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Biomimetic Construction of the Hydroquinoline Ring System. Diastereodivergent Enantioselective Synthesis of 2,5-Disubstituted *cis*-Decahydroquinolines†

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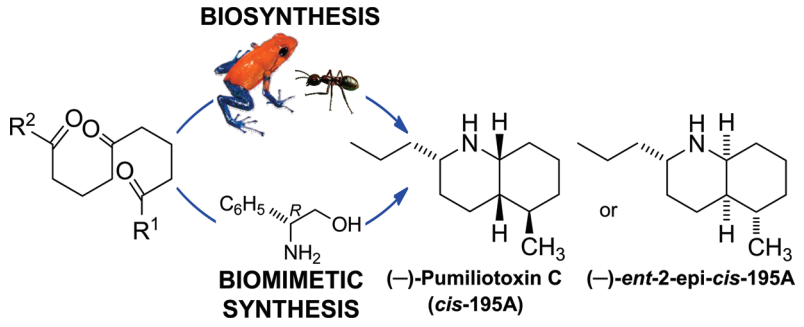

The straightforward enantioselective construction of the hydroquinoline ring system from 1,5-polycarbonyl derivatives, using (*R*)-phenylglycinol as a chiral latent form of ammonia, is reported. The process mimics the key steps believed to occur in nature in the biosynthesis of amphibian decahydroquinoline alkaloids. Diastereodivergent routes to enantiopure *cis*-2,5-disubstituted decahydroquinolines, including the alkaloid pumiliotoxin C (*cis*-**195A**), are developed.

Introduction

2,5-Disubstituted decahydroquinolines (Figure 1) represent one of the major classes of amphibian alkaloids,[1] which were first isolated from the skin extracts of dendrobatid frogs.[2] These biologically active natural products, unprecedented in the plant kingdom, also occur in bufonid toads,[3] tunicates,[4] marine flatworms,[4b] and myrmicine ants.[5] The biosynthetic origin of decahydroquinoline amphibian alkaloids remains an intriguing question and a major research challenge for chemical ecologists,[1] particularly since the isolation of some of these alkaloids from ants has opened a dietary hypothesis for their presence in frogs.[5]

† Dedicated to Prof. José Barluenga on the occasion of his 70th birthday.

(1) (a) Witkop, B.; Gössinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, pp 139−253. (b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1−274. (c) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1993; Vol. 43, pp 185−288. (d) Daly, J. W. In *The Alkaloids*; Cordell, G. A, Ed.; Academic Press: New York, 1998; Vol. 50, pp 141−169. (e) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon, New York, 1999; Vol. 13, pp 1−161. (f) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.

(2) (a) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453–3460. (b) Tokuyama, T.; Tsujita, T.; Shimada, A.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5401–5414. (c) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016–1038.

(3) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat Prod.* **1993**, *56*, 357–373.

(4) (a) Steffan, B. *Tetrahedron* **1991**, *47*, 8729–8732. (b) Kubanek, J.; Williams, D. E.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189–6192. (c) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454–457. (d) Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067–3072.

(5) (a) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21. (b) Jones, T. H.; Gorman, J. S. T.; Snelling, R. R.; Delabie, J. H. C.; Blum, M. S.; Garraffo, H. M.; Jain, P.; Daly, J. W.; Spande, T. F. *J. Chem. Ecol.* **1999**, *25*, 1179–1193. (c) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73–85.

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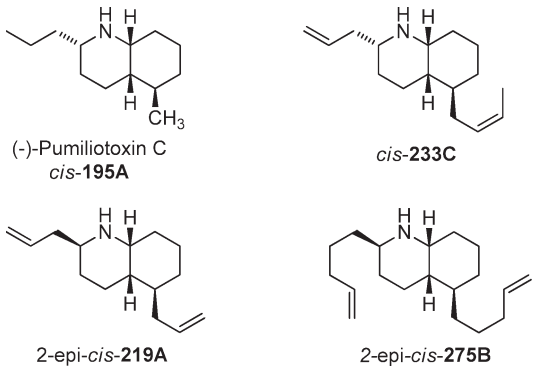
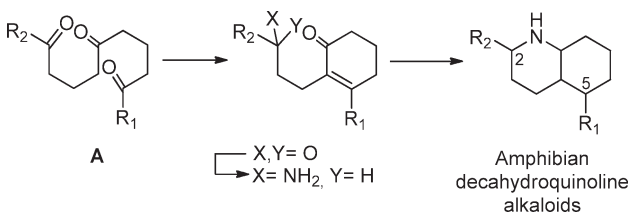


FIGURE 1. Representative amphibian *cis*-decahydroquinoline alkaloids.

SCHEME 1. Biogenetic Hypothesis



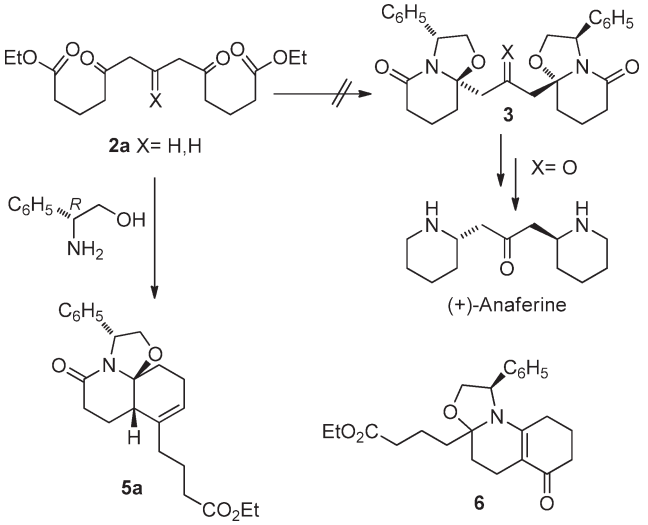
The structural diversity and pharmacological activities of these alkaloids, as well as the limited amounts available from natural sources, have stimulated considerable synthetic effort in this area,[6] including some biomimetic approaches.[7] Although there are no conclusive studies concerning their biosynthesis, it is thought that decahydroquinoline alkaloids might derive from the polyketide pathway, by aminocyclization of straight-chain 1,5-polycarbonyl derivatives **A**, via cyclohexenone intermediates, as outlined in Scheme 1.[8]

Mimicking these key steps believed to occur in nature, we present here a straightforward enantioselective construction of the hydroquinoline ring system from 1,5-polycarbonyl derivatives, using (*R*)-phenylglycinol as a chiral latent form of ammonia. Appropriate elaboration of the resulting tricyclic lactams results in diastereodivergent routes to enantiopure *cis*-2,5-disubstituted decahydroquinolines, including the most representative alkaloid of this group, pumiliotoxin C (*cis*-**195A**).[9]

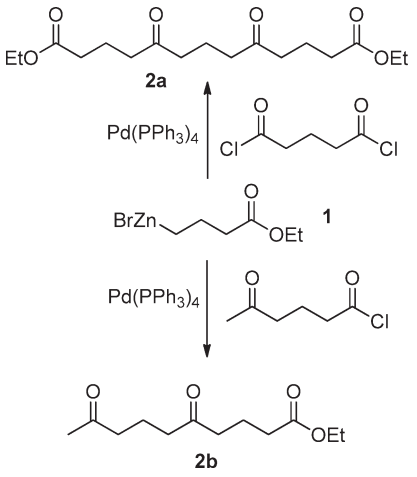
Results and Discussion

Our biomimetic approach was inspired by a serendipitous observation when attempting a double phenyglycinol-induced cyclocondensation from the polycarbonyl derivative **2a** in the context of model studies on the synthesis of (+)-anaferine (Scheme 2).

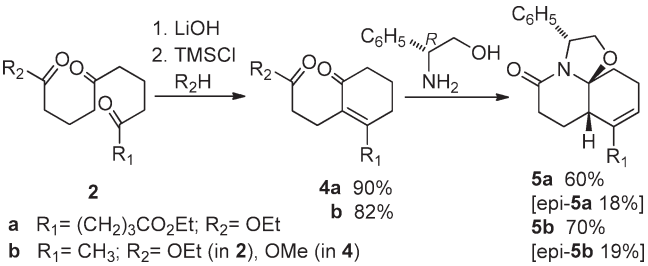
SCHEME 2. Discovery of the Biomimetic Aminocyclization



SCHEME 3. Synthesis of 1,5-Polycarbonyl Derivatives 2



SCHEME 4. Biomimetic Construction of the Hydroquinoline Ring System



Thus, treatment of diketo diester **2a**, which was prepared in excellent yield (82%) by Pd-catalyzed coupling of glutaryl dichloride with the functionalized organozinc derivative **1** (Scheme 3), with (*R*)-phenylglycinol in refluxing benzene containing AcOH unexpectedly led to the tricyclic hydroquinoline lactam **5a** (37% yield) instead of the desired bis(oxazolopiperidone) lactam **3** (X =H,H). Cyclohexenone

(6) For a review, see: Kibayashi, C.; Aoyagi, S. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: Amsterdam, The Netherland, 1997; Vol. 19, pp 3−88.

