JOC Article

Total Syntheses of (±)-Axamide-1 and (±)-Axisonitrile-1 via 6-*Exo-dig* Radical Cyclization

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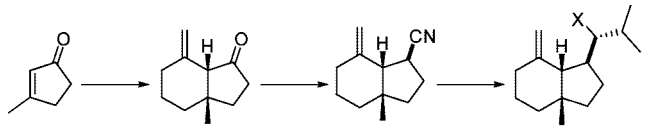
Received December 5, 2008



Axamide-1 (**1**) X = NHCHO

Axisonitrile-1 (**2**) X = NC

Total syntheses of (±)-axamide-1 (**1**) and (±)-axisonitrile-1 (**2**) were accomplished by using the α-carbonyl radical cyclization as the key step. Thienylcyanocuprate **24** mediated conjugated addition of 5-(trimethylsilyl)-4-pentynylmagnesium chloride (**23**) to 3-methylcyclopenten-1-one (**22**) and subsequent treatment with TMSCl afforded silyl enol ether **25**. Iodination of **25** with NaI and *m*-CPBA afforded α-iodoketone **21**. 6-*Exo-dig* radical cyclization of **21** and subsequent desilylation furnished hydroindane derivative **20**. Bicyclic ketone **20** was converted to nitrile **19** via a three-step sequence involving Luche reduction, mesylation, and S_N2 substitution reaction. Finally, tandem alkylation−reduction on nitrile **19** and subsequent functional group transformations afforded (±)-axamide-1 (**1**) and (±)-axisonitrile-1 (**2**).

Introduction

(+)-Axamide-1 (**1**), (+)-axisonitrile-1 (**2**), and (+)-axisothiocyanate-1 (**3**) are representatives of a small family of sesquiterpenoids isolated from the marine sponge *Axinella cannabina*.[1−7] The structural characteristics of these sesquiterpenoids are a *cis*-fused hexahydroindane framework with four contiguous stereogenic centers and a functionalized side chain containing a stereogenic carbon (Figure 1). In 1973, Cafieri and co-workers[1] first isolated axane-type sesquiterpenoids. Later the absolute stereochemistry[3,7] of axane sesquiterpenoids was determined on the basis of an X-ray crystal structure analysis. Axane sesquiterpenoids displayed a modest number of biological properties. Axisonitrile-1 (**2**) even at low concentration (8 ppm) is a potent ichthyotoxin toward the marine damselfish *Chromis chromis* and the fresh water gold fish *Carassius carassius*.[6,8] The interesting biological properties coupled with unusual structural features of these sesquiterpenoids have attracted considerable attention from synthetic chemists.

In 1987, Piers et al. reported the first total syntheses of racemic axamide-1 (**1**) and axisonitrile-1 (**2**) employing a novel annulation sequence as the key step to assemble the perhydroindane skeleton.[9] In a series of accounts, Hart and co-workers reported the total syntheses of axane sesquiterpenoids using an intramolecular conjugate addition reaction as the key step.[10] The first asymmetric total syntheses of the antipodes of the natural products (+)-axamide-4 and (+)-axisonitrile-4 have also been described.[11] In all of these synthetic efforts, we found that six-membered ring compounds were used as starting materials to construct the central perhydroindane skeleton.

We envisioned that our methodology, radical cyclization of an α-iodoketone,[12] could be applied toward the total synthesis of the axane family of natural products. Herein we describe our concise total syntheses of axamide-1 (**1**) and axisonitrile-1 (**2**) via the radical cyclization of α-iodoketone.

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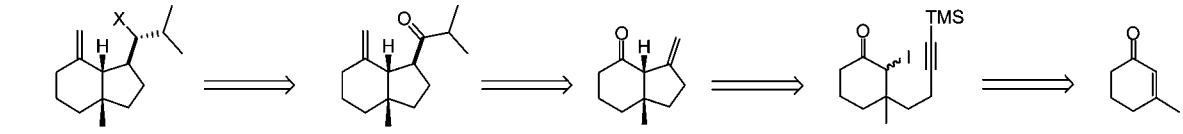
10.1021/jo802672t CCC: $40.75
Published on Web 01/27/2009

1 X = NHCHO (+)-Axamide-1
2 X = NC (+)-Axisonitrile-1
3 X = NCS (+)-Axisothiocyanate-1
4 X = NHCHO (+)-Axamide-4
5 X = NC (+)-Axisonitrile-4
6 X = NCS (+)-Axisothiocyanate-4

