Stereoselective Transformation of Enantiopure Cyclohexenol into *cis*-Hydrindan. An Enantioselective Formal Total Synthetic Route to (+)-Pumiliotoxin C

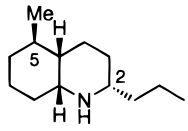
Masahiro Toyota, Takanobu Asoh, Masaki Matsuura, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

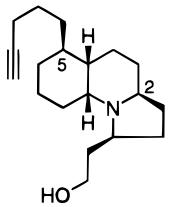
Received July 10, 1996

Introduction

Pumiliotoxin C (**1**)[1] was originally isolated from the skin extracts of *Dendrobates pumilio* (a striking colored Panamanian poison arrow frog[2]). X-ray analysis[3] of the crystalline hydrochloride of **1** established the structure, and the absolute configuration (2*S*,4a*S*,5*R*,8a*R*) of this toxin was confirmed in 1977 by its total synthesis.[4] Because of the scarcity of natural material (*e.g.*, 15 mg of **1** from 250 frogs)[5] coupled with the intriguing pharmacological properties,[6] pumiliotoxin C (**1**) and gephyrotoxin (**2**)[7] (isolated from Columbian poison frog *Dendrobates histrionicus*) have proved to be challenges in organic synthesis. These alkaloids have in common the unusual *cis*-decahydroquinoline ring system with side-chain substituents at the C-2 and C-5 positions (the C-2 side chain of **2** being attached at nitrogen). Pumiliotoxin C (**1**) has served as a target for the synthesis of *cis*-decahydroquinoline alkaloids and has frequently been used to illustrate new methodologies for construction of the decahydroquinoline ring system.



Pumiliotoxin C (1)



Gephyrotoxin (2)

While many approaches[8] for the preparation of pumiliotoxin C (**1**) have been put forward, there is still a need for general strategies for the construction of *cis*-decahydroquinoline alkaloids with control of both relative and absolute configurations. In recent years we have been interested in transformation of the enantiopure cyclohexenol **8** into *cis*-hydrindans, convertible to various kinds of biologically active natural products.[9] We expected that the above approach was suitable for an enantioselective synthesis of (+)-pumiliotoxin C (**1**). In this paper we would like to describe the details of the successful attainment of the above-mentioned application.

Results and Discussion

Preparation of Enantiopure Cyclohexenol 8 and Its Transformation into Alcohol 11. The synthesis of **8** started with the enantiomerically pure carboxylic acid **4**[10] [$[\alpha]^{32}_D$ −91.88 (*c* 1.8, MeOH) (lit.[11] $[\alpha]^{22}_D$ −95 (*c* 7, MeOH))], which Helmchen and co-workers[11] had prepared previously (Scheme 1). Treatment of the carboxylic acid **4** with iodine and potassium iodide in the presence of sodium hydrogen carbonate at 0 °C furnished the corresponding iodo lactone, which was next subjected to DIBALH reduction at −78 °C, providing the diol **5** (69% overall from **3**). After basic treatment of **5** with sodium hydride in DMF followed by benzylation, the epoxide **6** was obtained in 92% yield.

Conformational effects that favor *trans* diaxial ring-opening reaction (Fürst−Plattner rule[12]) are well known in the reactions of six-membered ring epoxides. The phenylselenium anion then approached from the β-side, and the diaxial compound **7** was produced in excellent yield. The β-hydroxy selenide **7** was oxidized by excess 30% hydrogen peroxide to the unstable selenoxide, which was immediately converted to the allylic alcohol **8**. The inversion of hydroxyl group in **8** under Mitsunobu reaction conditions [AcOH, DEAD, Ph_3P, HMPA, THF, 0 °C (81%); LAH, THF, 0 °C (82%) or *p*-nitrobenzoic acid,[13] Ph_3P, DEAD, THF, −30 °C → rt; LAH, THF (80% overall)] resulted in the formation of the alcohol **9**. Claisen rearrangement of **9** with triethyl orthoacetate was conducted in the presence of *o*-nitrophenol at 160

(1) Physiological property: (a) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, p 162. (b) *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, p 185.

(2) Witkop, B. *Experientia* **1971**, *27*, 1121−1248.

(3) Isolation: Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebigs Ann. Chem.* **1969**, *729*, 198−204.

(4) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204−207.

(5) Ibuka, T.; Masaki, N.; Saji, I.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2779−2790.

(6) Physiological property of **2**: Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1968**, *16*, 189−194.

(7) Isolation: Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128−1140.

(8) For chiral syntheses of natural (−)-pumiliotoxin C: (a) Reference 4 (b) Bonin, M.; Royer, J.; Grielson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1986**, *27*, 1569−1572. (c) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521−2523; *Tetrahedron* **1993**, *49*, 8805−8826. (d) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838−1839. (e) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213−9216. The unnatural (+)-epimer: (f) Reference 4. (g) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493−6502. For recent syntheses of (±)-pumiliotoxin C: (h) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697−5700. (i) Braudi, A.; Cordero, F. M.; Goti, A.; Guarua, A. *Tetrahedron Lett.* **1992**, *33*, 6697−6700. (j) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103−4110. (k) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652−6660. (l) Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279−280.

(9) (a) Toyota, M.; Matsuura, M.; Fukumoto, K. *Heterocycles* **1995**, *41*, 661−664. (b) Toyota, M.; Wada, T.; Matsuura, M.; Fukumoto, K. *Synlett* **1995**, 761−762.