(7) (a) Glanzmann, M.; Karalai, C.; Ostersehlt, B.; Schön, U.; Frese, C.; Winterfeldt, E. *Tetrahedron* **1982**, *38*, 2805–2810. (b) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett*. **1986**, *27*, 1569–1572. For reviews, see: (c) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep*. **2000**, *17*, 349–366. (d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun*. **2003**, 551–564. (e) De la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed*. **2004**, *43*, 160–181.

(8) Winterfeldt, E. *Heterocycles* **1979**, *12*, 1631–1650. See also refs 1a, 1b, and 7c.

(9) For a preliminary account on the synthesis of pumiliotoxin C, see: Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed*. **2008**, *47*, 3348–3351.

4a (22% yield, see Scheme 4) and enaminone **6** (25% yield; ~1:1 mixture of stereoisomers) were also isolated.

The formation of **5a** can be rationalized by considering that the starting symmetrical diketone **2a** undergoes an aldol cyclocondensation leading to cyclohexenone **4a**, which then undergoes an in situ phenylglycinol-promoted cyclocondensation reaction in an overall process that parallels the biogenetic postulate outlined in Scheme 1.

In accordance with this interpretation, diketo diester **2a** was first converted to the intermediate cyclohexenone **4a** (Scheme 4) in excellent yield (90%) by sequential treatment with aqueous LiOH and TMSCl-EtOH, and then this ketone was satisfactorily cyclized (60% yield) to lactam **5a** by treatment with (*R*)-phenylglycinol.[10]

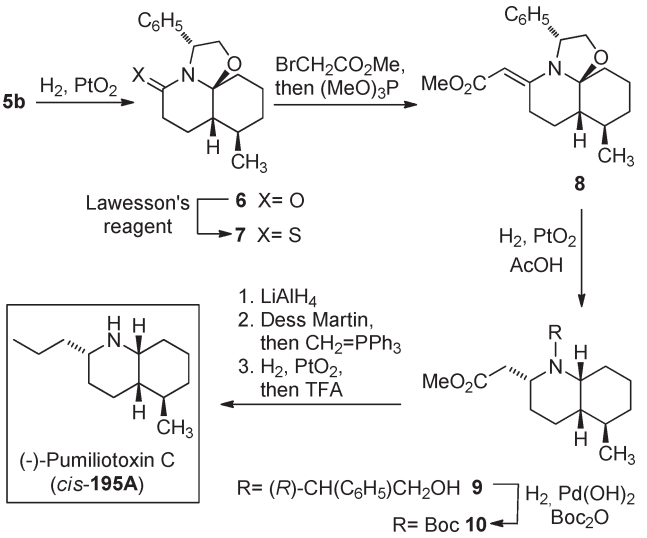
The application of this biomimetic double cyclocondensation methodology to the enantioselective synthesis of the decahydroquinoline alkaloid *cis*-**195A**, which incorporates a C-5 methyl substituent, required starting from a diketoester **2b**, bearing a methyl ketone moiety. This 1,5-polycarbonyl derivative was prepared in 65% yield by Pd-catalyzed coupling of the organozinc derivative **1** with 5-oxohexanoyl chloride. In this series, the initial aldol cyclocondensation to **4b** took place in 82% yield, whereas the phenylglycinol-promoted cyclocondensation stereoselectively provided tricyclic lactam **5b** in 70% yield. The configuration of the stereogenic ring fusion carbon atoms generated in this step was unambiguously established by X-ray crystallographic analysis.

The conversion of lactam **5b** to the target alkaloid required the stereoselective hydrogenation of the carbon−carbon double bond, the introduction of the propyl substituent at C-2, and the reductive removal of the chiral inductor. The catalytic hydrogenation of **5b** with PtO_2 as the catalyst took place in nearly quantitative yield and complete selectivity from the most accessible face to give lactam **6**, whose absolute configuration was unambiguously established by X-ray crystallographic analysis (Scheme 5).

The lactam carbonyl present in tricyclic lactam **6** allows the introduction of substituents at the 2-position of the hydroquinoline ring, ultimately leading to enantiopure 2,5-disubstituted *cis*-decahydroquinolines. Thus, lactam **6** was converted into the corresponding thioamide, which was then subjected to Eschenmoser sulfide contraction[11] conditions ($BrCH_2CO_2Me$; then $(MeO)_3P$, Et_3N) to give β enamino ester **8** in 50% overall yield.

At this point, the complete relative stereochemistry of the target alkaloid *cis*-**195A** was installed by hydrogenation of **8** in the presence of PtO_2 under acidic conditions (AcOH, MeOH, 24 h), which brought about both the stereoselective reduction of the vinylogous urethane double bond[12] and the cleavage of the oxazolidine C−O bond. A subsequent debenzylation with hydrogen and $Pd(OH)_2$ in the presence of Boc_2O led to the protected *cis*-decahydroquinoline **10**.

SCHEME 5. Enantioselective Synthesis of Pumiliotoxin C



Finally, the conversion of ester **10** into pumiliotoxin C was accomplished in satisfactory overall yield by $LiAlH_4$ reduction to alcohol **11**, followed by methylenation of the corresponding aldehyde, subsequent catalytic hydrogenation of the resulting *N*-Boc-2-allyldecahydroquinoline, and finally deprotection of the piperidine nitrogen. The NMR spectroscopic data and $[\alpha]^{22}_D$ value (−15.3, *c* 0.5 in MeOH) of *cis*-**195A** (pumiliotoxin C) hydrochloride were consistent with those reported in the literature.[13]

Unexpectedly, reversing the order of the catalytic hydrogenation of the endocyclic double bond and the Eschenmoser sulfide contraction reactions resulted in a dramatic change in the overall stereochemical outcome of the process. Thus, catalytic hydrogenation of enamino ester **13** (PtO_2, AcOH, MeOH, 16 h), which was prepared in 76% overall yield from lactam **5b** as outlined in Scheme 6, followed by reaction of the resulting secondary amine with Boc_2O did not lead to the expected decahydroquinoline-2-acetate derivative **10**, but to a stereoisomer, *ent*-2-epi-**10**, instead (45% overall yield).[14] The configuration of this ester was initially misassigned as that of 2-epi-**10** on the basis of the 2,8a-*trans*, 4a,5-*trans*, 4a,8a-*cis* relationship (evident by X-ray crystallography) of the alcohol resulting from its $LiAlH_4$ reduction and bearing in mind the known C-4a absolute configuration of the starting material **13**.

(10) For related cyclocondensation reactions, see: (a) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 7872–7881. (b) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794–1797. For reviews on the use of phenylglycinol-derived lactams, see: (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207.

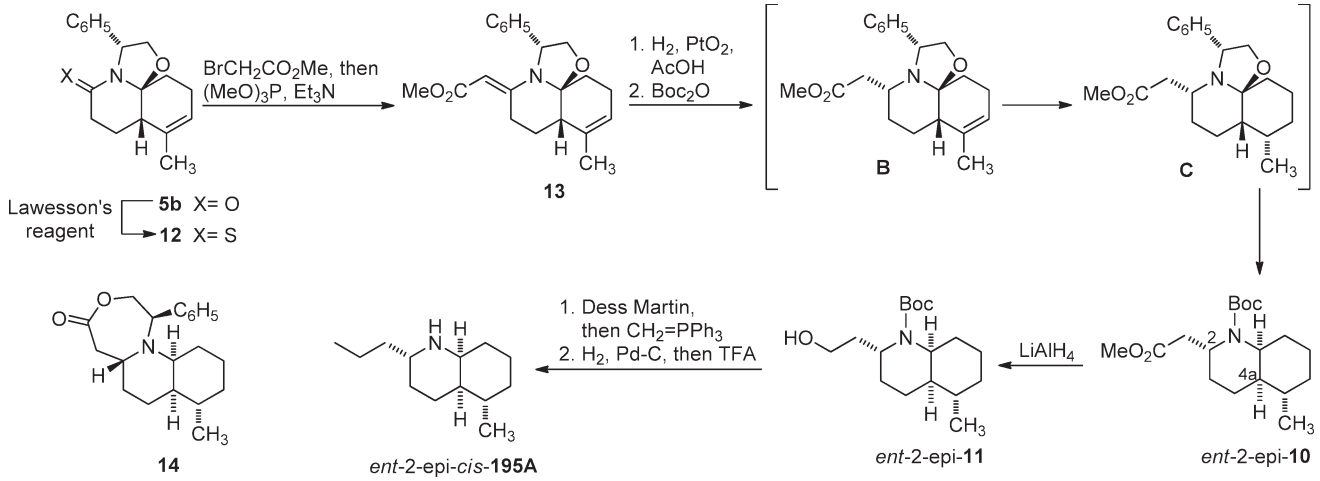
(11) Shiozaki, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991, pp 865−892.