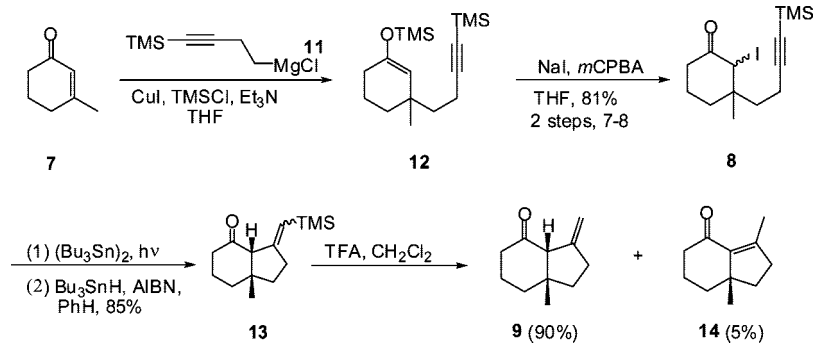
FIGURE 1. Structures of axane sesquiterpenoids.

SCHEME 1. Retrosynthetic Analysis Based on the 5-*Exo-dig* Radical Cyclization



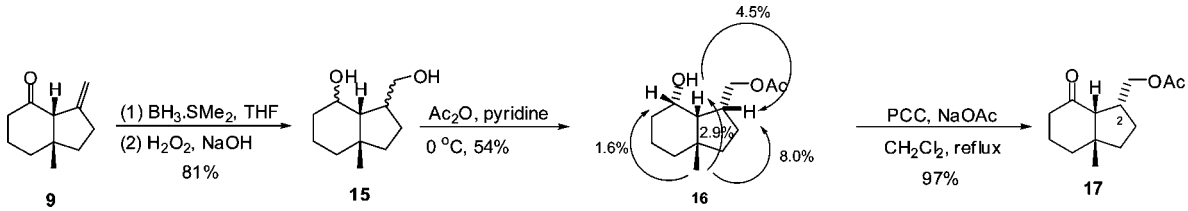
Axamide-1 (**1**) X = NHCHO
Axisonitrile-1 (**2**) X = NC
10 **9** **8** **7**

SCHEME 2. Synthesis of *cis*-Fused Hydroindane 9



7 **12** **8**
13 **9** (90%) **14** (5%)

SCHEME 3. Synthesis of Hydroindane 17



9 **15** **16** **17**

Results and Discussion

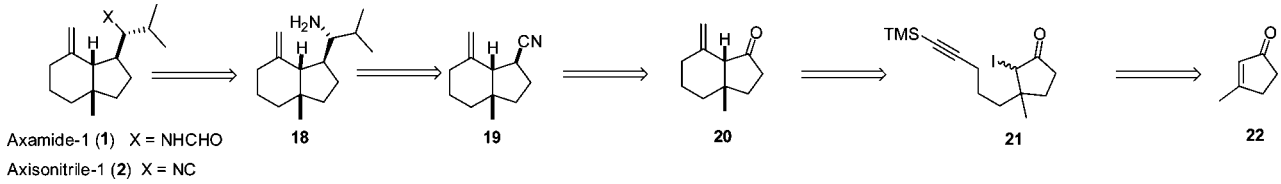
We envisaged that axamide-1 (**1**) and axisonitrile-1 (**2**) could be obtained from ketone **10**. Compound **10** could be derived from hexahyroindanone **9**. Compound **9** would be readily available via the 5-*exo-dig* radical cyclization of iodoketone **8**. Iodoketone **8** would be prepared by using our method starting from 3-methylcyclohexanone, Scheme 1.

CuI-mediated conjugated addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride (**11**) to 3-methylcyclohex-2-enone (**7**) followed by trapping the resulting enolate with chlorotrimethylsilane afforded the TMS-enol ether **12**. As compound **12** was labile to the silica gel chromatography, crude compound **12** was used immediately for the next step. Treatment of **12** with a mixture of NaI and *m*-CPBA furnished unstable iodoketone **8** as a mixture of diastereomers. Photolysis with a sunlamp in the presence of hexabutylditin, α-iodoketone **8** underwent *5-exo-dig* radical cyclization[13,19] smoothly. Subsequent reduction with tributyltin hydride and AIBN afforded vinylsilane ketone **13** as a mixture of *E*/*Z* isomers in 85% yield. Desilylation of ketone **13** with trifluoroacetic acid afforded ketone **9** along with a small amount of the isomeric enone **14** (Scheme 2).