(10) It is necessary at this point to comment on the determination of enantiomeric excess of our synthetic material **4**. Even though **4** and its derivatives appeared to be homogeneous by ^{1}H NMR, suggesting a very high diastereoselectivity for the asymmetric Diels−Alder reaction, a Mosher analysis was carried out to confirm the enantiomeric purity of **4**. First, the carboxylic acid **4** was reduced with LAH in THF at −78 °C to give rise to (1*S*)-3′-cyclohexenylmethanol (100%) and then the alcohol was condensed with (*S*)-(−)-2-methoxy-2-(trifluoromethyl)-phenylacetic acid (MTPA) to afford the corresponding Mosher ester in 62% yield after chromatography. Care was taken with this esterification to minimize fortuitous resolution of the Mosher ester diastereomers. The ester was shown to be >99% pure by comparison of its ^{1}H NMR spectrum (500 MHz) with that of a diastereomeric mixture deliberately synthesized from commercially available racemic alcohol and (−)-MTPA. Mosher ester: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

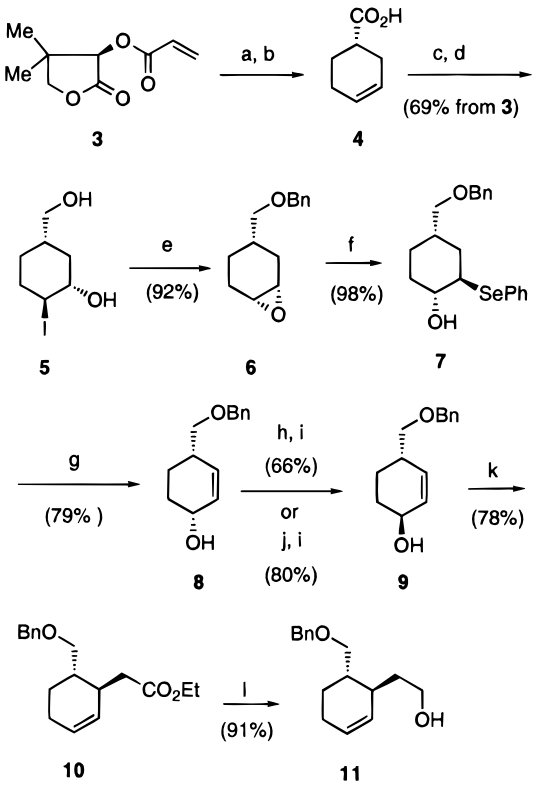
(11) Poll, T.; Sobczak, A.; Hartman, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095−3098

(12) (a) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275−283. (b) Smith, J. G. *Synthesis* **1984**, 629−656.

(13) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

S0022-3263(96)01308-4 CCC: $12.00

Scheme 1 [a]



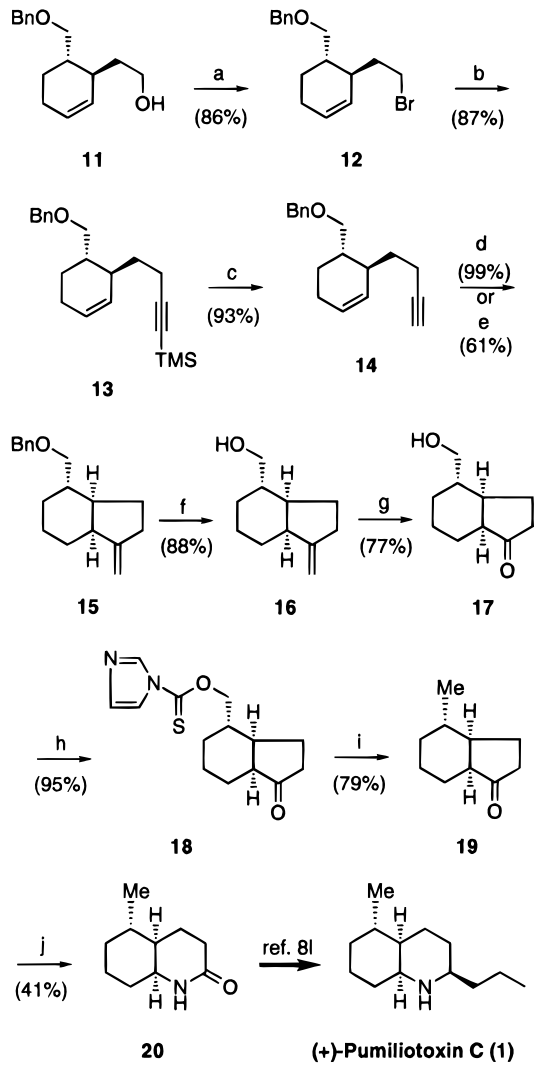
[a] Key: (a) 1,3-butadiene, $TiCl_4$, CH_2Cl_2−PE (4:1 v/v), −20 °C, 7 days; (b) LiOH·H_2O, THF−H_2O (5:4 v/v); (c) I_2, KI, $NaHCO_3$, CH_2Cl_2−H_2O (1:1 v/v), 0 °C; (d) DIBALH, THF, −78 °C; (e) NaH, BnBr, DMF, 0 °C → rt; (f) $(PhSe)_2$, $NaBH_4$, EtOH; (g) 30% H_2O_2, THF, 0 °C → rt; reflux, THF; (h) AcOH, HMPA, Ph_3P, DEAD, THF, 0 °C; (i) LAH, THF; (j) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF, −30 °C → rt; (k) triethyl orthoacetate, *o*-nitrophenol, 160 °C; (l) LAH, THF.

°C for 3 h to afford the ester **10** (78%), which was reduced with LAH to furnish the alcohol **11** in 91% yield.

Preparation of the *cis*-Hydrindan 15 *via* Radical Cyclization or Palladium-Catalyzed Reductive Cyclization. To prepare the requisite enyne **14** for both radical cyclization and palladium-catalyzed reductive cyclization, the compound **11** was converted efficiently into the bromide **12** (CBr_4, Ph_3P, 86%), which was treated with lithium (trimethylsilyl)acetylide in the presence of HMPA in THF to give rise to **13** in 87% yield (Scheme 2). The use of low temperature (−78 °C) and of HMPA as cosolvent is pivotal to the success of this coupling. Exposure of the TMS-acetylene **13** to 1 N methanolic sodium hydroxide furnished the key enyne **14** in 93% yield.