(12) Calvet-Vitale, S.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron* **2005**, *61*, 7774–7782.

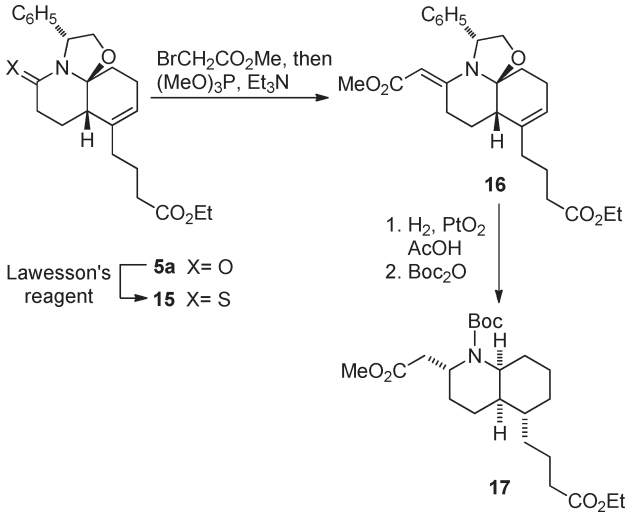
(13) For previous enantioselective syntheses of *cis*-**195A** ((−)-pumiliotoxin C), see: (a) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204–207. (b) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805–8826. (c) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838–1839. (d) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1113–1124. (e) Riechers, T.; Krebs, H. C.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem.* **1998**, 2641–2646. (f) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141–145. (g) Dijk, E. W.; Panella, L.; Pinho, P.; Naasz, R.; Meetsma, A.; Minaard, A. J.; Feringa, B. L. *Tetrahedron* **2004**, *60*, 9687–9693. For the synthesis of (+)-pumiliotoxin C, see: (h) Dieter, R. K.; Fishpaugh, J. R. *J. Org. Chem.* **1983**, *48*, 4441–4444. (i) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493–6502. (j) Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687–8691. (k) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perrault, S.; DeSève, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239–6250.

(14) In some runs, the seven-membered lactone **14** was isolated as a byproduct, which was subsequently converted to *ent*-2-epi-**10** by catalytic hydrogenation (Pd-C, MeOH) in the presence of Boc_2O.

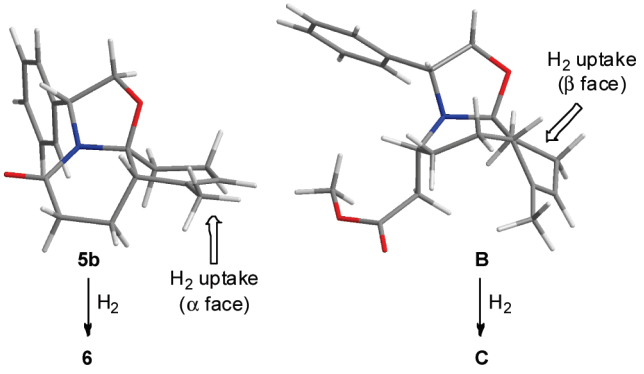
SCHEME 6. Enantioselective Synthesis of *ent*-2-Epi-*cis*-195A



SCHEME 7



SCHEME 8. Stereochemical Outcome of the C−C Double Bond Hydrogenation



The correct absolute configurations of the above ester and alcohol were only unambiguously established as those depicted in Scheme 6 for *ent*-2-epi-**10** and *ent*-2-epi-**11**, respectively, once this alcohol was converted to *ent*-2-epi-*cis*-**195A**[15] following a synthetic sequence similar to that previously developed in the above pumiliotoxin C series. This compound showed NMR spectroscopic data[16] and an $[\alpha]^{22}_{D}$ value[13f] consistent with those reported in the literature for (−)-4a,5,8a-epipumiliotoxin C.[17]

The formation of *ent*-2-epi-**10** from **13** involves six chemical transformations: stereoselective hydrogenation of two carbon−carbon double bonds, reductive cleavage of the oxazolidine ring, epimerization at the perhydroquinoline C-4a position, debenzylation, and, finally, introduction of the protective group.

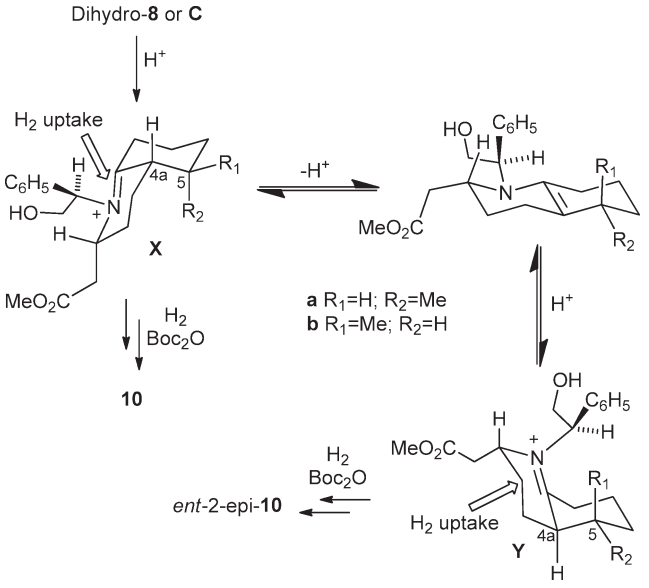
The hydrogenation of the exocyclic C−C double bond of **13** is the first event of this multistep sequence, as evidenced by the rapid disappearance (3 h) of the NMR singlet at δ 4.38 attributable to the vinyl proton α to the carbonyl group when operating under neutral conditions (PtO_2, MeOH). The resulting intermediate **B** is then converted to the perhydro derivative **C**, as indicated by the successive disappearance of the NMR signals due to the exocyclic and endocyclic (broad singlet at δ 5.42) double bonds, when the hydrogenation was effected by using Pd/C as the catalyst in methanol. Under acidic conditions (PtO_2, MeOH, excess AcOH), this intermediate was formed in 30 min, and after prolonged reaction times it evolved into the secondary amine precursor of *ent*-2-epi-**10**.

A similar stereochemical result was obtained starting from diester **16**. Catalytic hydrogenation of **16** in the presence of PtO_2 under acidic conditions (AcOH, EtOH), followed by protection of the resulting secondary amine with Boc_2O, led to the *cis*-decahydroquinoline **17** (Scheme 7). Diester **16** was prepared in 71% overall yield from lactam **5a** by Eschenmoser sulfide contraction of the corresponding thiolactam **15**.

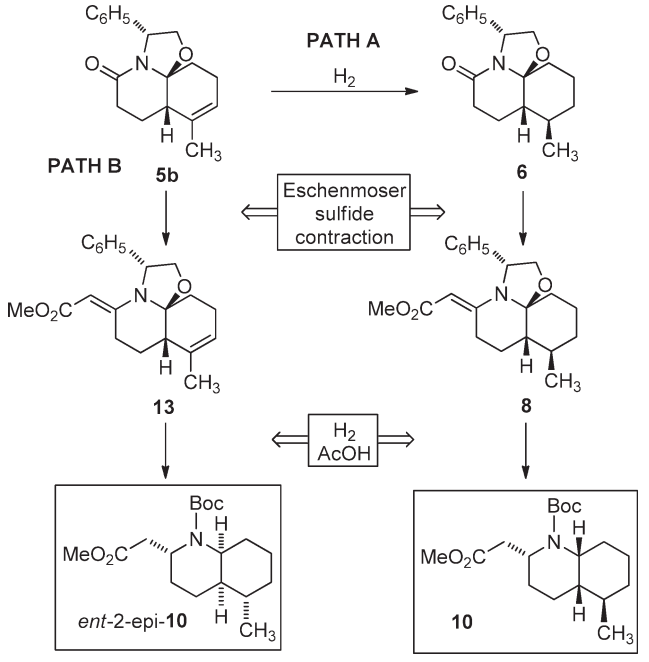
The stereochemical outcome of the hydrogenation of **13** was quite surprising because two configurationally related substrates (**5b** and **13**) lead to two diastereoisomers (**10** and *ent*-2-epi-**10**, respectively) differing in the absolute configuration of three stereocenters. This result can be rationalized by

(15) For a previous enantioselective synthesis, see ref 13f.
(16) (a) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103–4110. (b) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652–6660. (c) Back, T. G.; Nakajima, K. *Tetrahedron Lett.* **1997**, *38*, 989–992. (d) Lebrun, M.-E.; Pfeiffer, J. Y.; Beauchemin, A. M. *Synlett* **2009**, *7*, 1087–1090. See also ref 13f.
(17) For a previous enantioselective synthesis of 2-epi-*cis*-**195A**, see: Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566–6571.