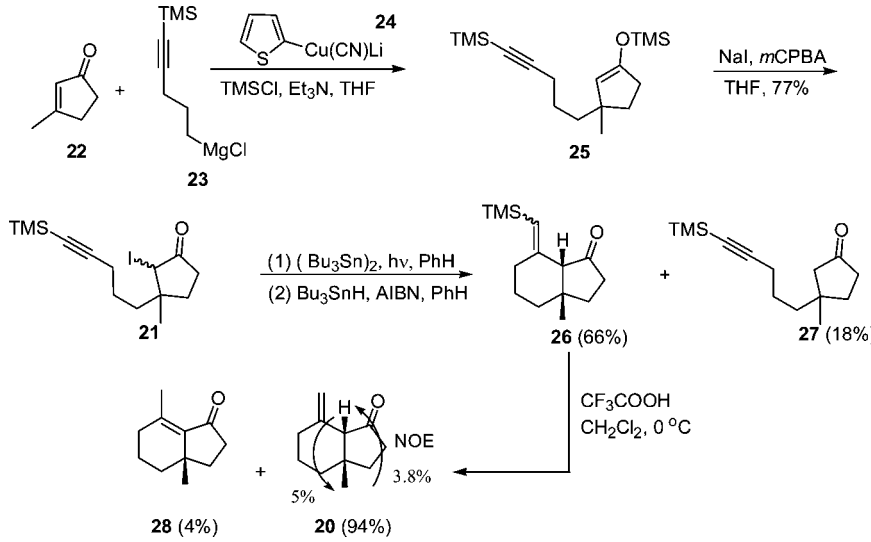
Hydroboration of ketone **9** with a solution of $BH_3 \cdot SMe_2$ complex in THF followed by oxidation with basic H_2O_2 produced a mixture of diastereomeric diol **15**.[12b] To protect the primary alcohol, the mixture of diastereomeric diol **15** was treated with Ac_2O in pyridine[14] to furnish acetate **16** with undesired stereochemistry along with a small amount of a mixture of diacetates identified as side products. The stereochemistry of acetate **16** was assigned on the basis of NOE experiment. Oxidation of the alcohol **16** with PCC[15] afforded ketone **17** (Scheme 3). In an effort to attain the requisite stereochemistry at C2 we examined various conditions for hydroboration and acetylation reactions. But we found always the undesired acetate **16** as the major product. Thus, the unsuccessful establishment of stereochemistry stopped us from proceeding with this approach toward the total syntheses.

Having unsuccessful attempts via the 5-*exo-dig* cyclization, we turned our attention toward an alternative protocol, the 6-*exo-*

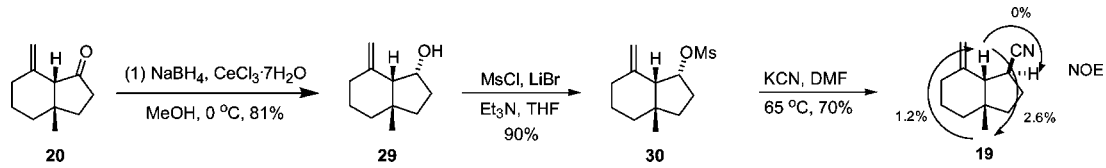
SCHEME 4. Retrosynthetic Analysis Based on 6-*Exo-dig* Radical Cyclization



SCHEME 5. Synthesis of *cis*-Fused Hydroindane 20



SCHEME 6. Synthesis of Nitrile 19



dig cyclization. The retrosynthetic analysis for the revised strategy is outlined in Scheme 4. We envisioned that these sesquiterpenoids could be obtained from Piers's intermediate **18**.[9] The requisite primary amine **18** might be synthesized from nitrile **19** according to Hall's tandem alkylation−reduction procedure.[17] Nitrile **19** could be derived from ketone **20** by a sequence of synthetic transformations. Bicyclic ketone **20** would be accessible through the 6-*exo-dig* radical cyclization followed by desilylation. Radical precursor **21** could be prepared according to our method from readily available 3-methylcyclopenten-1-one (**22**).

Our synthetic efforts commenced with readily available 3-methylcyclopenten-1-one (**22**). Lithium 2-thienylcyanocuprate (**24**) mediated conjugated addition of 5-(trimethylsilyl)-4-pentynylmagnesium chloride (**23**) to 3-methylcyclopenten-1-one (**22**)[18] followed by trapping the resulting enolate with trimethylchlorosilane yielded trimethylsilyl enol ether **25** (Scheme 5). Compound **25** was labile to silica gel chromatography and was used without purification for the next step. Thus, the crude product **25** was treated with a mixture of NaI and *m*-CPBA in THF to furnish the pivotal but rather unstable α-iodoketone **21** as a mixture of diastereoisomers. Isolation of these diastereoisomers and the assignments of the stereochemistry are inconsequential with respect to the subsequent synthetic transformations.