With the enyne **14** in hand, first of all, radical cyclization[14] for the construction of the *cis*-hydrindan ring system was examined. Treatment of **14** with tributyltin hydride in the presence of AIBN under refluxing benzene then served to generate the cyclization product, which suffered protodestannylation[14] with SiO_2 in CH_2Cl_2 for 2 days, so that the *exo*-olefin was isolated in 99% yield. In the enyne radical cyclization (**14** → **15**) high dilution condition and destannylation (>2 days) were necessary to complete the reaction. In view of these difficulties, a new enyne cyclization process was sought. As a result

Scheme 2 [a]



[a] Key: (a) CBr_4, Ph_3P, CH_2Cl_2; (b) LiC≡CTMS, HMPA, THF, −78 °C → rt; (c) 1 N NaOH, MeOH; (d) Bu_3SnH, AIBN, C_6H_6, reflux; SiO_2, CH_2Cl_2; (e) $(dba)_3Pd_2$·$CHCl_3$, BBEDA, PHMS, AcOH, 1,2-DCE; (f) Na, liquid NH_3, THF, −78 °C; (g) O_3, MeOH−CH_2Cl_2 (3:1 v/v), −78 °C; Me_2S; (h) $(imid)_2C$=S, DMAP, CH_2Cl_2, reflux; (i) Bu_3SnH, AIBN, C_6H_6, reflux; (j) NH_2OH·HCl, AcONa, MeOH; TsCl, NaOH, THF−H_2O (2:3 v/v).

of testing, the cyclization[15] of **14** in 1,2-dichloroethane (DCE) in the presence of $(dba)_3Pd_2$·$CHCl_3$ (2.5 mol %), *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) (5.0 mol %), polymethylhydrosiloxane (PMHS) (10 equiv), and acetic acid (1 equiv) proceeded quite nicely to give the *exo*-olefin **15** in 61% yield. This facile preparation of the *cis*-hydrindan **15** under mild conditions underscores the likely utility of this approach in target-directed synthesis.

Completion of Formal Total Synthesis of (+)-Pumiliotoxin C. Having found conditions for the preparation of **15**, the completion of a formal total synthesis of (+)-pumiliotoxin C (**1**) seemed imminent. The benzyl ether **15** was converted to the hydroxy ketone **17** by the standard procedure utilizing sodium in liquid ammonia (88%), followed by ozonolysis [O_3, MeOH−CH_2Cl_2 (3:1 v/v), −78 °C; Me_2S (77%)]. After treatment of **17** with 1,1′-(thiocarbonyl)diimidazole in the presence of

(14) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829−2831.

(15) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161−3163. For a recent review: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

4-(dimethylamino)pyridine (DMAP), the corresponding thioimidazolide **18** was obtained in 95% yield, whereupon **18** was subjected to radical deoxygenation with tributyltin hydride in the presence of AIBN, giving the ketone **19** (79%), which displays the same spectra with those provided by Mehta in a total synthesis of (±)-pumiliotoxin C (**1**).[8l] Finally, Beckmann rearrangement of **19** to the lactam **20** was conducted, in 41% yield, under standard conditions.[8l] The spectral properties (^{1}H NMR, IR, MS) of (+)-**20** were identical in all respects to those of (±)-**20** prepared by the established method.[16−18]

Experimental Section

General Procedures. Unless otherwise noted, nonaqueous reactions were carried out under argon in rigorously dried glassware. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Anhydrous solvents were freshly distilled as follows: Tetrahydrofuran (THF) and Et_2O were distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2) and pyridine were distilled under argon from CaH_2 and used immediately. Toluene and benzene (C_6H_6) were distilled under argon from phosphorus pentaoxide (P_2O_5). Dimethylformamide (DMF) was distilled under argon from $MgSO_4$ prior to use. Hexamethylphosphoramide (HMPA), 2-methyl-2-propanol, and EtOH were distilled under argon and used immediately. The concentration of commercially available butyllithium in hexane was checked by titration by using diphenylacetic acid.[19] Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out by using Merck 60 (230−400 mesh) or Cica 60 (spherical/40−100 μm) silica gel according to the procedure described by Still.[20] Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^{1}H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz except when otherwise noted. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. *J* values are in hertz.

(1*S*,2*S*,4*S*)-4-(Hydroxymethyl)-1-iodo-2-cyclohexanol (5). To a stirred solution of the Diels−Alder adduct (24.2 g, 0.10 mol), obtained (96%) from the acrylate **3** (19.5 g, 0.106 mol) and 1,3-butadiene (29.3 g, 0.543 mol) in the presence of $TiCl_4$ (2.34 g, 12.3 mmol) in a 5:1 mixture of CH_2Cl_2−petroleum ether (180 mL), in a mixture of THF (285 mL) and H_2O (228 mL) was added lithium hydroxide monohydrate (11.7 g, 0.28 mol) at rt, whereupon it was allowed to stir at the same temperature for 10 h. After removal of the solvent, the residue was acidified with 10% HCl solution (pH 4), and then the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to provide the carboxylic acid **4** (12.5 g) as a yellowish green oil. An analytical sample was obtained by chromatography eluting with hexane−EtOAc (2:1): $[\alpha]^{32}_D$ −91.88 (*c* 1.8, MeOH) [lit.[11] $[\alpha]^{22}$D −95 (*c* 7, MeOH)].