SCHEME 9. The Configuration of the Ring Junction



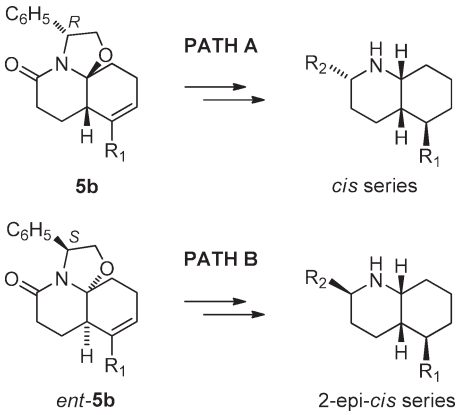
SCHEME 10. Diastereodivergent Enantioselective Synthesis of 2,5-Disubstituted *cis*-Decahydroquinolines



considering that the hydrogenation of the endocyclic C−C double bond of the conformationally rigid tricyclic derivatives **5b** and **B** occurs with differing facial selectivity and that the absolute configuration of the stereocenter generated in this step (C-5) determines the stereochemistry of the configurationally labile C-4a stereocenter under the acidic conditions required for the reductive cleavage of the oxazolidine ring.

A reasonable explanation for the contrasting stereoselectivity in the above hydrogenation step can be obtained by analyzing the most stable conformations of **5b** and **B** obtained by molecular orbital calculations (Scheme 8). Thus, although the presence of an axial C−O bond in **5b** directs the uptake of hydrogen to the opposite α face to give **6**, the axial acetate chain

SCHEME 11. A Synthetic Approach to *cis*-Decahydroquinoline Alkaloids Epimeric at C-2



on the concave face of the hydroquinoline moiety in **B** reverses this situation and the hydrogenation occurs on the less hindered β-face to provide the intermediate **C**.

On the other hand, the C-4a configuration in *ent*-2-epi-**10**, opposite to that in **13**, can be accounted for by considering that the acid-promoted opening of the oxazolidine ring in **C** leads to an intermediate iminium salt **Xa** (Scheme 9), which is in equilibrium via the corresponding enamine with the most stable epimer **Ya** (equatorial methyl group) in a process involving the inversion of the configuration at the C-4a stereocenter. A subsequent stereoselective hydrogenation of the iminium function and debenzylation, followed by protection with Boc_2O, leads to *cis*-decahydroquinoline *ent*-2-epi-**10**.[18]

In contrast, the C-4a epimerization does not occur in the pumiliotoxin C series, in which the iminium intermediate **Xb** (equatorial methyl group), generated after an initial stereoselective reduction of the exocyclic double bond of **8**, is directly converted to the *cis*-decahydroquinoline **10**.

Conclusion

In summary, starting from an easily accessible (*R*)-phenylglycinol-derived tricyclic lactam **5b**, depending on the order of the synthetic transformations (paths A or B), it is possible to enantioselectively access 5-substituted *cis*-decahydroquinoline-2-acetate derivatives that differ in the configuration of the 4a, 5, and 8a stereocenters (Scheme 10).

The results reported in this paper not only provide experimental support for the presumed biosynthetic pathway to amphibian decahydroquinoline alkaloids but also open general enantioselective routes to both the *cis* and the 2-epi-*cis* series of these alkaloids, which differ in the nature of the substituents at the 2 and 5 positions and in the relative C-2 configuration (see Figure 1). Starting from an appropriate (*R*)-phenylglycinol-derived tricyclic lactam, the above path A provides access to the normal *cis* series, whereas when using an (*S*)-phenylglycinol-derived lactam, the above path B would lead to decahydroquinoline alkaloids of the 2-epi-*cis* series (Scheme 11).

(18) For related examples on the reduction of 5-substituted-1,2,3,4,5,6,7,8-octahydroquinoline derivatives to give 4a,5-*trans*,*cis*-decahydroquinolines, see: (a) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805–8826. (b) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368–2378. (c) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2002**, *66*, 7873–7874.

Experimental Section

Diethyl 5,9-Dioxotridecanedioate (2a). $Pd[P(C_6H_5)_3]_4$ (2.9 g, 2.5 mmol) was added to a solution of 4-ethoxy-4-oxobutylzinc bromide (**1**; 100 mL of a 0.5 M solution in THF, 50 mmol) in THF (150 mL), and the mixture was stirred at rt for 30 min. Glutaryl dichloride (3.2 mL, 25 mmol) was added, and the mixture was stirred at rt for an additional 90 min. The mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated to give a solid. Flash chromatography (from 9:1 to 8:2 hexane−EtOAc) afforded **2a** (6.7 g, 82%): mp 73−74 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (m, 6H, $2CH_3$), 1.88 (m, 6H), 2.32 (m, 4H), 2.45 (m, 8H), 4.12 (m, 4H, $2CH_2$−ethyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.2 ($2CH_3$), 17.6 (CH_2), 18.8 ($2CH_2$), 33.3 ($2CH_2$), 41.4 ($2CH_2$), 41.5 ($2CH_2$), 60.3 ($2CH_2$), 173.0 (2COO), 209.4 (2CO); IR (NaCl) 1735, 1721 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_6$: C 71.52, H 7.37, N 3.79. Found: C 71.50, H 7.42, N 3.84.

Ethyl 5,9-Dioxodecanoate (2b). A mixture of oxalyl chloride (38 mL, 0.44 mol) and 5-oxohexanoic acid (12 mL, 0.1 mol) in anhydrous Et_2O (100 mL) was stirred at rt for 6 h. The solution was concentrated, and the resulting residue was dried to give the acid chloride, which was used in the next step without further purification. A solution of 4-ethoxy-4-oxobutylzinc bromide (**1**; 200 mL of a 0.5 M solution in THF, 0.1 mol) and $Pd[P(C_6H_5)_3]_4$ (5.8 g, 5 mmol) in THF (400 mL) was stirred at rt for 30 min. Then, the above acid chloride was added, and the resulting mixture was stirred at rt for 16 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated to give an oil. Flash chromatography (from 9:1 to 8:2 hexane−EtOAc) afforded diketoester **2b** (14.8 g, 65%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H, CH_3−ethyl), 1.76−1.96 (m, 4H), 2.13 (s, 3H, CH_3), 2.84−2.36 (m, 2H), 2.41−2.51 (m, 6H), 4.12 (q, J=7.1 Hz, 2H, CH_2−ethyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.2 (CH_3−ethyl), 17.6 (CH_2), 18.8 (CH_2), 29.8 (CH_3), 33.2 (CH_2), 41.4 ($2CH_2$), 42.4 (CH_2), 60.3 (CH_2−ethyl), 172.9 (COO), 208.1 (CO), 209.4 (CO); IR (NaCl) 1715 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_4$: C 63.14, H 8.83. Found: C 63.05, H 8.91.

Ethyl 2-(2-Ethoxycarbonylethyl)-3-oxocyclohexenebutyrate (4a). A solution of $LiOH\cdot H_2O$ (8 g, 0.2 mol) in water (125 mL) was added to a solution of **2a** (6 g, 18.3 mmol) in THF (300 mL) and EtOH (350 mL), then the mixture was stirred at rt for 3 h. The mixture was concentrated, and the residue was taken up in 2 N aqueous HCl and extracted with EtOAc. The combined organic extracts were dried and concentrated to give 2-(2-carboxyethyl)-3-oxocyclohexenebutyric acid, which was used in the next step without further purification. Me_3SiCl (10 mL, 80 mmol) was added to a solution of the acid in EtOH (105 mL), and the mixture was stirred at rt for 16 h. The mixture was concentrated, and the residue was taken up in EtOAc and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried and concentrated to give ketodiester **4a** (5.1 g, 90%) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, J =7.2 Hz, 3H), 1.27 (t, J =7.2 Hz, 3H), 1.72−2.05 (m, 4H), 2.28−2.41 (m, 10H), 2.55−2.63 (m, 2H), 4.10 (q, J=7.2 Hz, 2H), 4.14 (q, J =7.2 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1 ($2CH_3$), 20.7 (CH_2), 22.2 (CH_2), 22.9 (CH_2), 30.4 (CH_2), 33.5 (CH_2), 33.7 (CH_2), 34.0 (CH_2), 37.8 (CH_2), 60.0 (CH_2), 60.3 (CH_2), 133.9 (C), 158.7 (C), 172.6 (COO), 172.8 (COO), 198.4 (CO); IR (NaCl) 1778, 1664 cm^{-1}; HRMS calcd for $[C_{17}H_{26}O_5]$ 310.1780, found 310.1778.

