (d), 82.1 (d), 120.4 (s), 143.1 (d), 181.0 (s); HRMS m/z 241.9944 (241.9942 calcd for $C_{10}H_{11}$-$^{79}BrO_2$).

3-Chloro-7-methyl-5-oxatricyclo[5.2.1.0^{4,8}]dec-2-en-6-one (6a). The reaction of ester 5 (2.5 g, 15 mmol), benzyltriethylammonium chloride (0.125 g), 50% KOH (12 mL), and benzene (12 mL) with chloroform (20 mL) during 2 days gave, after subsequent processing in the same way, lactone **6a** (1.86 g, 62.4%; mp 95−96 °). IR (neat) ν_{max} 1768 cm^{-1}; ^1H NMR δ 1.22 (3H, s), 1.59−1.66 (1H, m), 1.76−1.84 (2H, m), 1.89−1.94 (1H, m), 2.65 (1H, br s), 2.75 (1H, br s), 4.84 (1H, d, J = 7.5 Hz), 6.33 (1H, d, J = 7.5 Hz); ^{13}C NMR δ 23.4 (q), 36.0 (t), 36.6 (d), 44.0 (t), 46.4 (s), 50.0 (d), 80.7 (d), 130.3 (s), 138.7 (d), 181.1 (s); HRMS m/z 200.0421 (200.0418 calcd for $C_{10}H_{11}{}^{37}$-ClO_2).

3-Bromo-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-ene-6-*endo*-carboxylic Acid (7b). To a cold solution (−40 °C) of copper(I) iodide (8.2 g, 43.2 mmol) and dimethyl sulfide (20 mL) and dry THF (165 mL) under argon was added a freshly prepared Grignard reagent from methyl iodide (10.8 mL, 0.17 mol) and magnesium (4.2 g, 0.17 mol) in ether (60 mL) over 0.5 h. The resulting mixture was stirred for 0.5 h, treated with a solution of lactone **6b** (10.5 g, 43.2 mmol) in dry THF (40 mL), and stirred for 2 h at −40 °C and warmed to −10 °C for 8 h more. It was poured into NH_4Cl solution and acidified with 6 N HCl. The organic solution was decanted from the solid and washed with 0.5 M NaOH. The alkaline solution was acidified and extracted with ether. Drying the ether solutions with $MgSO_4$ and concentration gave the desired acid **7b** (9.01 g, 81%) as a white solid, which was recrystallized from 2.5% EtOAc in hexane, mp 138−140 °C. IR (neat) ν_{max} 3300−2400 (br), 1701 cm^{-1}; ^1H NMR δ 1.15 (3H, d, J = 7.0 Hz), 1.32 (3H, s), 1.66−1.74 (3H, m), 2.19−2.37 (4H, m), 6.21 (1H, d, J = 7.0 Hz); ^{13}C NMR δ 19.6 (q), 27.3 (q), 28.3 (t), 40.5 (t), 41.2 (d), 45.9 (d), 48.9 (d), 57.5 (s), 129.2 (s), 132.9 (d), 193.0 (s); HRMS 258.0263 (258.0256 calcd for $C_{11}H_{15}{}^{79}BrO_2$). Anal. Calcd for $C_{11}H_{15}BrO_2$: C 50.98, H 5.83; found C 50.94, H 5.90.

3-Chloro-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-ene-6-*endo*-carboxylic Acid (7a). Employing the same procedure the lactone **6a** (1.26 g, 6.3 mmol) was converted to acid **7a**

(1.27 g, 93.3%). IR (neat) ν_{max} 3300−2400 (br), 1697 cm^{-1}; ^{1}H NMR δ 1.34 (3H, d, J = 7.0 Hz), 1.32 (3H, s), 1.65−1.72 (3H, m), 2.08−2.27 (3H, m), 2.36 (1H, br s), 5.96 (1H, d, J = 6.6 Hz); ^{13}C NMR δ 18.7 (q), 27.4 (q), 28.5 (t), 40.5 (t), 40.9 (d), 44.5 (d), 47.1 (d), 57.6 (s), 128.6 (s), 137.3 (d), 183.2 (s); HRMS 216.0733 (216.0731 calcd for $C_{11}H_{15}{}^{37}ClO_2$).

