

INOC REACTION IN ALKALOID SYNTHESIS— STEREOCONTROLLED FORMAL TOTAL SYNTHESIS OF (+)-PUMILIOTOXIN C

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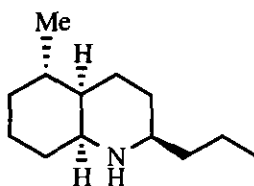
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Abstract — A formal total synthesis of (+)-pumiliotoxin C (**1**), the antipode of the arrow poison frog toxin, starting from the chirally homogeneous (1'S, 6'S)-2-(6'-benzyloxymethyl-2'-cyclohexyl)ethanol (**2**) is described. The synthesis features the intramolecular nitrile oxide cycloaddition (INOC) reaction of the nitro olefin (**5**) to furnish the isoxazoline (**6**).

As exemplified by its broad application to the stereo- and regiochemically defined synthesis of a wide variety of natural products, the intramolecular nitrile oxide cycloaddition (INOC) reaction is one of the most important reaction steps.¹

In the course of works directed toward a total synthesis of biologically active natural products, we recently reported a route to the *cis*-hydrindan derivative, a potential synthon for the E ring segment of (–)-reserpine, which utilized INOC reaction.²

As an extension of this methodology, we herein disclose a diastereoselective formal total synthesis of (+)-pumiliotoxin C (**1**) by means of INOC reaction as the key step.



Pumiliotoxin C (1)

Pumiliotoxin C (**1**)³ was originally isolated from the skin of *Dendrobates pumilio*.⁴ X-Ray analysis⁵ of the crystalline hydrochloride of **1** established the structure, and the absolute configuration was confirmed by its

total synthesis.⁶ The pharmacological properties,⁷ coupled with its unusual *cis*-decahydroquinoline framework have made pumiliotoxin (1) an attractive synthetic target.

While many synthetic approaches⁸ for the synthesis of pumiliotoxin C (1) have been reported, there is still a need for concise strategies for the preparation of *cis*-decahydroquinoline alkaloids with correct stereochemistry.

First of all, the chirally homogeneous alcohol (2) was prepared by the established procedure.⁹ After oxidation of 2 with tetrapropylammonium perruthenate (TPAP) in the presence of 4-methylmorpholin *N*-oxide (NMO) and 4A-molecular sieves (4A-MS) in dichloromethane, chain extension was next conducted by sequential Henry reaction (MeNO₂, KF, Bu₄NCl, toluene, room temperature, 71%), acetylation (Ac₂O, pyridine) and reduction with NaBH₄ in EtOH (61% overall).¹⁰

With the efficient synthesis of the nitro olefin (5) realized, the stage was now set for INOC reaction of 5. The compound (5) was heated with *p*-chlorophenyl isocyanate in the presence of triethylamine at 60 °C for 6 h. The transient nitrile oxide was intercepted by the tethered olefin to deliver the single isoxazoline (6) in 99% yield. The stereochemistry of 6 was made clearly apparent through NOE measurements. The relevant NOE data for the isoxazoline (6) were shown by arrows in Figure I. 6 was transformed into the β-hydroxyketones (7) by hydrogenation over freshly prepared Raney nickel (W2) in a 15:1 mixture of MeOH and H₂O containing 8 equivalents of trimethoxyborane. Surprisingly, this hydrogenation gave a 1:1 diastereomeric mixture of the secondary alcohol (7) probably due to retro aldol reaction of 7. In order to confirm that the dehydration of the both diastereomers (7) proceeds, the β-hydroxyketones (7) were separated and each was subjected to the same transformational conditions, which yielded the same product (8) in both instances. Catalytic hydrogenation of the enone (8) afforded the ketone (9) as a single isomer. Having found conditions for the preparation of 9, the completion of a formal total synthesis of (+)-pumiliotoxin C (1) seemed imminent. After treatment of 9 with 1,1'-thiocarbonyldiimidazole in the presence of 4-dimethylaminopyridine (DMAP), the corresponding thioimidazolide (10) was obtained in 95% yield, whereupon 10 was subjected to radical deoxygenation with tributyltin hydride in the presence of AIBN, giving the ketone (11) (79%), which displays the same spectra with those provided by Mehta in a total synthesis of (±)-pumiliotoxin C (1).⁸¹ Finally Beckmann rearrangement of 11 to the lactam (12) was conducted, in 41% yield, under standard conditions.⁸¹ The spectral properties (¹H nmr, ir, ms) of (+)-12 were identical with in all respects to those of (±)-12 prepared by the established method.^{11,12}