Methyl 2-Methyl-6-oxocyclohexenepropionate (4b). Operating as in the above preparation of **4a**, from diketoester **2b** (7.5 g, 33 mmol), $LiOH\cdot H_2O$ (15 g, 0.35 mol), and EtOH (375 mL) for 5 h, and then Me_3SiCl (13 mL, 0.1 mol) and MeOH (80 mL), ketoester **4b** (5.5 g, 85%) was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88−1.96 (m, 2H), 1.97 (s, 3H, CH_3), 2.33−2.40 (m, 6H), 2.59−2.64 (m, 2H), 3.65 (s, 3H, CH_3O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (CH_2), 21.1 (CH_3), 22.1 (CH_2), 32.8 (CH_2), 33.0 (CH_2), 37.7 (CH_2), 51.4 (CH_3O), 133.6 (C), 156.5 (C), 173.5 (COO), 198.2 (CO); IR (NaCl) 1738, 1663 cm^{-1}; HRMS calcd for $[C_{11}H_{16}O_3 + Na]$ 219.100, found 219.099.

Ethyl (3*R*,7a*S*,11a*S*)-5-Oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline-8-butyrate (5a). (*R*)-Phenylglycinol (466 mg, 3.4 mmol) was added to a solution of ketodiester **4a** (350 mg, 1.1 mmol) and AcOH (0.2 mL, 3.4 mmol) in benzene (15 mL). The mixture was heated at reflux for 48 h with azeotropic elimination of water produced by a Dean−Stark apparatus. The resulting mixture was cooled and concentrated. Flash chromatography (from 3:2 to 1:1 hexane−EtOAc) afforded lactam **5a** (253 mg, 60%) as a solid and its 3*R*,7a*R*,11a*R* diastereomer (76 mg, 18%). **5a** (higher R_f): mp 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HSQC) δ 1.26 (t, J =7.2 Hz, 3H, CH_3), 1.65−1.92 (m, 4H, H-7, H-2′), 2.07−2.11 (m, 7H, H-7a, H-10, H-11, H-1′), 2.18−2.76 (m, 4H, H-6, H-3′), 3.89 (t, J=8.8 Hz, 1H, H-2), 4.13 (q, J=7.2 Hz, 2H, CH_2−ethyl), 4.56 (t, J=8.8 Hz, 1H, H-2), 5.30−5.45 (m, 2H, H-3, H-9), 7.17−7.37 (m, 5H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.9 (CH_2), 23.1 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 31.4 (CH_2), 33.7 ($2CH_2$), 43.3 (C-7a), 58.5 (C-3), 60.2 (CH_2−ethyl), 69.5 (C-2), 94.3 (C-11a), 121.0 (C-9), 125.3 (CH-*o*), 127.1 (CH-*p*), 128.6 (CH-*m*), 136.4 (C-8), 140.3 (C-*i*), 169.6 (COO), 173.5 (COO); IR (NaCl) 1731, 1655 cm^{-1}; $[\alpha]^{22}_D$ −97.3 (*c* 1.0, MeOH). Anal. Calcd for $C_{23}H_{29}NO_4$: C 72.04, H 7.62, N 3.65. Found: C 71.63, H 7.62, N 3.53. 7a*R*,11a*R*-epi-**5a** (lower R_f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J =7.2 Hz, 3H, CH_3), 1.61−1.97 (m, 4H), 2.00−2.48 (m, 11H), 3.93 (dd, J=9.2 Hz, 1H, 1.8 Hz, H-2), 4.15 (q, J=7.2 Hz, 2H, CH_2−ethyl), 4.41 (dd, J=9.2 Hz, 1H, 7.2 Hz, H-2), 4.98 (dd, J=7.2 Hz, 1H, 1.8 Hz, H-3), 5.45 (s, 1H, H-9), 7.26−7.31 (m, 5H, H−Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3), 23.0 (CH_2), 23.3 (CH_2), 25.7 (CH_2), 26.0 (CH_2), 30.5 (CH_2), 33.6 (CH_2), 33.9 (CH_2), 42.3 (C-7a), 59.3 (C-3), 60.1 (CH_2−ethyl), 70.9 (C-2), 93.6 (C-11a), 120.0 (C-9), 126.1 (CH-*o*), 127.2 (CH-*p*), 128.4 (CH-*m*), 137.5 (C-8), 141.6 (C-*i*), 167.1 (COO), 173.4 (COO); IR (NaCl) 1731, 1657 cm^{-1}; $[\alpha]^{22}_D$ +53.1 (*c* 0.9, MeOH); HRMS calcd for $[C_{23}H_{29}NO_4]$ 383.2097, found 383.2099.

(3*R*,7a*S*,11a*S*)-8-Methyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (5b). Operating as in the above preparation of **5a**, from ketoester **4b** (9.5 g, 48 mol), (*R*)-phenylglycinol (20 g, 145 mol), and AcOH (8.3 mL, 145 mol) in benzene (750 mL), lactam **5b** (9.5 g, 70%) and its 3*R*,7a*R*,11a*R* diastereomer (2.4 g, 19%) were obtained after flash chromatography (from 3:2 to 1:1 hexane−EtOAc). **5b** (higher R_f): mp 115−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HSQC) δ 1.59−1.79 (m, 2H, H-7, H-11), 1.78 (s, 3H, CH_3), 1.86 (dd, J =13.2 Hz, 1H, 6.6 Hz, H-11), 1.96−2.13 (m, 3H, H-7a, H-10), 2.20−2.29 (m, 1H, H-7), 2.44−2.56 (m, 1H, H-6), 2.70 (dd, J =18.6 Hz, 1H, 6.0 Hz, H-6), 3.91 (t, J =8.5 Hz, 1H, H-2), 4.57 (t, J=8.5 Hz, 1H, H-2), 5.44−5.50 (m, 2H, H-3, H-9), 7.18−7.36 (m, 5H, H−Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5 (CH_3), 22.9 (C-10), 24.7 (C-7), 25.7 (C-11), 31.3 (C-6), 44.8 (C-7a), 58.3 (C-3), 69.4 (C-2), 94.3 (C-11a), 120.9 (C-9), 125.1 (CH-*o*), 127.0 (CH-*p*), 128.4 (CH-*m*), 133.0 (C-8), 140.2 (C-*i*), 169.6 (NCO); IR (NaCl) 1657 cm^{-1}; $[\alpha]^{22}_D$ −102.6 (*c* 1.1, MeOH). Anal. Calcd for $C_{18}H_{21}NO_2$: C 76.29, H 7.47, N 4.94. Found: C 76.60, H 7.52, N, 4.92. 7a*R*,11a*R*-epi-**5b** (lower R_f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56−1.72 (m, 2H), 1.82 (s, 3H, CH_3), 1.96−2.45 (m, 7H), 3.94 (dd, J=9.0, 2.0 Hz, 1H, H-2), 4.42 (dd, J=9.0, 7.5 Hz, 1H, H-2), 4.98 (dd, J =7.5, 2.0 Hz, 1H, H-3), 5.45 (s, 1H, H-9), 7.20−7.35 (m, 5H, H−Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.7 (CH_3), 23.4 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 30.7 (C-6), 43.9 (C-7a),

59.4 (C-3), 71.1 (C-2), 93.8 (C-11a), 120.2 (C-9), 126.2 (CH-*o*), 127.4 (CH-*p*), 128.5 (CH-*m*), 134.4 (C-8), 141.8 (C-*i*), 167.3 (NCO); IR (NaCl) 1657 cm^{-1}; $[\alpha]^{22}_D$ +13.7 (*c* 1.2, MeOH). Anal. Calcd for $C_{18}H_{21}NO_2$: C 76.29, H 7.47, N 4.94. Found: C 76.25, H 7.54, N 4.83.