(3-Bromo-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methanol (8b). A solution of acid **7b** (6.0 g, 23.2 mmol) in THF (40 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.14 g, 30 mmol) in THF (15 mL). The mixture was brought up to reflux temperature and maintained overnight. On cooling the excess hydride was carefully destroyed with aqueous NH_4Cl followed by treatment with 2 N HCl. Filtration, drying with $MgSO_4$, and concentration afforded the alcohol **8b** (5.56 g, 98%; mp 74−75 °C). IR (neat) ν_{max} 3288 (br) cm^{-1}; ^{1}H NMR δ 1.01 (3H, s), 1.08 (2H, d, J = 7.2 Hz), 1.15 (1H, s), 1.52−1.66 (3H, m), 2.03−2.11 (2H, m), 2.93 (1H, s), 3.38 (1H, d, J = 10.2 Hz), 3.56 (1H, d, J = 10.2 Hz), 6.12 (1H, d, J = 6.0 Hz); ^{13}C NMR δ 19.5 (q), 25.4 (q), 28.7 (t), 41.3 (d), 42.2 (t), 45.2 (d), 49.2 (d), 51.8 (s), 69.7 (t), 127.7 (s), 133.8 (d); HRMS 244.0467 (244.0463 calcd for $C_{11}H_{17}{}^{79}BrO$).

(3-Chloro-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methanol (8a). The reduction of acid **7a** (0.26 g, 1.21 mmol) with LAH (0.092 g, 2.42 mmol) in THF (6 mL) afforded alcohol **8a** (0.42 g, 90%). IR (neat) ν_{max} 3355 (br) cm^{-1}; ^{1}H NMR δ 1.08 (3H, s), 1.15 (3H, d, J = 6.9 Hz), 1.21−1.23 (1H, m), 1.44 (2H, br s), 1.58−1.65 (2H, m), 1.71−1.73 (1H, m), 2.01−2.04 (1H, m), 2.12−2.17 (1H, m), 3.45 (1H, d, J = 10.2 Hz), 3.63 (1H, d, J = 10.2 Hz), 5.92 (1H, d, J = 6.9 Hz); ^{13}C NMR δ 18.6 (q), 25.5 (q), 29.0 (t), 41.0 (d), 42.2 (t), 43.8 (d), 47.5 (d), 51.9 (s), 69.6 (t), 129.5 (d), 135.8 (s); HRMS 200.0968 (200.0969 calcd for $C_{11}H_{17}{}^{35}ClO$).

(3-Bromo-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methyl Tosylate (9b). To the alcohol **8b** (2.05 g, 8.4 mmol) in pyridine (4 mL) at ambient temperature was added a solution of *p*-toluenesulfonyl chloride (3.19 g, 16.7 mmol) in pyridine (25 mL). The mixture was stirred overnight, poured into ice−water, and extracted with CH_2Cl_2. The organic layer was washed with 2 N HCl, H_2O, aqueous $NaHCO_3$, and brine and dried with $MgSO_4$. Concentration of the filtered solution gave tosylate **9b** (3.31 g, 98%; mp 115−117 °C). ^{1}H NMR δ 1.06 (3H, s), 1.09 (3H, d, J = 7.5 Hz), 1.50 (1H, s), 1.56−1.68 (3H, m), 1.96−2.14 (3H, m), 2.44 (3H, s), 3.86 (2H, s), 5.64 (1H, d, J = 7.5 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.77 (2H, d, J = 8.4 Hz); ^{13}C NMR δ 19.5 (q), 21.7 (q), 25.5 (q), 28.8 (t), 41.2 (d), 42.1 (t), 45.2 (d), 49.3 (d), 49.9 (s), 77.0 (t), 128.0 (d), 128.5 (s), 130.0 (d), 132.9 (d), 132.9 (s), 144.6 (s); HRMS 398.0555 (398.0552 calcd for $C_{18}H_{23}{}^{79}BrO_3S$).