To a stirred solution of the above carboxylic acid **4** (12.5 g, 99.2 mmol) in an equivolume mixture of CH_2Cl_2 and H_2O (320 mL) were added $NaHCO_3$ (50 g, 0.60 mol), iodine (50 g, 0.20 mol), and potassium iodide (50 g, 0.30 mol) at 0 °C, whereupon it was allowed to stir at the same temperature for 1.5 h. The mixture was washed with saturated $Na_2S_2O_3$ solution and saturated NaCl solution and dried. After addition of pyridine (3 drops), the solvent was removed under reduced pressure to give the iodo lactone (24.3 g) as a yellowish crystal, which was used in the next step without purification.

To a stirred solution of the above iodo lactone (24.3 g, 96.4 mmol) in THF (500 mL) was added dropwise DIBALH (0.93 M in hexane, 220 mL, 0.24 mol) at −78 °C, whereupon it was allowed to stir at the same temperature for 0.5 h. After addition of H_2O (120 mL) at −78 °C, the resulting mixture was diluted with Et_2O (600 mL) and hexane (900 mL), and then the mixture was allowed to warm to rt. After 10 h of stirring, Celite and $MgSO_4$ were added, and then the resulting suspension was filtered through Celite. The filtrate was concentrated to furnish the diol **5** (18.8 g, 72% from **4**) as a powder: ^{1}H NMR δ 0.98−1.14 (2H, m), 1.55−1.77 (2H, m), 2.05−2.15 (2H, m), 2.48 (1H, dq, J = 4.0, 13.2), 3.39 (2H, t, J = 6.0), 3.58−3.68 (1H, m), 3.60 (1H, t, J = 5.3), 3.99 (1H, ddd, J = 4.5, 10.0, 14.0), 4.13 (1H, d, J = 5.3); ^{13}C NMR δ 32.0, 39.4, 39.7, 40.1, 40.3, 67.5, 76.5; HRMS(EI) calcd for $C_7H_{13}O_2I$ (M^+) 255.9960, found 255.9975.

(1*R*,2*S*,4*S*)-4-(Benzyloxymethyl)-1,2-epoxycyclohexane (6). To a stirred solution of the diol **5** (18.8 g, 73.5 mmol) in DMF (350 mL) was added NaH (60% in oil, 11.8 g, 0.30 mol) at 0 °C, whereupon it was allowed to stir at the same temperature for 15 min. Benzyl bromide (97%, 9.6 mL, 78.3 mmol) was added dropwise at ambient temperature, and then the resulting mixture was stirred at rt for 1 h. Saturated NH_4Cl solution was added dropwise at 0 °C and then the resulting mixture was extracted with Et_2O. The ethereal layer was washed with saturated NaCl solution, dried, and evaporated to leave an oil, which was chromatographed. Elution with a 20:1 mixture of hexane−EtOAc gave the epoxide **6** (16.8 g, 92%) as a colorless oil: $[\alpha]^{24}_D$ −40.9 (*c* 1.88, $CHCl_3$); IR 1118 cm^{-1}; ^{1}H NMR δ 1.15 (1H, dq, J = 5.0, 13.0), 1.47−1.78 (4H, m), 2.06−2.18 (2H, m), 3.12−3.15 (2H, m), 3.23 (2H, d, J = 6.5), 4.48 (2H, s), 7.28 (5H, m); ^{13}C NMR δ 21.2, 24.6, 27.4, 33.0, 51.1, 52.3, 72.8, 75.0, 127.3, 128.1, 138.3; MS(EI) *m/e* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.86; H, 8.21.

(1*R*,2*R*,4*S*)-4-(Benzyloxymethyl)-2-(phenylseleno)-1-cyclohexanol (7). To a stirred solution of diphenyl diselenide (8.0 g, 25.6 mmol) in EtOH (220 mL) was added $NaBH_4$ (4.0 g, 0.11 mmol) at ambient temperature, whereupon it was allowed to stir at rt for 0.5 h. An EtOH solution (10 mL) of the epoxide **6** (10.1 g, 46.2 mmol) was added at rt, and then the resulting mixture was stirred at the same temperature for 1 h. After removal of the solvent under reduced pressure, Et_2O and saturated NH_4Cl solution were added, and then the resulting mixture was separated. The ethereal layer was washed with saturated NaCl solution, dried, and evaporated to afford an oil, which was chromatographed. Elution with a 4:1 mixture of hexane−EtOAc gave the selenide **7** (17.1 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ −11.39 (*c* 1.99, $CHCl_3$); IR: 3400 cm^{-1}; ^{1}H NMR δ 1.45−1.76 (4H, m), 1.95−2.08 (2H, m), 3.36−3.46 (2H, m), 3.54−3.62 (1H, m), 4.36−4.63 (2H, m), 7.22−7.40 (8H, m) and 7.50−7.60 (2H, m); ^{13}C NMR δ 24.2, 28.6, 32.1, 33.9, 48.1, 70.8, 72.7, 72.9, 127.4, 127.7, 127.9, 128.9, 135.0, 138.3; MS(EI) *m/e* 376 (M^+). Anal. Calcd for $C_{20}H_{24}O_2Se$: C, 64.00; H, 6.44. Found: C, 63.72; H, 6.45.

(1*R*,4*S*)-4-(Benzyloxymethyl)-2-cyclohexen-1-ol (8). To a stirred solution of the selenide **7** (5.01 g, 13.4 mmol) in THF (100 mL) was added dropwise 30% H_2O_2 (15.6 mL, 0.14 mol) at 0 °C, whereupon it was allowed to stir at the same temperature for 0.5 h. The mixture was allowed to warm to rt over a period of 0.5 h, and then it was allowed to stir at the same temperature for 5 h. The organic layer was washed with saturated NaCl solution, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated NaCl solution, dried, and evaporated to leave the selenoxide (4.67 g,

(16) El-Abbady, A. M.; El-Ashry, M.; Doss, S. H. *Can. J. Chem.* **1969**, *47*, 1483−1486.