Scheme I

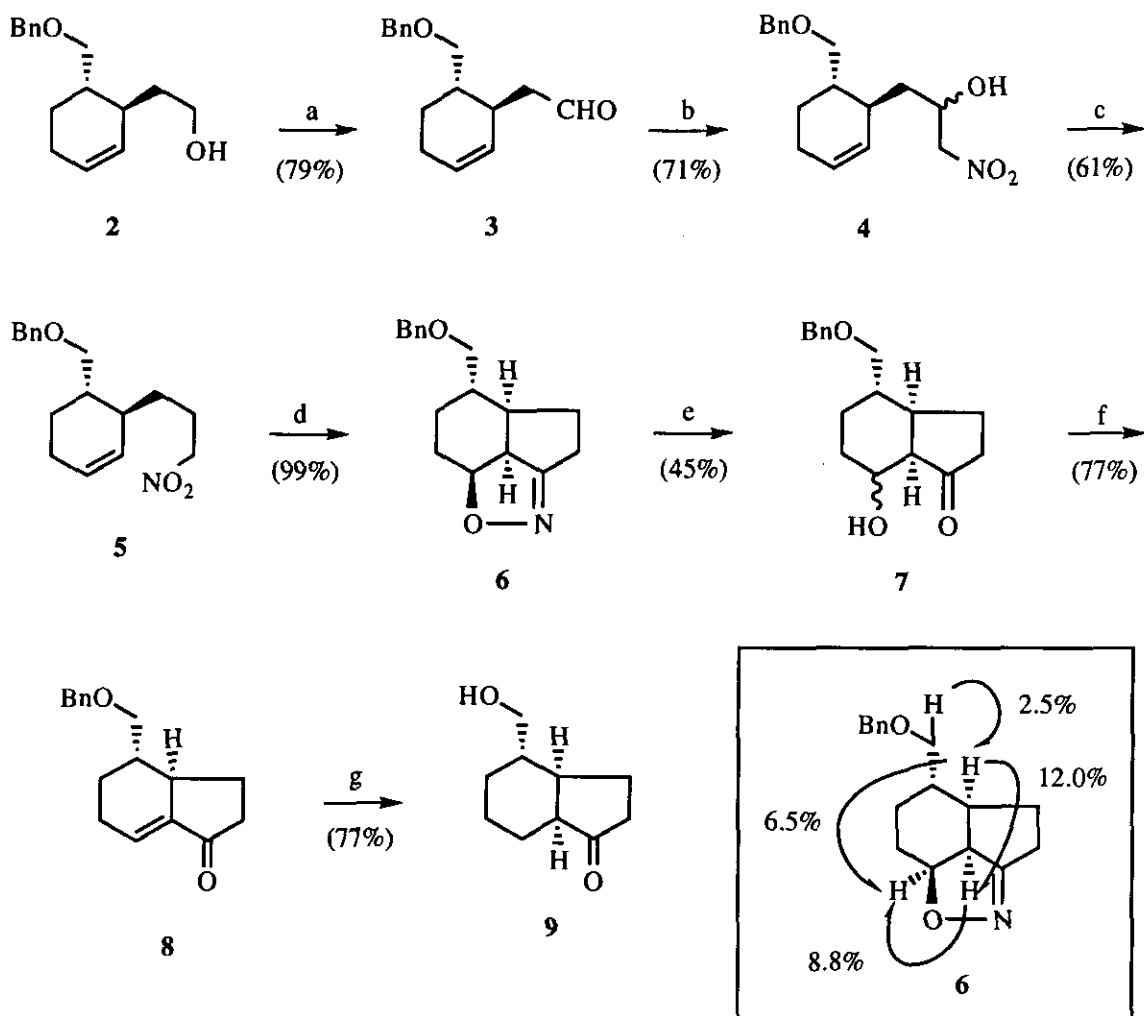


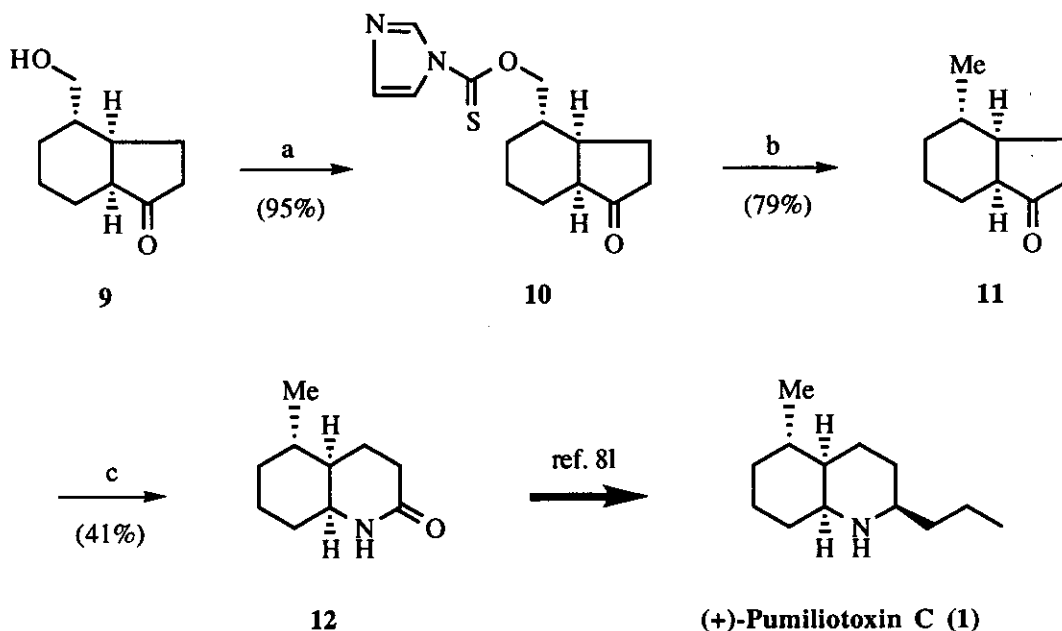
Figure I

(a) TPAP, NMO, 4A-MS, CH_2Cl_2 . (b) MeNO_2 , KF, Bu_4NCl , toluene. (c) Ac_2O , pyridine; NaBH_4 , EtOH. (d) *p*-chlorophenyl isocyanate, Et_3N , toluene, sealed tube, 60°C . (e) H_2 , Raney Ni(W2), $(\text{MeO})_3\text{B}$, $\text{MeOH-H}_2\text{O}$ (15:1 v/v). (f) $\text{TsOH-H}_2\text{O}$, C_6H_6 , 60°C . (g) H_2 , 10% Pd-C, EtOAc.

EXPERIMENTAL

General. Unless otherwise noted, nonaqueous reactions were carried out under argon in rigorously dried glassware. Materials were obtained from commercial supplier 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

Scheme II



(a) $(\text{imid})_2\text{C}=\text{S}$, DMAP, CH_2Cl_2 , reflux. (b) Bu_3SnH , AIBN, C_6H_6 , reflux. (c) $\text{NH}_2\text{OH}\cdot\text{HCl}$, AcONa , MeOH ; TsCl , NaOH , $\text{THF-H}_2\text{O}$ (2:3 v/v).

(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 pentoxide (P_2O_5). Dimethylformamide (DMF) was distilled under argon from MgSO_4 prior to use. Hexamethylphosphoramide (HMPA), *tert*-butanol 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.