Irradiation of α-iodoketone **21** with a sunlamp in the presence of hexabutylditin effected iodine atom transfer cyclization.[19] Subsequent reduction with tributyltin hydride and AIBN afforded vinylsilane ketone **26** as a mixture of *E*/*Z* isomers (*E*/*Z* = 1/1.3)[20] along with the reduced product **27**. Exposure of the isomeric mixture of **26** to CF_3COOH in CH_2Cl_2 afforded bicyclic ketone **20** in good yield along with a small amount of isomeric enone **28** as the side product. The stereochemistry of **20** was assigned on the basis of the NOE experiments. In the literature,

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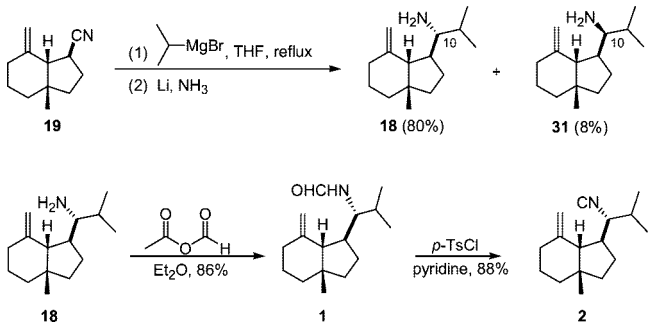
SCHEME 7. Total Syntheses of Axamide (1) and Axisonitrile (2)



the synthesis of *cis*-fused hydroindane with an exocyclic double bond has been reported with only a 7% yield via a Pd-catalyzed cycloalkenylation of silyl enol ethers.[21] It is noteworthy that we synthesized the pivotal *cis*-fused hydroindane **20** with 66% yield in two steps from iodo precursor **21**.

The *cis*-fused bicyclic ketone **20** was then subjected to stereoselective Luche reduction by using $NaBH_4/CeCl_3 \cdot 7H_2O$[22] to give the corresponding alcohol **29** in 80% yield (Scheme 6). Treatment of **29** with triethylamine and methanesulfonyl chloride produced mesylate **30**. Compound **30** was then treated with KCN to afford nitrile **19** in 70% yield. The stereochemistry of **19** was assigned on the basis of the NOE experiments.

In the final stage of total syntheses, crucial conversion of nitrile **19** to amine **18** was accomplished with Hall's tandem alkylation−reduction procedure.[17] Reaction of nitrile **19** with isopropylmagnesium chloride followed by reduction with lithium in ammonia afforded amine **18** in good yield along with a small amount of its C-10 epimer **31** (Scheme 7). The stereochemistry of amine **18** was assigned based on Piers's report.[23] Formylation of amine **18** with acetic formic anhydride finally afforded (±)-axamide-1 (**1**) in 86% yield. Subsequently, dehydration of (±)-axamide-1 (**1**) with *p*-toluenesulphonyl chloride furnished axisonitrile-1 (**2**) in 88% yield. The physical and spectral data of (±)-axamide-1 (**1**) and (±)-axisonitrile-1 (**2**) were in good agreement with the literature data.[9]

In summary, we have accomplished efficient total syntheses of (±)-axamide-1 (**1**) and (±)-axisonitrile-1 (**2**) in 16% and 14% overall yield, respectively. The 6-*exo-dig* radical cyclization was used as the key step to construct the pivotal hydroindane ring system **20**. Hall's tandem alkylation−reduction method was successfully applied to afford Piers's amine **18**. Finally, functional group transformations on **18** led to the total syntheses of **1** and **2**.