(3*R*,7a*S*,8*R*,11a*S*)-8-Methyl-5-oxo-3-phenyldecahydrooxazolo-[2,3-*j*]quinoline (6). A solution of lactam **5b** (2 g, 7.1 mmol) in MeOH (150 mL) containing 40% PtO_2 (0.8 g) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration and washed with MeOH. The combined organic solutions were concentrated, and the resulting oil was chromatographed (98:2 hexane−Et_2O) affording pure compound **6** (1.98 g, 98%) as a colorless solid: mp 81−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.21 (d, *J* =7.6 Hz, 3H, 3H, CH_3), 1.35−1.44 (m, 2H, H-10, H-11), 1.57−1.83 (m, 6H, H-7, H-7a, H-9, H-10, H-11), 1.90−1.98 (m, 1H, H-8), 2.08−2.19 (m, 1H, H-7), 2.46 (ddd, *J* =18.4, 11.2, 7.6 Hz, 1H, H-6), 2.63 (dd, *J* =18.4, 7.6 Hz, 1H, H-6), 3.84 (t, *J* =8.4 Hz, 1H, H-2), 4.52 (t, *J* =8.4 Hz, 1H, H-2), 5.30 (t, *J*=8.4 Hz, 1H, H-3), 7.15−7.33 (m, 5H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.7 (C-10), 20.2 (CH_3), 24.8 (C-7), 26.4 (C-11), 30.3 (C-9), 31.2 (C-6), 34.2 (C-8), 45.2 (C-7a), 57.9 (C-3), 69.7 (C-2), 95.5 (C-11a), 125.3 (CH-*o*), 127.0 (CH-*p*), 128.5 (CH-*m*), 140.3 (C-*i*), 169.4 (NCO); IR (NaCl) 1654 cm^{-1}; $[\alpha]^{22}_D$ −113.5 (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91. Found: C 75.86, H 8.06, N 4.88.

(3*R*,7a*S*,8*R*,11a*S*)-8-Methyl-3-phenyl-5-thiodecahydrooxazolo-[2,3-*j*]quinoline (7). Lawesson's reagent (640 mg, 1.6 mmol) was added to a solution of saturated lactam **6** (718 mg, 2.5 mmol) in benzene (50 mL). The resulting mixture was heated at reflux for 3 h, cooled, and concentrated to give an oil. Flash chromatography (9:1 hexane−EtOAc) afforded **7** (500 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.20 (d, *J* =7.2 Hz, 3H, CH_3), 1.37−1.47 (m, 2H, H-10, H-11), 1.58−1.79 (m, 5H, H-7, H-7a, H-9, H-10, H-11), 1.84−1.90 (m, 1H, H-9), 1.92−1.98 (m, 1H, H-8), 1.99−2.11 (m, 1H, H-7), 3.08−3.26 (m, 2H, H-6), 3.94 (t, *J* =8.6 Hz, 1H, H-2), 4.59 (t, *J* =8.6 Hz, 1H, H-2), 5.79 (t, *J* =8.6 Hz, 1H, H-3), 7.10−7.12 (m, 2H, H−Ar), 7.22−7.34 (m, 3H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.6 (C-10), 20.0 (CH_3), 24.7 (C-7), 26.0 (C-11), 29.2 (C-9), 34.2 (C-8), 40.7 (C-6), 44.2 (C-7a), 63.5 (C-3), 69.2 (C-2), 97.6 (C-11a), 125.4 (CH-*o*), 127.1 (CH-*p*), 128.5 (CH-*m*), 138.7 (C-*i*), 198.3 (NCS); IR (NaCl) 1452 cm^{-1}; $[\alpha]^{22}_D$ −138.1 (*c* 1.5, MeOH); HRMS calcd for $[C_{18}H_{23}NSO + H]$ 302.1579, found 302.1573.

(3*R*,7a*S*,8*R*,11a*S*)-5-(Methoxycarbonylmethylene)-8-methyl-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (8). A solution of **7** (1.4 g, 4.7 mmol) and methyl bromoacetate (4.3 mL, 46.5 mmol) in $CHCl_3$ (18 mL) was stirred at rt for 17 h in the dark. The mixture was concentrated, and the residue was taken up with $CHCl_3$ (18 mL). Trimethyl phosphite (2.2 mL, 18.6 mmol) and Et_3N (6 mL) were added, and the resulting solution was heated at reflux for 24 h. The mixture was allowed to cool to rt and concentrated. The residue was chromatographed (9:1 hexane−EtOAc) to afford **8** (1.2 g, 75%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.18 (d, *J*=7.2 Hz, 3H, CH_3), 1.33−1.43 (m, 2H, H-10, H-11), 1.56−1.99 (m, 8H, H-7, H-7a, H-8, H-9, H-10, H-11), 3.11−3.21 (m, 1H, H-6), 3.25−3.37 (m, 1H, H-6), 3.49 (s, 3H, CH_3O), 3.70 (t, *J*=8.4 Hz, 1H, H-2), 4.29 (s, 1H, H-1′), 4.51 (t, *J* =8.4 Hz, 1H, H-2), 4.73 (t, *J* =8.4 Hz, 1H, H-3), 7.11−7.17 (m, 2H, H−Ar), 7.23−7.36 (m, 3H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9 (C-10), 20.2 (CH_3), 23.9 (C-7), 26.1 (C-6), 26.2 (C-11), 30.2 (C-9), 34.5 (C-8), 44.7 (C-7a), 49.8 (CH_3O), 61.7 (C-3), 70.2 (C-2), 84.7 (C-1′), 96.0 (C-11a), 125.3 (CH-*o*), 127.4 (CH-*p*), 128.8 (CH-*m*), 139.2 (C-*i*), 159.0 (C-5), 169.0 (COO); IR (NaCl) 1788 cm^{-1}; $[\alpha]^{22}_D$ −132.2 (*c* 0.5, MeOH); HRMS calcd for $[C_{21}H_{27}NO_3 + H]$ 342.2069, found 342.2063.

(2*R*,4a*S*,5*R*,8a*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-2-(methoxycarbonylmethyl)-5-methyldecahydroquinoline (9). A solution of **8** (340 mg, 1.0 mmol) and AcOH (2.5 mL, 44 mmol) in MeOH (25 mL) containing 40% PtO_2 (14 mg) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration through a Celite pad, the filtrate was concentrated, and the residue was taken up with EtOAc. The organic solution was washed with 10% aqueous KOH, dried, and concentrated. The resulting oil was chromatographed (from 9:1 to 8:2 hexane−EtOAc) to afford **9** (170 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.91 (d, *J*=7.2 Hz, 3H, CH_3), 1.12−1.20 (m, 3H, H-4, H-6, H-7), 1.24−1.33 (m, 1H, H-8), 1.35−1.51 (m, 5H, H-3, H-4a, H-6, H-7, H-8), 1.52−1.67 (m, 2H, H-3, H-5), 1.74 (qd, *J*=13.2, 3.6 Hz, 1H, H-4), 2.49 (dd, *J*=14.4, 9.2 Hz, 2H, H-1″), 2.68 (dd, *J*=14.4, 4.8 Hz, 1H, H-1″), 2.86−2.96 (m, 1H, H-8a), 3.54−3.63 (m, 1H, H-2), 3.64−3.71 (m, 1H, H-1′), 3.70 (s, 3H, CH_3), 3.84−3.94 (m, 1H, H-1′), 7.21−7.38 (m, 5H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 (CH_3), 20.9 (C-7), 21.4 (C-4), 27.1 (C-6), 28.5 (C-3), 29.3 (C-8), 34.5 (C-5), 39.2 (C-1″), 42.0 (C-4a), 49.3 (C-2), 51.6 (CH_3O), 55.5 (C-8a), 62.5 (C-2′), 68.9 (C-1′), 127.6 (CH-*o*), 128.3 (CH-*p*), 128.4 (CH-*m*), 140.6 (NCO), 173.4 (COO); IR (NaCl) 2925, 1736 cm^{-1}; $[\alpha]^{22}_D$ −10.9 (*c* 1.4, MeOH); HRMS calcd for $[C_{21}H_{31}NO_3 + H]$ 346.2376, found 346.2387.