¹³ 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.¹⁴ 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. ^1H 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,6S')-(6'-Benzyloxymethyl-2'-cyclohexyl)acetaldehyde (3). To a stirred solution of the alcohol (2) (23 mg, 0.093 mmol) in CH_2Cl_2 (2 ml) were added 4A-MS (30 mg), TPAP (2.0 mg, 5.7 μmol) and NMO (16 mg, 0.14 mmol) at ambient temperature, whereupon it was continued to stir at room temperature for 1.5 h. After removal of the solvent, Celite and Et_2O 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 leave an oil, which was chromatographed. Elution with a 10:1 mixture of hexane-EtOAc provided the aldehyde (3) (18 mg, 79%) as a colorless oil, which was rapidly used in the next step. Ir (CHCl_3): 1720 cm^{-1} . ^1H Nmr: δ 1.53–1.85 (3H, m), 2.00 (2H, br s), 2.40 (1H, ddd, $J = 18.0, 8.1$ and 3.0), 2.58–2.68 (2H, m), 3.43 (2H, ddd, $J = 13.8, 7.8$ and 4.8), 4.48 (2H, dd, $J = 17.1$ and 12.0), 5.50 (1H, dd, $J = 12.0$ and 10.2), 5.72 (1H, dd, $J = 10.2$ and 2.1), 7.25–7.35 (5H, m) and 9.74 (1H, d, $J = 2.1$). HRms(EI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2$ (M^+) 244.1463, found 244.1481.