Experimental Section

2-Iodo-3-methyl-3-[4-(trimethylsilyl)-3-butynyl]-1-cyclohexanone (8). To a suspension of magnesium turnings (0.6 g, 26.8 mmol) in anhydrous THF (10 mL) was added 1,2-dibromoethane (0.05 mL). The reaction mixture was heated at reflux and then a solution of 1,2-dibromoethane (0.1 mL) in THF (25 mL) and 4-chloro-1-trimethylsilyl-1-butyne (**11**) (3.2 g, 19.6 mmol) was added dropwise over a period of 1 h. The reaction mixture was heated at reflux for 2 h and then cooled to −78 °C. CuI (4.2 g, 22.3 mmol) was added and the resulting mixture was stirred for 30 min. A solution of 3-methylcyclohex-2-enone (**7**) (1.1 g, 8.9 mmol) in THF (20 mL) and TMSCl (2.3 mL, 17.9 mmol) was add at −78 °C. After the reaction mixture was stirred for 10 min, Et_3N (2.2 mL, 17.9 mmol) was added. The reaction mixture was allowed to reach rt and then stirred for 16 h. Diluted with diethyl ether, the resulting mixture was filtered through Celite and the filtrate was extracted with diethyl ether (50 mL). The combined organic extract was washed with $NaHCO_3$ (50 mL) and brine (20 mL) and dried over $MgSO_4$. Concentration gave crude **12**, which was immediately used for the next step without purification. To a solution of crude product **12** and NaI (3.9 g, 25.9 mmol) in THF (100 mL) was added a solution of *m*-CPBA (70%, 0.95 g, 3.9 mmol) in THF (10 mL) dropwise at 0 °C. The reaction mixture was stirred for 3 h, diluted with water (20 mL), and extracted with diethyl ether (3 × 100 mL). The organic layer was washed with $Na_2S_2O_3$ (50 mL), $NaHCO_3$ (100 mL), and brine (20 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) afforded **8** (896 mg, 76%) as a yellow liquid. Data for **8**: IR (neat) ν 2959, 2175, 1710, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (s, 0.5H), 4.21 (s, 0.5H), 3.39−3.30 (m, 0.5H), 3.25−3.16 (m, 0.5H), 2.35−2.17 (m, 3H), 1.87−1.53 (m, 6H), 1.10 (s, 1.5H), 1.04 (s, 1.5H), 0.13 (s, 4.5H), 0.12 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 203.7, 106.0, 105.7, 84.9, 84.5, 48.6, 46.5, 41.4, 40.5, 39.5, 35.5, 34.8, 34.3, 31.9, 31.0, 26.5, 20.8, 20.7, 19.5, 15.0, 13.8; MS (EI) *m*/*z* 362 (M^+, 11), 347 (77), 234 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{23}IOSi$ 362.0563, found 362.0580.

7a-Methyl-3-[(*E* and *Z*)-1-(trimethylsilyl)methylidene]perhydro-4-indenone (13). To a solution of **8** (0.5 g, 1.4 mmol) in anhydrous benzene (92 mL) was added $(Bu_3Sn)_2$ (0.4 mL, 1.6 mmol). The reaction mixture was refluxed and simultaneously irradiated with a sunlamp for 1 h. The sunlamp was removed and the reaction mixture was allowed to cool to rt. A solution of Bu_3SnH (0.8 mL, 2.97 mmol) and AIBN (60 mg, 0.30 mmol) was added to the reaction mixture and refluxed for 1 h. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) gave **13** (*E*/*Z* = 1/2.4) (613 mg, 88%) as a colorless liquid. Data for **13**: IR (neat) ν 3054, 2987, 1605, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57−5.56 (dd, J = 3.2, 1.6 Hz, 0.5H), 5.12−5.10 (dd, J = 5.1, 2.5 Hz, 0.5 H), 2.79 (br s, 1H), 2.54−2.23 (m, 4H), 1.91−1.41 (m, 6H), 1.02 (s, 1.5H), 0.98 (s, 1.5H), −0.01 (s, 4.5H), −0.05 (s, 4.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 210.2, 158.8, 157.1, 124.9, 121.8, 68.9, 65.6, 48.0, 46.4, 40.9, 39.2, 37.6, 34.2, 32.9, 32.4, 31.6, 30.3, 28.4, 25.0, 23.0, 22.3, −0.27, −0.77; MS (EI) *m*/*z* 236 (M^+, 7), 221 (100), 183 (29), 147 (68); HRMS (EI) *m*/*z* calcd for $C_{14}H_{24}OSi$ 236.1596, found 236.1604.

7a-Methyl-3-methyleneperhydro-4-indenone (9). To a solution of **13** (359 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) was added CF_3COOH (0.1 mL, 1.5 mmol) at 0 °C. The reaction mixture was stirred for 10 min and neutralized with NaOH (1 N) solution. The resulting mixture was extracted with CH_2Cl_2 (100 mL). The combined organic layer was washed with $NaHCO_3$ (20 mL) and brine (20 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) afforded **9** (226 mg, 97%) as a colorless liquid. Data for **9**: IR (neat) ν 3054, 2987, 1703, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (q, J = 2.4 Hz, 1H), 4.70 (q, J = 2.4 Hz, 1H), 2.81 (br s, 1H), 2.59−2.34 (m, 3H), 1.90−1.60 (m, 5H), 1.58−1.36 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 150.4, 108.3, 66.1, 47.4, 38.5, 37.7, 31.9, 30.0, 25.3, 22.4; MS (EI) *m*/*z* 164 (M^+, 1), 150 (12), 149 (100), 71 (11); HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}O$ 164.1201, found 164.1215.