(3-Chloro-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methyl Tosylate (9a). Alcohol **8a** (0.42 g, 2.08 mmol) in pyridine (1 mL) was tosylated with TsCl (0.76 g, 4 mmol) to give tosylate **9a** (0.728 g, 98%). ^{1}H NMR δ 0.95 (3H, s), 1.00 (3H, d, J = 6.6 Hz), 1.21−1.30 (1H, m), 1.47−1.60 (3H, m), 1.82.1.84 (1H, m), 1.98−2.02 (2H, m), 2.35 (3H, s), 3.77 (1H, d, J = 6 Hz), 3.83 (1H, d, J = 6 Hz), 5.38 (1H, d, J = 7.5 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.69 (2H, d, J = 8.1 Hz); ^{13}C NMR δ 18.3 (q), 21.4 (q), 25.2 (q), 28.7 (t), 40.6 (d), 41.7 (t), 43.5 (d), 47.1 (d), 49.6 (s), 76.8 (t), 127.6 (d), 128.2 (d), 129.7 (d), 132.3 (s), 136.5 (s), 144.6 (s); HRMS 356.1059 (356.1028 calcd for $C_{18}H_{23}{}^{37}ClO_3S$).

(3-Bromo-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methyl Cyanide (10b). A suspension of tosylate **9b** (3.30 g, 8.3 mmol) and NaCN (0.61 g, 12.4 mmol) in DMF (23 mL) was heated at 120 °C for 10h. The reaction mixture was cooled, diluted with ether, washed thoroughly with water, 2N HCl, and dried over $MgSO_4$. Evaporation of solvent gave the nitrile **10b** (2.10 g, 99%) as an oil. IR (neat) ν_{max} 2242 cm^{-1}; ^{1}H NMR δ 1.08 (3H, d, J = 7.2 Hz), 1.13 (3H, s), 1.26 (1H, d, J = 13.8 Hz), 1.63−1.80 (3H, m), 2.06−2.14 (3H, m), 2.39 (2H, br s), 6.06 (1H, d, J = 7.5 Hz); ^{13}C NMR δ 19.0 (q), 27.4 (q), 28.1 (t), 28.4 (t), 41.3 (d), 44.3 (t), 46.1 (d), 48.0 (s), 49.0 (d), 118.5 (s), 129.1 (s), 132.4 (d); HRMS 253.0459 (253.0467 calcd for $C_{12}H_{16}$-^{79}BrN).

(3-Chloro-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)methyl Cyanide (10a). Reaction of tosylate **9a** (0.69 g, 1.95 mmol) with NaCN (0.12 g, 2.44 mmol) in DMF (5 mL) afforded nitrile **10a** (0.39 g, 95.7%). IR (neat) ν_{max} 2240 cm^{-1}; ^{1}H NMR δ 1.08 (3H, d, J = 6.6 Hz), 1.14 (3H, s), 1.23−1.27 (1H, m), 1.58−1.62 (1H, m), 1.70−1.80 (2H, m), 2.00−2.01 (1H, m), 2.07−2.13 (2H, m), 2.38 (2H, s), 5.86 (1H, d, J = 7.2 Hz); ^{13}C NMR δ 17.9 (q), 27.2 (q), 27.9 (t), 28.4 (t), 40.8 (d), 44.1 (t), 44.6 (d), 47.0 (d), 47.9 (s), 118.2 (s), 127.8 (d), 137.0 (s); HRMS 211.0947 (211.0943 calcd for $C_{12}H_{16}{}^{37}ClN$).

2-(3-Bromo-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)acetaldehyde (11b). To a solution of nitrile **10b** (1.78 g, 7.01 mmol) in dry toluene at −78 °C under N_2 was added DIBAL (1.0 M in hexane, 8.40 mL) all at once. After 30 min, the reaction mixture was warmed to ambient temperature over 2.5 h. Methanol was added to quench the reaction. On further treatment with water, the mixture was stirred at room temperature for an additional 30 min. Filtration and evaporation gave a crude product which was purified by chromatography over silica (eluent EtOAc/hexane 7.5:92.5) to give pure aldehyde **11b** (1.71 g, 95%) as a colorless oil. IR (neat) ν_{max} 1722 cm^{-1}; ^{1}H NMR δ 1.07 (3H, s), 1.15 (3H, d, J = 6.6 Hz), 1.43 (1H, d, J = 13.2 Hz), 1.64−1.87 (4H, m), 2.12−2.21 (2H, m), 2.58 (2H, br s), 6.09 (1H, d, J = 7.2 Hz), 9.75 (1H, t, J = 2.4 Hz); ^{13}C NMR δ 19.4 (q), 27.9 (q), 28.4 (t), 41.3 (d), 45.6 (t), 47.0 (d), 47.8 (s), 49.6 (d), 53.9 (t), 128.7 (s), 133.9 (d), 202.8 (d); MS m/z 256, 258 ($M^{+\cdot}$).