(1'S,6'S)-3-(6'-Benzyloxymethyl-2'-cyclohexenyl)-1-nitro-2-propanol (4). To a stirred solution of the aldehyde (3) (35 mg, 0.14 mmol) in toluene (3 ml) were added tetrabutylammonium chloride (64 mg, 0.23 mmol), nitromethane (12.3 mg, 0.20 mmol) and KF (10 mg, 0.17 mmol) at room temperature, whereupon it was continued to stir at the same temperature for 3 h. After addition of saturated NH_4Cl solution, the resulting mixture was extracted with Et_2O several times. The combined ethereal layers were washed with saturated NaCl solution, dried and evaporated to yield an oil, which was chromatographed. Elution with a 5:1 mixture of hexane-EtOAc furnished the nitro aldol (4) (31 mg, 71%) as a colorless oil. $[\alpha]_D^{30} +444.50^\circ$ (c 0.553, CHCl_3). Ir (CHCl_3): 3450 and 1560 cm^{-1} . ^1H Nmr: δ 1.39–1.88 (4H, m), 1.88–2.12 (3H, m), 2.21–2.38 (1H, m), 2.70 (0.5H, d, $J = 4.8$), 3.25 (0.5H, d, $J = 4.2$), 3.41–3.48 (2H, m), 4.32–4.53 (1H, m), 4.34–4.36 (2H, m), 4.48–4.52 (2H, m), 5.44–5.67 (2H, m), 5.75 (1H, br d, $J = 10.3$) and 7.25–7.38 (5H, m). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.57; N, 4.46.

(1'S,6'S)-3-(6'-Benzyloxymethyl-2'-cyclohexenyl)nitropropane (5). To a stirred solution of the nitro aldol (4) (31 mg, 0.10 mmol) in pyridine (0.5 ml, 61.8 mmol) was added acetic anhydride (0.5 ml, 53.1 mmol) at room temperature, whereupon it was continued to stir at the same temperature for 0.5 h. After removal of the solvent, the crude acetate was rapidly used without purification.

To a stirred solution of the crude acetate in EtOH (2 ml) was added NaBH₄ (126 mg, 3.3 mmol) at 0 °C, whereupon it was continued to stir at the same temperature for 0.5 h. After removal of the solvent under reduced pressure, Et₂O and saturated NaCl solution were added, then the resulting mixture was separated. The aqueous layer was extracted with Et₂O several times. The combined ethereal layers were washed with saturated NaCl solution, dried and evaporated to provide an oil, which was chromatographed. Elution with a 10:1 mixture of hexane–EtOAc gave rise to the nitro olefin (**5**) (18 mg, 61%) as a colorless oil. $[\alpha]_D^{29} +46.91^\circ$ (*c* 0.890, CHCl₃). Ir (CHCl₃): 1560 and 1380 cm⁻¹. ¹H Nmr: δ 1.12–1.38 (5H, m), 1.62–1.88 (2H, m), 1.92–2.14 (3H, m), 3.31–3.49 (2H, m), 4.31 (1H, dt, *J* = 7.5 and 1.5), 4.34 (1H, t, *J* = 7.5), 4.41–4.56 (2H, m), 5.51 (1H, br d, *J* = 9.9), 5.72 (1H, br d, *J* = 9.9) and 7.30–7.40 (5H, m). *Anal.* Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.89. Found: C, 70.55; H, 7.94; N, 4.78.