(17) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831−2843.

(18) In order to confirm the structures of compounds (+)-**19** and (+)-**20**, racemic **19** and **20** were prepared utilizing the established method.[16,17] Beginning with 2-methylcyclohexanone, condensation with dimethyl succinate in the presence of potassium *tert*-butoxide, followed by cyclization of the resulting half ester, led to the 3-carbomethoxy-4-methyl-4,5,6,7-tetrahydroindan-1-one in 57% overall yield. After hydrolysis and decarboxylation of the ester, 4-methyl-4,5,6,7-tetrahydroindan-1-one, obtained in 72% overall yield, was subjected to catalytic hydrogenation in the presence of propionic acid to provide (±)-**19** as a major stereoisomer; (±)-**19** was transformed into the racemic **20**. Direct comparison of the spectral data of (+)-**19** and (+)-**20** with those synthesized as above showed them to be completely superimposable. Since the lactam **20** has been transformed previously into pumiliotoxin C (**1**),[8l] the present enantioselective synthesis of **20** gives rise to the formal total synthetic route to (+)-pumiliotoxin C (**1**).

(19) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879−1880.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

90%) as colorless needles, which was used in the next step without purification.

A suspension of the above selenoxide (651 mg, 1.66 mmol) in THF (15 mL) was refluxed for 0.5 h. After removal of the solvent, the residue was chromatographed. Elution with a 20:7 mixture of hexane−EtOAc furnished the allylic alcohol **8** (320 mg, 88%) as a colorless oil; $[\alpha]^{24}_D$ −5.68 (*c* 1.09, $CHCl_3$); IR 3400, 1630 cm^{-1}; ^1H NMR δ 1.47−1.81 (4H, m), 2.31−2.44 (1H, m), 3.33−3.44 (2H, m), 4.11−4.20 (1H, br s), 4.51 (2H, s), 5.76−5.89 (2H, m), 7.22−7.40 (5H, m); ^{13}C NMR δ 21.1, 29.7, 35.9, 64.2, 72.9, 73.5, 127.4, 128.2, 130.4, 131.3 and 138.1; MS(EI) *m/e* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.27.

(1*S*,4*R*)-4-(Benzyloxymethyl)-2-cyclohexen-1-ol (9). Method A. To a stirred solution of **8** (54 mg, 0.25 mmol) in THF (5 mL) were added HMPA (0.1 mL, 0.54 mmol), PPh_3 (103 mg, 0.40 mmol), and acetic acid (13.6 μL, 0.40 mmol) at 0 °C. After 10 min, diethyl azodicarboxylate (62 μL, 0.40 mmol) was added at 0 °C, whereupon the resulting mixture was allowed to stir at the same temperature for 0.5 h. The mixture was diluted with 10% HCl solution, and then the resulting mixture was extracted with Et_2O (×3). The combined ethereal layers were washed with saturated NaCl solution, dried, and evaporated to afford an oil, which was chromatographed. Elution with a 10:3 mixture of hexane−EtOAc gave the acetate (52 mg, 81%) as a colorless oil: $[\alpha]^{26}_D$ −101.90 (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 1.38−1.68 (2H, m), 1.92−2.14 (2H, m), 2.07 (3H, s), 2.42−2.58 (1H, m), 3.27−3.39 (2H, m), 4.51 (2H, s), 5.22−5.32 (1H, m), 5.70 (1H, br d, *J* = 10.2), 5.85 (1H, br d, *J* = 10.2), 7.22−7.40 (5H, m); MS(EI) *m/e* 260 (M^+). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.89; H, 7.74. Found: C, 73.70; H, 7.72.

To a suspension of LAH (2.16 g, 63.6 mmol) in THF (100 mL) was added dropwise a THF solution (40 mL) of the acetate (4.25 g, 16.4 mmol) at 0 °C, whereupon it was allowed to stir at the same temperature for 1 h. H_2O (2 mL) was cautiously added followed by 15% aqueous NaOH solution (2 mL) and then H_2O (6 mL). After the mixture was stirred at rt for 20 min, hexane and $MgSO_4$ were added, whereupon the resulting suspension was filtered through Celite. The filtered solids were washed with Et_2O several times, then the combined filtrates were concentrated to provide an oil, which was chromatographed. Elution with a 1:1 mixture of hexane−EtOAc gave rise to the allylic alcohol **9** (2.93 g, 82%) as a colorless oil: $[\alpha]^{27}_D$ −82.83 (*c* 1.536, $CHCl_3$); IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR δ 1.28−1.54 (3H, m), 1.84−1.96 (1H, m), 2.02−2.14 (1H, m), 2.40−2.52 (1H, m), 3.28−3.40 (2H, m), 4.08−4.32 (1H, m), 4.53 (2H, s), 5.79 (2H, s), 7.22−7.40 (5H, m); MS(EI) *m/e* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.86; H, 8.39.

Method B. A mixture of Ph_3P (1.11 g, 4.25 mmol), *p*-nitrobenzoic acid (709.8 mg, 4.25 mmol), and DEAD (0.668 mL, 4.25 mmol) in THF (10 mL) was stirred at −30 °C for 20 min, and then to the resulting mixture was added dropwise a THF solution (2 mL) of the allylic alcohol **8** (712 mg, 3.27 mmol) at the same temperature. The mixture was allowed to warm to rt, whereupon it was allowed to stir for 2 h. Saturated $NaHCO_3$ solution was added, and then the resulting mixture was extracted with Et_2O. The organic layer was dried and evaporated to leave an oil, which was chromatographed. Elution with a 4:1 mixture of hexane−EtOAc provided the benzoate (1.35 g) as a colorless oil containing trace impurities: IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 1.40−1.52 (1H, m), 1.72−1.84 (1H, m), 1.92−2.08 (1H, m), 2.14−2.28 (1H, m), 3.33−3.44 (2H, m), 4.54 (2H, s), 5.55−5.59 (1H, m), 5.72 (1H, br d, *J* = 7.8), 5.86 (1H, br d, *J* = 9.9), 7.24−7.38 (5H, m); HRMS(EI) calcd for $C_{21}H_{21}NO_5$ (M^+) 367.1420, found 367.1406.