(2*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethyl)-5-methyldecahydroquinoline (10). A solution of **8** (560 mg, 1.6 mmol) and AcOH (4.1 mL, 69 mmol) in MeOH (40 mL) containing 40% PtO_2 (230 mg) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration through a Celite pad, the filtrate was concentrated, and the residue was taken up with EtOAc. The organic solution was washed with 10% aqueous KOH, dried, and concentrated, affording an oil, which was used without further purification in the next step. A solution of the oil and di-*tert*-butyl dicarbonate (700 mg, 3.2 mmol) in MeOH (30 mL) containing 40% $Pd(OH)_2$/C (200 mg) was stirred under hydrogen at rt for 16 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. The residue was chromatographed (9:1 hexane−Et_2O) to afford unsaturated ester **10** (280 mg, 54%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.06 (d, *J* =7.2 Hz, 3H, CH_3), 1.25−1.30 (m, 2H, H-3, H-4), 1.44−1.53 (m, 6H, H-3, H-4a, H-6, H-7), 1.46 (s, 9H, ^{t}Bu), 1.67−1.71 (m, 2H, H-8), 1.78−1.84 (m, 2H, H-4, H-5), 2.45 (dd, *J* =14.7, 3.3 Hz, 1H, H-1′), 2.63 (dd, *J*=14.7, 10.5 Hz, 1H, H-1′), 3.67 (s, 3H, CH_3O), 4.17−4.21 (m, 1H, H-8a), 4.48−4.55 (m, 1H, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (CH_3), 20.3 (C-7), 20.9 (C-4), 26.7 (C-3), 28.4 (C-6), 28.5 (CH_3-^{t}Bu), 28.5 (C-8), 34.4 (C-5), 39.6 (C-1′), 41.6 (C-4a), 47.1 (C-2), 49.3 (C-8a), 51.6 (CH_3O), 79.5 (C-^{t}Bu), 155.0 (NCO), 172.1 (COO); IR (NaCl) 1740, 1687 cm^{-1}; $[\alpha]^{22}_D$ −25.9 (*c* 0.9, MeOH); HRMS calcd for $[C_{18}H_{31}NO_4 + H]$ 326.2331, found 326.2335.

(2*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-(2-hydroxyethyl)-5-methyldecahydroquinoline (11). $LiAlH_4$ (200 mg, 5.3 mmol) was slowly added to a cooled solution (0 °C) of **10** (173 mg, 0.53 mmol) in anhydrous THF (5 mL), and the mixture was stirred at rt for 1 h. The reaction was quenched with water, and the resulting mixture was extracted with EtOAc. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (8:2 hexane−EtOAc) to give alcohol **11** (150 mg, 94%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.06 (d, *J* =7.2 Hz, 3H, CH_3), 1.25−1.31 (m, 3H, H-3, H-4), 1.42−1.53 (m, 5H, H-3, H-4a, H-6, H-7), 1.48 (s, 9H, ^{t}Bu), 1.59−1.65 (m, 3H, H-1′, H-6, H-8), 1.75−1.86 (m, 4H, H-1′, H-5, H-8), 3.40 (br s, 1H, H-2′), 3.58 (br s, 1H, H-2′), 4.20 (br s, 1H, H-8a), 4.33 (br s, 1H, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 (CH_3), 20.3 (C-7), 21.4 (C-4), 26.7 (C-3), 28.3 (CH_3-^{t}Bu), 28.7 (C-6), 30.1 (C-8), 34.3 (C-5), 38.4 (C-1′), 42.0 (C-4a), 45.8 (C-2), 49.8 (C-8a), 58.9 (C-2′), 80.0 (C-^{t}Bu), 156.8 (NCO); IR (NaCl) 3449, 1659 cm^{-1}; $[\alpha]^{22}_D$ +15.5 (*c* 1.0, MeOH); HRMS calcd for $[C_{17}H_{31}NO_3 + H]$ 298.2382, found 298.2376.

(−)-Pumiliotoxin C. Dess−Martin reagent (360 mg, 0.86 mmol) was added to a solution of alcohol **11** (180 mg, 0.61 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was stirred at rt for 2.5 h. Then, Et_2O (9 mL), 1 M aqueous $Na_2S_2O_4$ (2 mL), and saturated aqueous $NaHCO_3$ (2 mL) were added, and the resulting mixture was stirred for 45 min. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried, and concentrated to give the corresponding aldehyde as an oil, which was used without further purification in the next step. BuLi (0.9 mL of a 1.6 M solution in hexane, 1.4 mmol) was added to a solution of methyltriphenylphosphonium bromide (535 mg, 1.5 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 1.5 h. Then, a solution of the above aldehyde in THF (2 mL) was added, and the resulting mixture was stirred at rt for 16 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed (95:5 hexane−EtOAc) to give (2*R*,4a*S*,5*R*,8a*R*)-2-allyl-1-(*tert*-butoxycarbonyl)-5-methyldecahydroquinoline (114 mg, 64%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.07 (d, J=7.2 Hz, 3H, CH_3), 1.20−1.37 (m, 3H, H-3, H-7), 1.42−1.50 (m, 5H, H-3, H-4, H-4a, H-6), 1.46 (s, 9H, ^{t}Bu), 1.50−1.84 (m, 4H, H-5, H-6, H-8), 2.23−2.32 (m, 2H, H-1′), 4.02−4.10 (m, 1H, H-2), 4.18−4.25 (m, 1H, H-8a), 4.99−5.05 (m, 2H, H-3′), 5.70−5.81 (m, 1H, H-2′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.4 (CH_3), 20.4 (C-4), 21.1 (C-7), 26.8 (C-3), 27.2 (C-6), 28.5 (CH_3-^{t}Bu), 28.6 (C-8), 34.5 (C-5), 40.0 (C-1′), 41.9 (C-4a), 49.3 (C-2), 50.2 (C-8a), 79.1 (C-^{t}Bu), 116.5 (C-3′), 136.7 (C-2′), 155.7 (NCO); IR (NaCl) 1686 cm^{-1}; $[\alpha]^{22}_D$ +4.7 (*c* 0.8, MeOH); HRMS calcd for [$C_{18}H_{31}NO_2$ +Na] 316.2252, found 316.2247. A solution of the above alkene (60 mg, 0.2 mmol) in MeOH (7 mL) containing 40% PtO_2 (25 mg) was stirred under hydrogen at rt for 1 h. The catalyst was removed by filtration and washed with MeOH. The combined organic solutions were concentrated, and the resulting oil was chromatographed (98:2 hexane−Et_2O) affording pure (2*S*,4a*S*,5*R*,8a*R*)-1-(*tert*-butoxycarbonyl)-5-methyl-2-propyldecahydroquinoline (56 mg, 95%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.92 (t, J=7.0 Hz, 3H, H-3′), 1.06 (d, J=7.2 Hz, 3H, CH_3), 1.20−1.26 (m, 3H, H-3, H-4), 1.40−1.56 (m, 9H, H-1′, H-2′, H-3, H-4a, H-7, H-8), 1.46 (s, 9H, ^{t}Bu), 1.62−1.67 (m, 2H, H-6), 1.77−1.84 (m, 2H, H-4, H-5), 4.00 (br s, 1H, H-8a), 4.20 (br s, 1H, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (C-3′), 19.3 (CH_3), 20.4 (C-2′), 20.8 (C-7), 21.4 (C-4), 26.8 (C-3), 28.0 (C-6), 28.5 (C-8), 28.5 (CH_3-^{t}Bu), 34.6 (C-5), 37.9 (C-1′), 42.1 (C-4a), 49.2 (C-2), 50.3 (C-8a), 78.9 (C-^{t}Bu), 155.4 (NCO); IR (NaCl) 1686 cm^{-1}; $[\alpha]^{22}_D$ +18.8 (*c* 1.5, MeOH); HRMS calcd for [$C_{18}H_{33}NO_2$ + H] 296.2590, found 296.2584. To a solution of the above saturated compound (50 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL, 6.5 mmol), and the mixture was stirred at rt for 15 min. Then, CH_2Cl_2 (3 mL) was added, and the solution was washed with 10% aqueous KOH, dried, and filtered. A 1 M HCl in MeOH sample was added to the filtrate, and the solution was concentrated to give (−)-pumiliotoxin C hydrochloride (39 mg, 99%) as a colorless solid: mp 248−250 °C; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.90 (d, J =6.4 Hz, 3H, CH_3), 0.92 (t, J=7.4 Hz, 3H, H-3′), 0.97−1.03 (m, 1H, H-6), 1.22−1.27 (m, 1H, H-2′), 1.40−1.45 (m, 4H, H-2′, H-3, H-4a, H-7), 1.46−1.62 (m, 2H, H-4, H-8), 1.76−1.88 (m, 2H, H-4, H-6), 2.07−2.17 (m, 4H, H-1′, H-3, H-5), 2.33−2.50 (m, 2H, H-7, H-8), 2.98 (br s, 1H, H-2), 3.32 (br s, 1H, H-8a), 8.40 (br s, 1H, NH), 9.45 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7 (C-3′), 19.1 (C-2′), 19.7 (CH_3), 20.4 (C-7), 23.1 (C-4), 25.1 (C-3), 27.1 (C-5), 29.1 (C-8), 34.3 (C-1′), 34.8 (C-6), 40.8 (C-4a), 58.0 (C-8a), 60.1 (C-2); IR (NaCl) 2930, 2872 cm^{-1}; $[\alpha]^{22}_D$ −15.3 (*c* 0.5, MeOH).