3-(Hydroxymethyl)-7a-methylperhydro-4-indenol (15). To a solution of **9** (146 mg, 0.9 mmol) in THF (2.5 mL) was added $BH_3 \cdot SMe_2$ (0.7 M in THF, 0.7 mL, 0.9 mmol) dropwise at 25 °C. The reaction mixture was stirred at 25 °C for 12 h and then cooled to 0 °C. At this temperature MeOH (2 mL) was added dropwise. The resulting mixture was concentrated and diluted with THF (5

(20) The ratio of *E* and *Z* isomer was determined from the ^1H NMR spectrum of compounds **13** and **27**.

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(23) Compounds **1** and **2** were prepared according to the modified Piers's procedure (see ref 9a).

mL). To the resulting solution was added a mixture of of 3 N NaOH (5 mL), H_2O_2 (30%, 5 mL), and THF (10 mL) at 25 °C. The reaction mixture was stirred for 24 h and brine (10 mL) was added. The mixture was extracted with ether (20 mL). The combined extract was washed with brine (10 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 2:1) gave **15** (134 mg, 82%) as a colorless liquid. Data for **15**: IR (neat) ν 3298, 2931, 2868, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10−4.00 (m, 1 H), 3.87 (dd, J = 10.6, 10.6 Hz, 1H), 3.66−3.60 (m, 2H), 3.57−3.49 (m, 1H), 2.74−2.66 (m, 1H), 2.60−2.53 (m, 1H), 1.87−1.18 (m, 20H), 1.07 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.5, 68.5, 64.9, 63.7, 53.9, 52.3, 43.5, 43.0, 39.0, 35.6, 35.5, 33.0, 32.6, 32.3, 30.7, 27.2, 25.4, 23.7, 19.9, 19.8; MS (EI) *m/z* 184 (M^+, 1), 135 (19), 82 (41), 57 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1470.

(7-Hydroxy-3a-methyloctahydro-1*H*-inden-1-yl)methyl Acetate (16). To a solution of **15** (297 mg, 1.6 mmol) in pyridine (0.13 mL) was added acetic anhydride (0.07 mL, 0.75 mmol) at 0 °C. The reaction was stirred for 24 h at 0 °C. Diluted with ethyl acetate (20 mL), the organic layer was washed with brine (5 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) gave **16** (209 mg, 54%). Data for **16**: IR (neat) ν 3385, 1740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.44 (dd, J = 10.4, 8 Hz, 1H), 4.25 (dd, J = 10.4, 8 Hz, 1H), 3.98 (dd, J = 8.8, 4 Hz, 1H), 2.67−2.60 (m, 1H), 1.97 (s, 3H), 1.85−1.19 (m, 11H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 67.7, 66.8, 50.7, 41.9, 39.7, 36.2, 34.9, 33.4, 30.2, 26.8, 21.1, 16.8; MS (EI) *m/z* 226 (M^+, <1), 166 (10), 148 (31), 96 (47), 85 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1576.

(3a-Methyl-7-oxooctahydro-1*H*-inden-1-yl)methyl Acetate (17). To a mixture of PCC (437.6 mg, 2.04 mmol) and NaOAc (166.9 mg, 2.04 mmol) in CH_2Cl_2 (2 mL) was added a solution of **16** (77 mg, 0.34 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was heated at reflux for 1 h. The resulting mixture was filtered through Celite and the filtrate was extracted with CH_2Cl_2 (20 mL). The combined organic extract was washed with brine (5 mL) and dried over $MgSO_4$. Concentration of CH_2Cl_2 gave **17** (73 mg, 97%). Data for **17**: IR (neat) ν_{max} 1741, 1708 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.23 (dd, J = 11.1, 5.4 Hz, 1H), 4.18 (dd, J = 11.1, 5.4 Hz, 1H), 2.62−2.58 (m, 1H), 2.41 (d, J = 9.3 Hz, 1H), 2.35−2.33 (m, 1H), 2.15−2.08 (m, 1H), 1.98 (s, 3H), 1.90−1.81 (m, 3H), 1.70−1.53 (m, 4H), 1.42−1.38(m, 1H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.7, 170.9, 65.9, 60.5, 46.4, 41.5, 41.2, 38.2, 34.8, 28.7, 27.4, 21.8, 20.9; MS (EI) *m/z* 224 (M^+, <1), 164 (30), 111 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1413.