To a suspension of LAH (248 mg, 6.53 mmol) in THF (20 mL) was added dropwise a THF solution (5 mL) of the above benzoate (1.35 g) at ambient temperature, whereupon it was stirred at rt for 1 h. The solution was then cooled to 0 °C, and H_2O (0.25 mL) was carefully added followed by 15% NaOH solution (0.25 mL) and then H_2O (0.75 mL). After 0.5 h, $MgSO_4$ was added, whereupon the resulting suspension was filtered through Celite. The filtered solids were washed with Et_2O several times, and then the combined filtrates were concentrated to give an oil, which was chromatographed. Elution with a 5:2 mixture of hexane−EtOAc furnished the alcohol **9** (570 mg, 80% form **8**).

Ethyl (1′*S*,6′*S*)-2-[6′-(Benzyloxymethyl)-2′-cyclohexyl]acetate (10). A mixture of the allylic alcohol **9**, *o*-nitrophenol (5.0 mg, 0.014 mmol), and triethyl orthoacetate (4.0 mL, 28 mmol) was heated at 160 °C for 3 h on a Dean−Stark apparatus. After removal of the solvent, the residue was chromatographed. Elution with a 20:1 mixture of hexane−EtOAc provided the ethyl ester **10** (87.4 mg, 78%) as a colorless oil: $[\alpha]^{28}_D$ +48.22 (*c* 1.766, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 1.52−1.62 (1H, m), 1.24 (3H, t, *J* = 6.9), 1.67−1.85 (2H, m), 1.94−2.08 (2H, m), 2.24 (1H, dd, *J* = 13.8 and 7.2), 2.41−2.58 (2H, m), 3.40 (1H, dd, *J* = 9.9, 6.9), 3.48 (1H, dd, *J* = 9.9, 5.4), 4.12 (2H, q, *J* = 7.5), 4.50 (2H, dd, *J* = 17.1, 12.0), 5.52 (1H, dd, *J* = 9.9, 2.4), 5.71 (1H, br d, *J* = 9.9), 7.25−7.38 (5H, br s); MS (EI) 288 (M^+). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.22; H, 8.39.

(1′*S*,6′*S*)-2-[6′-(Benzyloxymethyl)-2′-cyclohexyl]-ethanol (11). To a suspension of LAH (250 mg, 6.58 mmol) in THF (30 mL) was added dropwise a solution of the ester **10** (1.04 g, 3.61 mmol) in THF (3 mL) at 0 °C, whereupon it was allowed to stir at rt for 2 h. The solution was then cooled to 0 °C, and H_2O (0.3 mL) was cautiously added followed by 15% aqueous NaOH (0.3 mL) and then H_2O (0.9 mL). After 20 min, hexane and $MgSO_4$ were added, whereupon the resulting suspension was filtered through Celite. The filtered solids were washed with Et_2O several times, and then the combined filtrates were concentrated to yield an oil, which was chromatographed. Elution with a 2:1 mixture of hexane−EtOAc gave rise to the alcohol **11** (805.3 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ +67.11 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR δ 1.44−2.19 (8H, m), 3.41 (1H, dd, *J* = 9.3, 6.3), 3.48 (1H, dd, *J* = 9.3, 5.4), 3.67−3.77 (2H, m), 4.51 (2H, dd, *J* = 16.5, 12.0), 5.57 (1H, br d, *J* = 9.9), 5.69 (1H, br d, *J* = 9.9), 7.25−7.35 (5H, m); HRMS(EI) calcd for $C_{16}H_{22}O_2$ (M^+) 246.1620, found 246.1605.

(1′*S*,6′*S*)-2-[6′-(Benzyloxymethyl)-2′-cyclohexyl]bromoethane (12). To a stirred solution of the alcohol **11** (1.53 g, 6.22 mmol) in CH_2Cl_2 (20 mL) were added CBr_4 (2.75 g, 8.29 mmol) and PPh_3 (2.39 g, 9.10 mmol) at 0 °C, whereupon it was allowed to stir at rt for 12 h. After removal of the solvent, the residue was chromatographed. Elution with a 20:1 mixture of hexane−EtOAc provided the bromide **12** (1.64 g, 86%) as a colorless oil: $[\alpha]^{26}_D$ +89.90 (*c* 0.400, $CHCl_3$); ^1H NMR δ 1.48−2.21 (8H, m), 3.36−3.53 (4H, m), 4.52 (2H, dd, *J* = 19.8, 12.0), 5.54 (1H, br d, *J* = 10.3), 7.22−7.48 (5H, m). Anal. Calcd for $C_{16}H_{21}BrO$: C, 62.14; H, 6.84; Br, 25.88. Found: C, 61.93; H, 6.78; Br, 25.96.