2-(3-Chloro-2-*exo*,6-*exo*-dimethylbicyclo[3.2.1]oct-3-en-6-yl)acetaldehyde (11a). The nitrile **10a** (0.38 g, 1.81 mmol) was reduced with DIBAL to furnish aldehyde **11a** (0.315 g, 82%). IR (neat) ν_{max} 1720 cm^{-1}; ^{1}H NMR δ 1.07 (3H, s), 1.13 (3H, d, J = 7.5 Hz), 1.38 (1H, d, J = 13.2 Hz), 1.60−1.84 (3H, m), 2.02−2.04 (1H, m), 2.15−2.21 (2H, m), 2.55 (2H, s), 5.83 (1H, d, J = 7.2 Hz), 9.72 (1H, t, J = 2.3 Hz); ^{13}C NMR δ 18.3 (q), 27.8 (q), 28.4 (t), 40.7 (d), 45.35 (d), 45.37 (t), 47.6 (d), 47.6 (s), 53.7 (t), 129.3 (d), 136.6 (s), 202.5 (d); HRMS 212.0965 (212.0968 calcd for $C_{12}H_{17}{}^{35}ClO$).

3-Bromo-4-*exo*,7-*exo*-dimethyl-7-(3-methyl-2-butenyl)-bicyclo[3.2.1]oct-2-ene (12b). To a suspension of isopropyltriphenylphosphonium iodide (7.25 g, 16.74 mmol) in dry THF (70 mL) under Ar at 0 °C was added dropwise *n*-butyllithium (1.6M in hexane, 10.5 mL, 16.74 mmol). The resultant red solution was stirred at 0 °C for 20 min and treated with aldehyde **11b** (2.15 g, 8.37 mmol) in dry THF (10 mL). After 4 h, methanol was added and the mixture was evaporated to dryness. Chromatography of the crude mixture over silica gel (eluent: hexane) gave bromoalkene **12b** (1.82 g, 77%) as a colorless oil. ^{1}H NMR δ 0.95 (3H, s), 1.15 (3H, d, J = 6.9 Hz), 1.31 (1H, d, J = 13.5 Hz), 1.60 (3H, s), 1.70 (3H, s), 1.57−1.77 (4H, m), 1.94−1.98 (1H, m), 2.11−2.16 (3H, m), 5.09 (1H, t, J = 1.2 Hz), 6.11 (1H, d, J = 6.9 Hz); ^{13}C NMR δ 18.0 (q), 19.6 (q), 26.1 (q), 27.5 (q), 28.8 (t), 38.5 (t), 41.6 (d), 45.9 (t), 46.7 (d), 49.6 (d), 50.5 (s), 122.4 (d), 127.4 (s), 132.2 (s), 134.6 (d); HRMS 282.0990 (282.0984 calcd for $C_{15}H_{23}$79Br).

3-Chloro-4-*exo*,7-*exo*-dimethyl-7-(3-methyl-2-butenyl)-bicyclo[3.2.1]oct-2-ene (12a). The Wittig reaction of aldehyde **11a** (0.127 g, 0.6 mmol) with the ylide generated from isopropyltriphenylphosphonium iodide (0.50 g, 1.15 mmol) in dry THF (2 mL) at 0 °C led to chloroalkene **12a** (0.114 g, 80%). ^{1}H NMR δ 0.95 (3H, s), 1.14 (3H, d, J = 7.2 Hz), 1.02−1.29 (2H, m), 1.59 (3H, s), 1.70 (3H, s), 1.67−1.75 (2H, m), 1.97−2.12 (5H, m), 5.09 (1H, t, J = 4.3 Hz), 5.87 (1H, d, J = 7.5 Hz); ^{13}C NMR δ 17.9 (q), 18.6 (q), 26.0 (q), 27.5 (q), 28.8 (t), 38.5 (t), 41.2 (d), 45.3 (d), 45.8 (t), 47.8 (d), 50.5 (s), 122.4 (d), 130.4 (d), 132.4 (s), 135.5 (s); HRMS 240.1475 (240.1460 calcd for $C_{15}H_{23}{}^{37}Cl$).