(3aR,4S,7R,7aR)-3a,4,5,6,7,7a-Hexahydro-4-benzyloxymethylindano[1,7-cd]isoxazole

(6). A mixture of the nitro olefin (**5**) (105 mg, 0.36 mmol), *p*-chlorophenyl isocyanate (125 mg, 0.81 mmol) and Et₃N (0.1 ml, 0.99 mmol) in toluene (4 ml) was heated at 60 °C in a sealed tube for 6 h. After being cooled to room temperature, the mixture was filtered through Celite. The filtrate was concentrated to give an oil, which was chromatographed. Elution with a 10:3 mixture of hexane–EtOAc afforded the isoxazoline (**6**) (97 mg, 99%) as a colorless oil. ¹H Nmr: δ 0.80–0.90 (1H, m), 1.22–1.39 (2H, m), 1.68 (1H, ddd, *J* = 13.5, 6.5 and 3.0), 1.98–2.06 (2H, m), 2.24–2.35 (2H, m), 2.39–2.49 (2H, m), 3.31 (1H, dd, *J* = 9.3 and 6.2), 3.46 (1H, dd, *J* = 9.3 and 4.0), 3.36 (1H, t, *J* = 8.4), 4.48 (2H, dd, *J* = 20.2 and 12.0), 4.62 (1H, dd, *J* = 17.4 and 8.6) and 7.24–7.35 (5H, m). HRms(EI) calcd for C₁₇H₂₁NO₂ (M⁺) 271.1572, found 271.1560.

(3aR,4S,7aR)-4-Benzyloxymethyl-7-hydroxy-3a,4,5,6,7,7a-hexahydroindan-1-one (7). A mixture of the isoxazoline (**6**) (288 mg, 1.06 mmol), trimethoxyborane (1.0 ml, 8.80 mmol) and Raney Ni (W2) (about 100 mg) in a 15:1 mixture of MeOH–H₂O (15 ml) was stirred at room temperature for 12 h. After filtration through Celite, the filtrate was evaporated. The residue was diluted with saturated NaCl solution and Et₂O, then the resulting mixture was separated. The ethereal layer was washed with saturated NaCl solution, dried and evaporated to yield an oil, which was chromatographed. Elution with a 10:1 mixture of C₆H₆–Me₂CO provided the β-hydroxyketone (**7**) (128 mg, 45%) as a diastereomeric mixture.

less polar β -hydroxyketone: Ir (CHCl₃): 3460 and 1725 cm⁻¹. ¹H Nmr: δ 1.08–1.44 (3H, m), 1.78–2.14 (4H, m), 2.18–2.40 (3H, m), 2.63 (1H, t, $J = 6.5$), 3.37 (1H, dd, $J = 7.5$ and 4.8), 3.51 (1H, dd, $J = 7.5$ and 3.0), 3.70–3.84 (1H, m), 4.32 (1H, d, $J = 10.9$), 4.50 (2H, dd, $J = 16.5$ and 12.0) and 7.24–7.40 (5H, m). HRms(EI) calcd for C₁₇H₂₂O₃ (M⁺) 274.1569, found 274.1584.

more polar β -hydroxyketone: Ir (CHCl₃): 3450 and 1730 cm⁻¹. ¹H Nmr: δ 1.18–1.78 (5H, m), 1.82–1.96 (1H, m), 1.96–2.26 (3H, m), 2.28–2.44 (1H, m), 3.38–3.54 (3H, m), 3.68–3.80 (1H, m), 4.48 (2H, dd, $J = 16.5$ and 12.0) and 7.24–7.46 (5H, m). HRms(EI) calcd for C₁₇H₂₂O₃ (M⁺) 274.1569, found 274.1563.

(3aR,4S)-4-Benzyloxymethyl-3a,4,5,6-tetrahydroindan-1-one (8).

from less polar isomer: To a stirred solution of the less polar isomer (8 mg, 0.029 mmol) in C₆H₆ (2 ml) was added *p*-toluenesulfonic acid monohydrate (2 mg, 0.012 mmol) at room temperature, whereupon it was heated at 60 °C for 0.5 h. After being cooled to room temperature, saturated NaHCO₃ solution was added, then the resulting mixture was extracted with Et₂O. The ethereal layer was washed with saturated NaCl solution, dried and evaporated to furnish an oil, which was chromatographed. Elution with a 10:1 mixture of C₆H₆-Me₂CO provided the enone (8) (4.5 mg, 60%) as a colorless oil. Ir (CHCl₃): 1720 and 1650 cm⁻¹. ¹H Nmr: δ 1.28–1.62 (4H, m), 1.96 (1H, ddd, $J = 12.9$, 6.0 and 0.9), 2.14–2.48 (5H, m), 3.46 (1H, dd, $J = 9.9$ and 6.0), 3.60 (1H, dd, $J = 9.9$ and 4.8), 4.54 (2H, dd, $J = 16.8$ and 11.7), 6.69 (1H, dd, $J = 3.0$ and 0.9) and 7.22–7.40 (5H, m). HRms(EI) calcd for C₁₇H₂₀O₂ (M⁺) 254.1463, found 254.1476.

from more polar isomer: The enone (8) (7.5 mg, 72%) was obtained from the more polar isomer (7) (11 mg, 0.040 mmol) by using the above procedure.

from a diastereomeric mixture: The enone (8) (31 mg, 77%) was prepared from a diastereomeric mixture (43 mg, 0.16 mmol) by using the above procedure.