(1′*S*,6′*S*)-4-[6′-(Benzyloxymethyl)-2′-cyclohexyl]-1-(trimethylsilyl)butyne (13). To a stirred solution of (trimethylsilyl)acetylene (1.40 mL, 9.9 mmol) in THF (20 mL) was added dropwise butyllithium (15% hexane solution, 5.8 mL, 8.7 mmol) at −78 °C, whereupon it was allowed to warm to 0 °C. After 15 min, the mixture was recooled to −78 °C, and then a THF solution (2 mL) of the bromide **12** (1.70 g, 5.50 mmol) was added at −78 °C. After addition of HMPA (1.7 mL, 8.7 mmol), the resulting mixture was allowed to warm to rt over a period of 0.5 h. After 5 h of stirring, the mixture was quenched with saturated NH_4Cl solution, and then the resulting mixture was extracted with Et_2O. The ethereal layer was dried and evaporated to give an oil, which was chromatographed. Elution with a 20:1 mixture of hexane−EtOAc afforded the TMS-acetylene **13** (1.58 g, 87%) as a colorless oil: $[\alpha]^{22}_D$ + 86.34 (*c* 0.508, $CHCl_3$); IR ($CHCl_3$) 2150 cm^{-1}; ^1H NMR δ 0.13 (9H, s), 1.44−2.08 (8H, m), 2.12−2.36 (2H, m), 3.38 (1H, dd, *J* = 9.6, 7.5), 3.48 (1H, dd, *J* = 9.6, 5.1), 4.50 (2H, dd, *J* = 19.8, 12.0), 5.54 (1H, br d, *J* = 10.3), 5.69 (1H, br d, *J* = 10.3), 7.25−7.40 (5H, m); HRMS(EI) calcd for $C_{21}H_{20}OSi$ (M^+) 326.2066, found 326.2040.

(1′*S*,6′*S*)-4-[6′-(Benzyloxymethyl)-2′-cyclohexyl]butyne (14). A mixture of the TMS-acetylene **13** (1.17 g, 3.59 mmol) and 1 M NaOH−MeOH solution (50 mL) was stirred at rt for 3 h. After removal of the solvent, H_2O was added, and then the solution was extracted with Et_2O. The ethereal layer was washed with saturated NaCl solution, dried, and evaporated to give rise to an oil, which was chromatographed. Elution with a 20:1 mixture of hexane−EtOAc provided the acetylene **14** (833 mg, 93%) as a colorless oil: $[\alpha]^{22}_D$ +108.29 (*c* 0.310, $CHCl_3$); IR ($CHCl_3$) 2120 cm^{-1}; ^1H NMR δ 1.44−1.66 (2H, m), 1.67−1.92 (3H, m), 1.94−2.02 (3H, m), 2.02−2.14 (1H, m), 2.14−2.36 (2H, m), 3.38 (1H, dd, *J* = 9.3, 7.5), 3.49 (1H, dd, *J* = 9.3, 5.1), 4.50 (2H, dd, *J* = 18.0, 12.0), 5.55 (1H, br d, *J* = 9.9), 5.71 (1H, br d, *J* = 9.9), 7.25−7.40 (5H, m); HRMS(EI) calcd for $C_{18}H_{22}O$ (M^+) 254.1671, found 254.1627.

(3a*R*,4*S*,7a*R*)-4-(Benzyloxymethyl)-3a,4,5,6,7,7a-hexahydro-1-indene (15). Radical Cyclization. To a stirred solution

of the acetylene **14** (31 mg, 0.122 mmol) in C_6H_6 (6 mL) was added slowly a C_6H_6 solution (1 mL) of tributyltin hydride (0.04 mL, 0.123 mmol) and AIBN (2.0 mg, 0.012 mmol) under reflux, whereupon the resulting mixture was allowed to reflux for 3 h. After removal of the solvent, the residue was dissolved into CH_2Cl_2 (6 mL), and then SiO_2 (500 mg) was added. The resulting suspension was continued to stir at rt for 48 h. After filtration through Celite, the filtrate was concentrated to leave an oil, which was chromatographed. Elution with a 30:1 mixture of hexane−EtOAc furnished the *exo*-olefin **15** (31 mg, 99%) as a colorless oil: $[\alpha]^{24}_D$ + 101.71 (*c* 0.433, $CHCl_3$); IR ($CHCl_3$) 1660 cm^{-1}. ^1H NMR δ 1.02−1.90 (10H, m), 2.32−2.54 (3H, m), 3.28 (1H, dd, J = 9.3, 7.5), 3.48 (1H, dd, J = 9.3, 4.2), 4.49 (2H, dd, J = 21.2, 12.3), 4.78 (1H, d, J = 1.5), 4.88 (1H, d, J = 0.9), 7.22−7.41 (5H, m); MS(EI) *m/e* 256 (M^+). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 84.28; H, 9.43.

Palladium-Catalyzed Reductive Cyclization. To a stirred solution of the acetylene **14** (55.6 mg, 0.22 mmol) in 1,2-dichloroethane (5 mL) were added $(dba)_3Pd_2{\cdot}CHCl_3$ (5.1 mg, 5.5 μmol), BBEDA (2.57 mg, 0.011 mmol), and PHMS (264 mg, 2.2 mmol) at rt. After addition of AcOH (12.6 μL, 0.22 mmol), the resulting mixture was allowed to stir at the same temperature for 4.5 h. The mixture was directly chromatographed with CH_2Cl_2 on activity III basic alumina in order to remove insoluble impurities. The filtrate was neutralized with saturated $NaHCO_3$ solution, and then the mixture was separated. The organic layer was dried and evaporated to leave an oil, which was chromatographed. Elution with a 30:1 mixture of hexane−EtOAc gave rise to the *exo*-olefin **15** (34.1 mg, 61%) as a colorless oil.

(3a*R*,4*S*,7a*R*)-4-(Hydroxymethyl)-3a,4,5,6,7,7a-hexahydro-1-indene (16). To a stirred solution of sodium (729 mg, 31.7 mmol) in anhydrous liquid ammonia (100 mL) was added a THF solution (2 mL) of the *exo*-olefin **15** (812 mg, 3.17 mmol) at −78 °C, whereupon it was continued to stir at the same temperature for 3 h. After addition of NH_4Cl (3 g) at −78 °C, the resulting mixture was allowed to warm to rt. To the residue was added H_2O, and then the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried and evaporated to afford an oil, which was chromatographed. Elution with a 4:1 mixture of hexane−EtOAc furnished the alcohol **16** (458 mg, 88%) as a colorless oil: $[\alpha]^{23}_D$ +26.18 (*c* 0.380, $CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR δ 0.94−1.16 (1H, m), 1.16−1.64 (5H, m), 1.66−1.94 (4H, m), 2.32−2.39 (2H, m), 2.41 (1H, br s), 3.45 (1H, dd, J = 10.8, 6.9), 3.68 (1H, dd, J = 10.8, 3.9), 4.79 (1H, d, J = 1.8), 4.90 (1H, d, J = 0.9); HRMS(EI) calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1348.