1-{4-*exo*,7-*exo*-Dimethyl-7-*endo*-(3-methyl-2-butenyl)-bicyclo[3.2.1]oct-2-en-3-yl}-1-ethanone (12c). At −78 °C under argon, a solution of bromoalkene **12b** (2.70 g, 9.45 mmol) in dry THF (53 mL) was treated with *tert*-butyllithium (1.7 M in pentane, 14 mL, 23.86 mmol) dropwise and stirred for 40 min. A solution of freshly prepared *N*-methoxy-*N*-methylacetamide (2.95 g, 28.60 mmol) in dry THF (8 mL) was introduced at −78 °C. After 1 h, the reaction mixture was warmed to −5 °C and then quenched with saturated NH_4Cl.

The organic layer was separated and evaporated, and the residue extracted with ether, dried, and evaporated to afford, after chromatrography over silica (eluent: EtOAc/hexane 2.5:97.5), methyl ketone **12c** (1.24 g, 54%) as a colorless oil. IR (neat) ν_{max} 1668 cm^{-1}; ^1H NMR δ 0.93 (3H, s), 0.96 (3H, s), 1.13 (1H, d, J = 13.8 Hz), 1.53 (3H, s), 1.58−1.65 (2H, m), 1.67 (3H. s), 1.74 (1H, br s), 1.98 (3H, d, J = 6.9 Hz), 2.11 (1H, br s), 2.19 (3H, s), 2.38 (1H, d, J = 6.3 Hz), 5.08 (1H, t, J = 3.8 Hz), 6.91 (1H, d, J = 6.9 Hz); ^{13}C NMR δ 17.9 (q), 19.5 (q), 25.8 (q), 25.9 (q), 27.5 (q), 28.2 (t), 38.3 (t), 38.9 (d), 40.0 (d), 44.9 (d), 45.4 (t), 50.7 (s), 122.1 (d), 132.5 (s), 142.1 (s), 146.5 (d), 199.3 (s); HRMS 246.1981 (246.1985 calcd for $C_{17}H_{26}O$).

3-*exo*-6,6,8,13-*exo*-Pentamenthyl-7-oxatetracyclo-[7.3.1.0^{3,11}.0^{5,10}]tridec-8-ene (13). A solution of ketone **12c** (0.36 g, 1.46 mmol) in toluene (1 mL) was heated in a sealed tube for 2 days at 225 °C. Evaporation of the solution gave the cycloadduct, which was purified by chromatography over silica (eluent EtOAC/hexane 2.5:97.5) to afford **13** (0.31 g, 86%) as an oil. IR (neat) ν_{max} 1652 cm^{-1}; ^1H NMR δ 0.97 (3H, d, J = 7.2 Hz), 0.98 (3H, s), 1.13 (3H, s), 1.16 (3H, s), 1.28−1.38 (1H, m), 1.45−1.57 (3H, m), 1.67 (3H, s), 1.71−2.03 (5H, m), 2.25−2.34 (2H, m); ^{13}C NMR δ 16.8 (q), 18.1 (q), 26.5 (t), 27.4 (q), 28.6 (q), 30.2 (q), 37.8 (d), 38.0 (d), 42.1 (t), 42.5 (d), 45.0 (s), 48.1 (d), 49.7 (t), 54.2 (d), 73.5 (s), 103.9 (s), 143.7 (s); HRMS 246.1981 (246.1985 calcd for $C_{17}H_{26}O$).