(3aR,4S,7aR)-4-Hydroxymethyl-3a,4,5,6,7,7a-hexahydroindan-1-one (9). A mixture of the enone (8) (26 mg, 0.10 mmol) and 10% palladium-charcoal (2 mg) in EtOAc (5 ml) was stirred at room temperature under hydrogen for 12 h. After filtration through Celite, the filtrate was concentrated and then the residue was chromatographed. Elution with a 10:3 mixture of C₆H₆-Me₂CO furnished the keto alcohol (9) (13.2 mg, 77%) as a colorless oil. $[\alpha]_D^{27} + 80.43^\circ$ (c 0.416, CHCl₃). Ir (CHCl₃): 3500 and 1730 cm⁻¹.

$^1\text{H Nmr}$: δ 1.02–1.96 (7H, m), 2.00–2.38 (6H, m), 3.45 (1H, dd, $J = 10.8$ and 7.2) and 3.68 (1H, dd, $J = 10.8$ and 3.6). Ms(EI) m/z 168 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 71.39; H, 9.50. Found: C, 71.50; H, 9.58.

(3aR,4S,7aR)-4-(1-Imidazothiocarbonyloxymethyl)-3a,4,5,6,7,7a-hexahydroindan-1-one (10). A mixture of the β -hydroxyketone (9) (140 mg, 0.83 mmol), DMAP (182 mg, 1.49 mmol) and 1,1'-thiocarbonyldiimidazole (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 (10) (220 mg, 95%) as a yellowish oil. Ir (CHCl_3): 1740 cm^{-1} . $^1\text{H Nmr}$: δ 1.04–1.74 (5H, m), 1.82–2.40 (7H, m), 4.53 (1H, dd, $J = 10.9$ and 7.2), 4.79 (1H, dd, $J = 10.9$ and 3.9), 7.05 (1H, s), 7.62 (1H, s) and 8.33 (1H, s). HRms(EI) calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (M^+) 278.1089, found 278.1104.

(3aR,4S,7aR)-4-Methyl-3a,4,5,6,7,7a-hexahydroindan-1-one (11). To a stirred solution of the thioimidazolide (10) (27 mg, 0.097 mmol) in a degassed C_6H_6 (8 ml) was added slowly 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, then the resulting mixture was stirred at room temperature for 10 h. The mixture was diluted with Et_2O , then the resulting 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 (11) (11.6 mg, 79%) as a colorless oil. $[\alpha]_{\text{D}}^{23} +80.70^\circ$ (c 0.64, CHCl_3). Ir (CHCl_3): 1740 cm^{-1} . $^1\text{H Nmr}$: δ 0.98 (3H, s) and 0.82–2.35 (13H, m). HRms(EI) calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ (M^+) 152.1201, found 152.1208.

(4aR,5S,8aS)-5-Methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1H)-quinolone (12). A mixture of the ketone (11) (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 room temperature for 12 h. After removal of the solvent, the residue was diluted with H_2O , then the resulting mixture was extracted with Et_2O several times. The combined ethereal layers were concentrated to leave an oil (21 mg) which 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 room temperature for 20 h. The solvent was removed under reduced pressure, 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 (**12**) (4.9 mg, 41%), mp 133–140 °C (lit.,^{8c} mp 146.5–147.5 °C), as a white solid. $[\alpha]_{\text{D}}^{28} +32.27^\circ$ (*c* 0.17, CHCl_3), {lit.,^{8c} $[\alpha]_{\text{D}}^{25} +60.4^\circ$ (*c* 1.00, CHCl_3)}. Ir (CHCl_3): 1650 cm^{-1} . $^1\text{H Nmr}$: 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 and 3.6) and 5.45 (1H, br s). HRms(EI) calcd for $\text{C}_{10}\text{H}_{17}\text{NO}$ (M^+) 167.1316, found 167.1311.

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