2-Iodo-3-methyl-3-[5-(trimethylsilyl)pent-4-yn-1-yl]cyclopentanone (21). To a suspension of magnesium turnings (1.5 g, 61.2 mmol) in anhydrous THF (10 mL) was added 1,2-dibromoethane (0.05 mL). The heterogeneous reaction mixture was heated to reflux. Then a solution of 1,2-dibromoethane (0.1 mL) in THF (25 mL) and 5-chloro-1-trimethylsilyl-1-pentyne (3.6 g, 20.4 mmol) was added dropwise over a period of 1 h. The reaction mixture was heated at reflux for 2 h and then cooled to −78 °C. A solution of thienyl cyanocuprate **24** (20.4 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 30 min at −78 °C. A solution of compound **22** (1.96 g, 20.4 mmol) in THF (20 mL) and TMSCl (5.1 mL, 40.8 mmol) was added at −78 °C. After the reaction mixture was stirred for 10 min, Et_3N (5.0 mL, 40.8 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with diethyl ether (20 mL). The resulting mixture was filtered through Celite and extracted with diethyl ether (50 mL). The combined organic extract was washed with saturated $NaHCO_3$ (50 mL) and brine (20 mL) and dried over $MgSO_4$. Concentration gave crude **25**. The crude **25** was immediately used for the next step without purification. To a solution of crude product **25** and NaI (9.4 g, 62.4 mmol) in THF (200 mL) was added a solution of *m*-CPBA (70%, 10.8 g, 62.4 mmol) in THF (20 mL) dropwise at 0 °C. The reaction mixture was stirred for 3 h and then diluted with water (20 mL) and extracted with diethyl ether (3 × 100 mL). The organic layer was washed with saturated $Na_2S_2O_3$ solution (50 mL), saturated $NaHCO_3$ solution (100 mL), and brine (20 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) afforded **21** (5.7 g, 77%) as a yellow liquid. Data for **21**: IR (neat) ν_{max} 2959, 2173, 1708, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (s, 0.5H), 4.18 (s, 0.5H), 2.45 (dd, J = 9.6, 3.2 Hz, 0.4H), 2.40 (dd, J = 10, 3.2 Hz, 0.7H), 2.35−2.17 (m, 7H), 2.05−1.84 (m, 3H), 1.76−1.68 (m, 1H), 1.60−1.44 (m, 9H), 1.11 (s, 1.5H), 1.08 (s, 1.5H), 0.12 (s, 4.5H), 0.11 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 211.2, 106.7, 106.4, 85.3, 85.0, 45.5, 44.5, 42.4, 42.1, 41.6, 37.2, 32.8, 32.4, 32.3, 31.4, 25.7, 23.9, 23.8, 20.4, 20.2, 20.1, 0.1, 0.1; MS (EI) *m/z* 362 (M^+, 11), 347 (77), 234 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{23}IOSi$ 362.0563, found 362.0580.

3-Methyl-7-[(trimethylsilyl)methylene]octahydro-1*H*-inden-1-one (26). To a solution of **21** (1.0 g, 2.76 mmol) in dry benzene (6 mL) was added $(Bu_3Sn)_2$ (0.28 mL, 0.55 mmol). The reaction mixture was heated to reflux and simultaneously irradiated with a sunlamp for 1 h. The sunlamp was removed and the reaction mixture was allowed to cool to rt. A solution of Bu_3SnH (0.74 mL, 2.79 mmol) and AIBN (60 mg, 0.30 mmol) was added. The reaction mixture was heated at reflux for 1 h. Concentration and chromatography on a silica gel column (hexane/EtOAc 50:1) gave **26** (*E*/*Z* = 1/1.3) (430 mg, 66%) as a colorless liquid. Data for **26**: IR (neat) ν_{max} 3053, 2987, 1609, 1422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (br s, 0.5H), 5.19 (br s, 0.5H), 2.75 (br s, 1H), 2.45 (br s, 1H), 2.35−2.29 (m, 5H), 2.14−2.10 (m, 1H), 1.81−1.35 (m, 14H), 1.14 (s, 1.5H), 1.10 (s, 1.5H), 0.09 (s, 4.5H), 0.05 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 217.2, 151.7, 151.7, 129.0, 70.1, 64.7, 42.0, 41.9, 37.3, 35.4, 35.3, 35.0, 34.4, 33.2, 33.2, 31.5, 25.5, 25.4, 23.3, 23.3, 0.38, 0.23; MS (EI) *m/z* 236 (M^+, 5), 221 (90), 145 (31), 75 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{24}OSi$ 236.1596, found 236.1579.