1-(2-*exo*,7-*exo*-dimethyl-3-oxotricyclo[5.2.1.0^{4,8}]dec-5-yl)-1-methylethyl Acetate (14). A solution of vinyl ether **13** (0.9 g, 3.66 mmol) in CH_2Cl_2 (120 mL) was treated with excess ozone at −78 °C. After nitrogen purge, Me_2S was added, and allowed to warm to room temperature over 12 h. Evaporation of the solvent followed by extraction of the residue with ether and concentration of the dried extracts afforded the keto acetate **14**, which was purified by chromatography over silica (eluent: EtOAc/hexane 5:95) to give a colorless oil (0.91 g, 89%). IR (neat) ν_{max} 1737, 1697 cm^{-1}; ^1H NMR δ 1.03 (3H, d, J = 7.1 Hz), 1.19 (3H, s), 1.42 (3H, s), 1.62 (3H, s), 1.79 (3H, s), 1.83−2.19 (9H, m), 2.32 (1H, q, J = 14.2, 7.1 Hz), 2.95 (1H, t, J = 6.4 Hz); ^{13}C NMR δ 16.9 (q), 21.7 (q), 24.3 (q), 25.4 (q), 30.5 (q), 31.2 (t), 42.8 (t), 43.6 (d), 46.3 (s), 50.4 (d), 52.2 (t), 53.7 (d), 55.2 (d), 59.0 (d), 81.2 (s), 169.8 (s), 215.5 (s); HRMS 278.1884 (278.1883 calcd for $C_{17}H_{26}O_3$).

5-Isopropenyl-2-*exo*, 7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]-decan-3-one (15). A solution of the keto acetate **14** (0.22 g, 0.79 mmol) in toluene (5 mL) was added dropwise by means of an additional funnel into a vertically mounted Pyrex column (350 × 14 mm) placed in a tubular furnace at 410 °C, while a slow stream of nitrogen was passed through the column. The pyrolysate was collected at the bottom in a flask charged with aqueous $NaHCO_3$ and ether and immersed in ice/water. At the end of the pyrolysis the column was rinsed two more times with toluene, and the combined solution was diluted with ether, separated into layers, and dried over $MgSO_4$. Solvent removal gave the oily **15** (0.17 g, 99%). IR (neat) ν_{max} 1698 cm^{-1}; ^1H NMR δ 1.06 (3H, d, J = 7.3 Hz), 1.18 (3H, s), 1.28−1.31 (2H, m), 1.42−1.75 (4H, m), 1.85 (3H, s), 2.02 (1H, q, J = 7.3 Hz), 2.09 (1H, br s), 2.19 (1H, br s), 2.54−2.64 (1H, m), 2.91 (1H, t, J = 6.2 Hz), 4.51 (1H, s), 4.75 (1H, s); ^{13}C NMR δ 18.4 (q), 23.2 (q), 30.3 (q), 30.9 (t), 42.8 (d), 45.3 (t), 46.0 (s), 49.9 (d), 51.2 (d), 51.5 (t), 52.9 (d), 60.7 (d), 109.6 (t), 145.5 (s), 215.9 (s); HRMS 218.1663 (218.1671 calcd for $C_{15}H_{22}O$).

5-Isopropyl-2-*exo*,7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]decan-3-one (16). A platinum oxide (40 mg) catalyst suspended in methanol (5 mL) was reduced under a hydrogen atmosphere for 30 min and cooled to 0 °C, and keto alkene **15** (97 mg, 0.45 mmol) in methanol (5 mL) was added. After 3 h of stirring under H_2, the reaction mixture was filtered and concentrated in vacuo to yield the ketone **16** (0.12 g, 99%) as an oil. IR (neat) ν_{max} 1696 cm^{-1}; ^1H NMR δ 0.74 (3H, d, J = 6.3 Hz), 0.98 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 7.5 Hz), 1.10 (3H, s), 1.32−1.66 (6H, m), 1.75−1.97 (2H, m), 1.98−2.10 (2H, m), 2.14−2.21 (1H, m), 2.75 (1H, t, J = 6.6 Hz); ^{13}C NMR δ 18.3 (q), 21.9 (q), 22.2 (q), 30.5 (q), 30.5 (d), 31.0 (t), 42.9 (d), 46.3 (s), 48.1 (t), 51.5 (t), 52.1 (d), 53.1 (d), 60.2 (d), 217.6 (s). HRMS 220.1823 (220.1828 calcd for $C_{15}H_{24}O$).