(3a*R*,4*S*,7a*R*)-4-(Hydroxymethyl)-3a,4,5,6,7,7a-hexahydroindan-1-one (17). Through a stirred solution of the *exo*-olefin **16** (469 mg, 2.86 mmol) in a 3:1 mixture of MeOH−CH_2Cl_2 (10 mL) at −78 °C was passed a stream of ozone. When the reaction mixture maintained a blue color for 1 h, the stream of ozone was replaced by nitrogen and the solution was stirred until the color dissipated. To the resulting clear reaction mixture was added dimethyl sulfide (1.25 mL, 16.2 mmol), and then the mixture was allowed to warm to rt over a period of 1 h. After removal of the solvent under reduced pressure, the residue was chromatographed. Elution with a 10:1 mixture of hexane−EtOAc provided the ketone **17** (366 mg, 77%) as a colorless oil.

(3a*R*,4*S*,7a*R*)-4-[[[1-Imidazo(thiocarbonyl)]oxy]methyl]-3a,4,5,6,7,7a-hexahydroindan-1-one (18). A mixture of the hydroxy ketone **17** (140 mg, 0.83 mmol), DMAP (182 mg, 1.49 mmol), and 1,1′-(thiocarbonyl)diimidazole (246.6 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) was refluxed for 2 h. After removal of the solvent, the residue was chromatographed. Elution with a 5:1 mixture of C_6H_6−Me_2CO furnished the thioimidazolide **18** (220 mg, 95%) as a yellowish oil: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR δ 1.04−1.74 (5H, m), 1.82−2.40 (7H, m), 4.53 (1H, dd, J = 10.9, 7.2), 4.79 (1H, dd, J = 10.9, 3.9), 7.05 (1H, s), 7.62 (1H, s), 8.33 (1H, s); HRMS(EI) calcd for $C_{14}H_{18}N_2O_2S$ (M^+) 278.1089, found 278.1104.

(3a*R*,4*S*,7a*R*)-4-Methyl-3a,4,5,6,7,7a-hexahydroindan-1-one (19). To a stirred solution of the thioimidazolide **18** (27 mg, 0.097 mmol) in degassed C_6H_6 (8 mL) was slowly added a degassed C_6H_6 solution (2 mL) of tributyltin hydride (0.032 mL, 0.119 mmol) and AIBN (2.0 mg, 0.012 mmol) under reflux. After 0.5 h of refluxing, 15% NH_4OH solution (6 mL) was added, and then the resulting mixture was stirred at rt for 10 h. The mixture was diluted with Et_2O, and then the mixture was separated. The organic layer was dried and evaporated to give an oil, which was chromatographed. Elution with a 10:1 mixture of hexane−EtOAc provided the ketone **19** (11.6 mg, 79%) as a colorless oil: $[\alpha]^{23}_D$ +80.70 (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR δ 0.98 (3H, s), 0.82−2.35 (13H, m); HRMS(EI) calcd for $C_{10}H_{16}O$ (M^+) 152.1201, found 152.1208.

(4a*R*,5*S*,8a*S*)-5-Methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolone (20). A mixture of the ketone **19** (11 mg, 0.072 mmol), hydroxylamine hydrochloride (10.4 mg, 0.15 mmol), and sodium acetate (13.1 mg, 0.16 mmol) in MeOH (4 mL) was stirred at rt for 12 h. After removal of the solvent, the residue was diluted with H_2O, and then the resulting mixture was extracted with Et_2O several times. The combined ethereal layers were concentrated to leave an oil (21 mg) that was dissolved in a 2:3 mixture of THF−H_2O (5 mL). After addition of sodium hydroxide (18 mg, 0.45 mmol) and *p*-toluenesulfonyl chloride (38 mg, 0.20 mmol) at 0 °C, the resulting mixture was stirred at rt for 20 h. The solvent was removed under reduced pressure, and then the residue was diluted with an equivolume mixture of saturated NaCl and CH_2Cl_2. The mixture was separated, and the organic layer was dried and evaporated to give a residue, which was chromatographed. Elution with a 20:1 mixture of EtOAc−MeOH gave rise to the lactam **20** (4.9 mg, 41%), mp 133−140 °C (lit.[8c] mp 146.5−147.5 °C), as a white solid: $[\alpha]^{28}_D$ +32.27 (*c* 0.17, $CHCl_3$) [lit.[8c] $[\alpha]^{25}_D$ +60.4 (*c* 1.00, $CHCl_3$)]; IR ($CHCl_3$) 1650 cm^{-1}; ^1H NMR δ 0.93 (3H, d, J = 6.5), 1.00−1.06 (1H, m), 1.42−1.80 (8H, m), 2.03−2.09 (1H, m), 2.28−2.33 (2H, m), 3.63 (1H, dd, J = 6.9, 3.6), 5.45 (1H, br s); HRMS(EI) calcd for $C_{10}H_{17}NO$ (M^+) 167.1316, found 167.1311.

Acknowledgment. We are very grateful to Professor G. Mehta (University of Hyderabad) for sending us copies of the spectral data of (±)-**19**.

Supporting Information Available: ^1H NMR spectra of compounds **5**−**20** and ^{13}C NMR spectra of compounds **5**−**8** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9613085