2-Methyl-1-[(1*S)-3a-methyl-7-methyleneoctahydro-1*H*-inden-1-yl]propan-1-amine (18).** To a solution of **19** (114 mg, 0.65 mmol) in THF (6 mL) was added isopropylmagnesium bromide (2 M in THF, 0.97 mL). The reaction mixture was heated to for 72 h. After cooling to −78 °C, ammonia (25 mL) was condensed into the vessel. Lithium wire (122.7 mg, 1.73 mmol) was then added. After stirring for 20 min, sodium benzoate (111 mg, 2.45 mmol) was added. After evaporation of ammonia, the residue was diluted with diethyl ether (20 mL) and quenched with HCl (2 N, 5 mL). The resulting mixture was extracted with diethyl ether (30 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution (30 mL) and brine (20 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 10:1) furnished **18** (115 mg, 80%) as a colorless liquid. Data for **18**: IR (neat) ν_{max} 3396, 3067, 1642, 1462, 889 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 2H), 2.48 (dd, J = 8.4, 3.6 Hz, 1H), 2.27−2.00 (m, 3H), 1.92 (d, J = 10 Hz, 1H), 1.83−1.32 (m, 8H), 1.17−1.11 (m, 2H), 0.90 (s, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 110.0, 63.0, 60.9, 45.3, 44.8, 39.8, 33.6, 31.3, 30.6, 26.7, 24.7, 24.6, 20.9, 15.1; MS (EI) *m/z* 221 (M^+, 12), 178 (81), 161 (45), 149 (35), 113 (34), 91 (35), 70 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{27}N$ 221.2143, found 221.2156.

{2-Methyl-1-[(1*S)-3a-methyl-7-methyleneoctahydro-1*H*-inden-1-yl]propyl}formamide (1).** To a solution of **18** (20 mg, 0.09 mmol) in diethyl ether (1 mL) was added acetic formic anhydride (15 mg, 0.18 mmol) and the mixture was stirred for 10 h at rt. The reaction mixture was quenched with water (3 mL) and extracted with diethyl ether (10 mL). The combined organic extract was washed with brine (5 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 3:1) furnished **1** (19 mg, 90%) as a colorless liquid. Data for **1**: IR (neat) ν_{max} 3270, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J =

1.6 Hz, 0.66H), 7.85 (d, J = 12 Hz, 0.34H), 5.60 (br s, 0.34H), 5.14 (br s, 0.66H), 4.77 (t, J = 1.6 Hz, 0.34H), 4.71 (t, J = 1.5 Hz, 0.66H), 4.64 (d, J = 2.4 Hz, 0.66H), 4.60 (br s, 0.34H), 3.87 (td, J = 9.8, 3.6 Hz, 0.66H), 2.91 (ddd, J = 10.4, 8.8, 4.0 Hz, 0.34H), 2.42−1.81 (m, 6H), 1.63−1.30 (m, 5H), 1.17−1.12 (m, 1H), 0.90 (s, 1.02H), 0.88 (s, 1.98H), 0.85 (d, J = 6.8 Hz, 1.02H), 0.84 (d, J = 6.8 Hz, 1.98H), 0.76 (d, J = 6.8 Hz, 1.02H), 0.75 (d, J = 6.8 Hz, 1.98H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 161.7, 149.9, 148.3, 111.7, 110.8, 64.0, 59.5, 58.9, 58.2, 45.2, 44.8, 42.1, 40.8, 39.7, 33.1, 32.8, 31.2, 31.1, 30.4, 30.1, 27.8, 27.7, 24.5, 24.3, 20.6, 16.3, 16.2; MS (EI) m/z 249 (M^+, 2), 220 (5), 161 (14), 119 (10), 88 (100); HRMS (EI) m/z calcd for $C_{16}H_{27}NO$ 249.2093, found 249.2103.

(1*S,3a*S**)-1-(1-Isocyano-2-methylpropyl)-3a-methyl-7-methyleneoctahydro-1*H*-indene (2).** To a solution of **1** (9 mg, 0.04 mmol) in pyridine (0.2 mL) was added toluenesulfonyl chloride (12 mg, 0.09 mmol). The reaction mixture was stirred for 3 h at rt and then quenched with water (3 mL) and extracted with pentane (10 mL). The combined extract was washed with brine (5 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (hexane/EtOAc 3:1) furnished **2** (7.35 mg, 88%) as a colorless solid. Data for **2**: mp 45−46 °C; IR (neat) ν_{max} 2138, 1640, 1390, 1375, 895 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.78 (dd, J = 3.6, 2.4 Hz, 2H), 3.23−3.18 (m, 1H), 2.48−2.42 (m, 1H), 2.19−1.91 (m, 5H), 1.65−1.39 (m, 5H), 1.23−1.19 (m, 2H), 0.99 (d, J = 6.4 Hz, 3H), 0.96 (s, 3H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.3, 111.7, 67.6, 57.2, 45.2, 40.2, 39.7, 33.4, 31.3, 29.8, 27.7, 24.4, 24.4, 19.8, 19.1; MS (EI) m/z 231 (M^+, 27), 176 (47), 134 (100), 96 (97), 54 (77); HRMS (EI) m/z calcd for $C_{16}H_{25}N$ 231.1987, found 231.1998.

Acknowledgment. The financial support from National Science Council of the Republic of China (Taiwan) is gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures, complete characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802672T