5-Isopropyl-2-*exo*,7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]decan-3-ol (17a). To a stirred suspension of lithium aluminum hydride (55.0 mg, 1.45 mmol) in THF (2 mL) was added a solution of ketone **16** (0.16 g, 0.73 mmol) in THF (3 mL). After stirring at room temperature for 15 min, the mixture was refluxed overnight, cooled, and quenched with aqueous NH_4Cl. Further treatment with 2 N HCl, filtration, drying over $MgSO_4$, and concentration in vacuo afforded the alcohol **17a** (0.13 g, 82%) as a colorless oil. IR (neat) ν_{max} 3479 (br) cm^{-1}; ^1H NMR δ 0.81 (3H, d, J = 6.5 Hz), 0.98 (3H, d, J = 6.5 Hz), 1.03 (3H, d, J = 6.4 Hz), 1.05 (3H, s), 1.23 (1H, d, J = 5.0 Hz), 1.27 (1H, d, J = 5.0 Hz), 1.43−1.56 (4H, m), 1.67 (1H, d, J = 12.0 Hz), 1.79−2.05 (4H, m), 2.58 (1H, q, J = 12.0, 7.5 Hz), 3.51 (1H, dd, J = 10.3, 8.0 Hz); ^{13}C NMR δ 22.1 (q), 23.3 (q), 23.5 (q), 27.9 (t), 30.5 (d), 30.6 (q), 42.7 (d), 43.4 (d), 45.7 (d), 46.1 (s), 47.3 (t), 50.9 (t), 53.1 (d), 53.8 (d), 76.8 (d); HRMS 222.1989 (222.1985 calcd for $C_{15}H_{26}O$).

5-Isopropyl-2-*exo*,7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]dec-3-yl Benzoate (17b). Pyridine (0.11 mL, 1.35 mmol) was added to an ice-cooled stirred mixture of alcohol **17a** (0.1 g, 0.45 mmol) and benzoyl chloride (0.1 mL, 0.68 mmol) in CH_2Cl_2 (3 mL) under nitrogen. After stirring for 10 min at 0 °C, the resulting solution was warmed to room temperature, kept overnight, and extracted with ether. The organic solution was washed with water, dried, evaporated, and chromatographed over silica gel (eluent: hexane/EtOAc 97.5:2.5) to afford benzoate **17b** (0.17 g, 96%) as an oil. IR (neat) ν_{max} 1699 cm^{-1}; ^1H NMR δ 0.59 (3H, d, J = 6.3 Hz), 0.76 (3H, d, J = 6.5 Hz), 0.87 (3H, d, J = 6.7 Hz), 1.09 (3H, s), 1.15−1.24 (1H, m), 1.29−1.37 (2H, m), 1.53−1.63 (3H, m), 1.75−1.99 (3H, m), 2.04 (2H, t, J = 6.5 Hz), 2.78−2.85 (1H, m), 5.08 (1H, dd, J = 11.1, 7.9 Hz), 7.38−7.44 (2H, m), 7.50−7.55 (1H, m), 8.02 (2H, d, J = 5.0 Hz); ^{13}C NMR δ 21.4 (q), 22.6 (q), 23.3 (q), 28.1 (t), 20.9 (d), 30.5 (q), 39.6 (d), 43.3 (d), 43.7 (d), 46.2 (t), 47.5 (s), 50.9 (t), 53.2 (d), 53.3 (d), 78.3 (d), 128.3 (d), 129.5 (d), 130.7 (s), 132.6 (d), 166.8 (s); HRMS 326.2255 (326.2247 calcd for $C_{22}H_{30}O_2$).

5-Isopropyl-2-*exo*,7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]dec-2-ene (18). A solution of keto benzoate **17b** (0.1 g, 0.31 mmol) in toluene (2 mL) was added dropwise by means of an addition funnel into a vertically mounted Pyrex column (350 by 14 mm) containing loosely packed glass wool and maintained at 410 °C, while a slow stream of nitrogen was passed through the column. The pyrolysate was collected at the bottom in a flask charged with aqueous $NaHCO_3$ and ether and immersed in ice/water. After the pyrolysis the column was rinsed two more times with toluene then the combined solution was extracted with ether. Solvent removal gave the alkene **18** (69.0 mg, 97%) as an oil. ^1H NMR δ 0.78 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.2 Hz), 1.05 (3H, s), 1.39−1.47 (4H, m), 1.49−1.52 (2H, m), 1.57 (2H, m), 1.65 (3H, s), 1.89 (1H, br s), 2.09 (1H, br s), 2.64 (1H, br s), 5.01 (1H, br s); ^{13}C NMR δ 22.1 (q), 22.2 (q), 23.1 (q), 29.7 (d), 30.5 (q), 33.6 (t), 41.8 (d), 45.7 (d), 46.4 (s), 47.4 (t), 52.1 (t), 53.2 (d), 53.2 (d), 117.4 (d), 143.6 (s); HRMS 204.1881 (204.1879 calcd for $C_{15}H_{25}$).

***N*-(5-Isopropyl-2-*exo*,7-*exo*-dimethyltricyclo[5.2.1.0^{4,8}]-dec-2-yl)formamide (19).** A solution of alkene **18** (60.0 mg, 0.29 mmol) in acetic acid (2 mL) at 0 °C under N_2 was treated, in sequence, with NaCN (0.12 g, 2.35 mmol) and concentrated sulfuric acid (0.13 mL, 2.35 mmol). After 5 min, the cold bath was removed and the reaction was continued at ambient temperature for 24 h. After several drops of H_2O were introduced to the mixture, the reaction mixture was poured slowly into a stirred mixture of ice and Na_2CO_3. Addition of 10% NaOH was followed by extraction with ether. Drying the extracts over $MgSO_4$ and evaporation furnished a pale yellow viscous oil which was chromatographed over silica gel using hexane/EtOAc (70:30) as eluent to give the formamide **19** (50.0 mg, 70%). IR (neat) ν_{max} 3283, 1662 cm^{-1}; ^1H NMR δ 0.77 (3H, d, J = 6.4 Hz), 0.81 (3H, d, J = 6.2 Hz), 1.03 (3H, s), 1.22 (3H, s), 1.29 (1H, br s), 1.45−1.54 (6H, m), 1.74−1.85 (3H, m), 2.01 (3H, m), 6.11 (1H, br s), 8.19 (1H, d, J = 12.4 Hz); ^{13}C NMR δ 21.9 (q), 22.0 (q), 27.8 (d), 28.2 (q), 29.8 (t), 30.1 (q), 33.2 (t),

37.5 (d), 43.5 (t), 45.2 (t), 45.4 (s), 45.5 (d), 52.7 (d), 54.0 (d), 57.6 (s), 160.8 (d); HRMS 249.2088 (249.2094 calcd for $C_{16}H_{27}NO$).

2-Isocyanoallopupukeanane (4). *p*-Toluenesulfonyl chloride (61 mg, 0.32 mmol) was added in three portions to a stirred solution of formamide **19** (40 mg, 0.16 mmol) in pyridine (2 mL) at 0 °C under N_2. The mixture was allowed to stand at room temperature for 3 h, treated with ice/water, and extracted with hexane. Drying of the extracts over $MgSO_4$, followed by evaporation and chromatography over silica gel (eluent: hexane/EtOAc 95:5), gave the product **4** (34 mg, 90%) as a colorless oil. IR (neat) ν_{max} 2125 cm^{-1}; ^1H NMR δ 0.77 (3H, d, $J = 6.4$ Hz), 0.82 (3H, d, $J = 6.4$ Hz), 1.04 (3H, s), 1.15 (1H, m), 1.31 (3H, br s), 1.44−1.59 (6H, m), 1.72−1.79 (3H, m), 2.06 (1H, t, $J = 5.9$ Hz), 2.10−2.16 (1H, m), 2.19 (1H, d, $J = 13.6$ Hz); ^{13}C NMR δ 21.8 (q), 21.9 (q), 28.3 (d), 29.0 (q), 29.4 (t), 29.9 (q), 33.2 (t), 37.5 (d), 44.4 (t), 45.3 (t), 45.4 (s), 45.5 (d), 52.7 (d), 53.8 (d), 61.2 (s), 153.1 (s); HRMS 231.1989 (231.1988 calcd for $C_{16}H_{25}N$).

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

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