(3*R*,7a*S*,11a*S*)-8-Methyl-3-phenyl-5-thio-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (12). Operating as in the preparation of **7**, from lactam **5b** (2.4 g, 8.5 mmol) and Lawesson's reagent (2.1 g, 5.3 mmol), thiolactam **12** (2.35 g, 93%) was obtained as a solid after flash chromatography (9:1 hexane−EtOAc): mp 117−122 °C; ^{1}H NMR (200 MHz, $CDCl_3$, COSY, HETCOR) δ 1.57−1.75 (m, 1H, H-7), 1.76−1.81 (m, 1H, H-11), 1.78 (s, 3H, CH_3), 1.85−1.98 (m, 1H, H-11), 1.98−2.18 (m, 2H, H-10), 2.20−2.28 (m, 2H, H-7, H-7a), 3.03−3.19 (m, 1H, H-6), 3.21−3.38 (m, 1H, H-6), 4.00 (dd, J=8.8, 7.8 Hz, 1H, H-2), 4.63 (t, J=8.8 Hz, 1H, H-2), 5.45 (s, 1H, H-9), 5.96 (t, J=7.8 Hz, 1H, H-3), 7.11−7.16 (m, 2H, H−Ar), 7.26−7.39 (m, 3H, H−Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5 (CH_3), 22.8 (C-10), 25.0 (C-11), 25.3 (C-7), 40.7 (C-6), 44.1 (C-7a), 64.1 (C-3), 69.0 (C-2), 96.0 (C-11a), 120.4 (C-9), 125.2 (CH-*o*), 127.1 (CH-*p*), 128.5 (CH-*m*), 133.5 (C-8), 138.6 (C-*i*), 199.0 (NCS); IR (NaCl) 1450 cm^{-1}; $[\alpha]^{22}_D$ −209.1 (*c* 0.6, MeOH); HRMS calcd for [$C_{18}H_{21}NOS$] 299.1344, found 299.1347.

(3*R*,7a*S*,11a*S*)-5-(Methoxycarbonylmethylene)-8-methyl-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (13). Operating as in the preparation of **8**, from thiolactam **12** (700 mg, 2.34 mmol), methyl bromoacetate (2 mL, 23.4 mmol) in $CHCl_3$ (10 mL), and then trimethyl phosphite (1.1 mL, 9.4 mmol) and Et_3N (3 mL), compound **13** (650 mg, 82%) was obtained as an oil after flash chromatography (7:3 hexane−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.45−1.59 (m, 1H, H-7), 1.72−1.83 (m, 1H, H-11), 1.77 (s, 3H, CH_3), 1.80−2.10 (m, 4H, H-7a, H-10, H-11), 2.20−2.30 (m, 1H, H-7), 3.15−3.39 (m, 2H), 3.50 (s, 3H, CH_3O), 3.77 (t, J=8.5 Hz, 1H, H-2), 4.38 (s, 1H, CH=), 4.55 (t, J=8.5 Hz, 1H, H-2), 4.86 (t, J =8.5 Hz, 1H, H-3), 5.42 (s, 1H, H-9), 7.15−7.18 (m, 2H, H−Ar), 7.27−7.38 (m, 3H, H−Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6 (CH_3), 23.0 (C-10), 24.4 (C-7), 25.9 (C-11), 26.4 (C-6), 44.7 (C-7a), 49.9 (CH_3O), 62.6 (C-3), 70.0 (C-2), 85.3 (CH=), 94.5 (C-11a), 120.2 (C-9), 125.2 (CH-*o*), 127.5 (CH-*p*), 128.9 (CH-*m*), 134.2 (C-8), 139.2 (C-*i*), 159.3 (C-5), 168.8 (COO); IR (NaCl) 1739 cm^{-1}; $[\alpha]^{22}_D$ −155.2 (*c* 0.8, MeOH); HRMS calcd for [$C_{21}H_{25}NO_3$] 339.1834, found 339.1832.

(2*R*,4a*R*,5*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethyl)-5-methyldecahydroquinoline (*ent*-2-epi-10). A solution of **13** (100 mg, 0.3 mmol) and AcOH (0.9 mL, 15 mmol) in MeOH (10 mL) containing 40% PtO_2 (40 mg) was stirred under hydrogen at rt for 16 h. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was taken up with EtOAc and extracted with 2 N aqueous HCl. The aqueous solution was basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc. These organic extracts were dried and concentrated to give an oil, which was used without further purification in the next step. A solution of the oil and di-*tert*-butyl dicarbonate (65 mg, 0.3 mmol) and Et_3N (50 μL, 0.3 mmol) in CH_2Cl_2 (5 mL) was stirred under hydrogen at rt for 16 h. The solution was washed with 2 N aqueous HCl, dried, and concentrated. The resulting residue was chromatographed (9:1 hexane−EtOAc) to afford *ent*-2-epi-**10** (43 mg, 45%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 0.78−0.86 (m, 2H, H-4), 0.99 (d, J=7.3 Hz, 3H, CH_3), 1.14−1.23 (m, 2H, H-6), 1.39 (s, 9H, ^{t}Bu), 1.48−1.91 (m, 8H, H-3, H-4a, H-5, H-7, H-8), 2.40 (dd, J=15.0, 10.0 Hz, 1H, H-1′), 2.65 (dd, J=15.0, 4.0 Hz, 1H, H-1′), 3.60 (s, 3H, CH_3O), 3.84 (dt, J=12.0, 4.5 Hz, 1H, H-8a), 4.12−4.19 (m, 1H, H-2); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.0 (CH_3), 19.7 (C-4), 19.9 (C-7), 24.0 (C-3), 25.9 (C-6), 28.5 (3CH_3-^{t}Bu), 29.7 (C-8), 33.2 (C-5), 36.8 (C-4a), 39.9 (C-1′), 48.0 (C-2), 50.1 (C-8a), 51.5 (CH_3O), 79.4 (C-^{t}Bu), 154.8 (COO), 172.1 (COO); IR (NaCl) 1740, 1690 cm^{-1}; $[\alpha]^{22}_D$ −5.1 (*c* 0.9, MeOH). Anal. Calcd for $C_{18}H_{31}NO_4$: C 66.43, H 9.60, N 4.30. Found: C 66.79, H 9.90, N 4.26.

(2*R*,4a*R*,5S,8a*S*)-1-(*tert*-Butoxycarbonyl)-2-(2-hydroxyethyl)-5-methyldecahydroquinoline (*ent*-2-epi-11). Operating as in the

preparation of **11**, from *ent*-2-epi-**10** (1.4 g, 4.3 mmol) and $LiAlH_4$ (1.7 g, 43.8 mmol), alcohol *ent*-2-epi-**11** (1.2 g, 94%) was obtained as a solid after flash chromatography (from 9:1 to 8:2 hexane−EtOAc): mp 85−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.05 (d, J =7.5 Hz, 3H, CH_3), 1.13−1.27 (m, 3H, H-6, H-8), 1.41−1.45 (m, 3H, H-4, H-7), 1.48 (s, 9H, ^{t}Bu), 1.58−1.78 (m, 5H, H-3, H-4, H-5, H-1′), 1.84−1.94 (m, 2H, H-4a, H-8), 1.96−2.06 (m, 1H, H-3), 3.47−3.65 (m, 2H, H-2′), 3.80 (dt, J=12, 4.2 Hz, 1H, H-8a), 4.06−4.16 (m, 1H, H-2); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.1 (CH_3), 19.5 (C-4), 19.7 (C-7), 25.0 (C-3), 25.9 (C-6), 28.4 (3CH_3-^{t}Bu), 29.9 (C-8), 32.8 (C-5), 35.9 (C-4a), 39.6 (C-1′), 46.8 (C-2), 50.8 (C-8a), 59.1 (C-2′), 79.7 (C-^{t}Bu), 156.7 (NCO); IR (NaCl) 3450, 1662 cm^{-1}; $[\alpha]^{22}_D$ −0.8 (*c* 1.0, MeOH). Anal. Calcd for $C_{17}H_{31}NO_3$: C 68.65, H 10.51, N 4.71. Found: C 68.62, H 10.85, N 4.62.

***ent*-2-epi-Pumiliotoxin C.** Operating as in the pumiliotoxin C series, from alcohol *ent*-2-epi-**11** (180 mg, 0.61 mmol) and Dess−Martin reagent (365 mg, 0.86 mmol), (2*R*,4a*R*,5*S*,8a*S*)-1-(*tert*-butoxycarbonyl)-5-methyl-2-(2-oxoethyl)decahydroquinoline (140 mg, 78%) was obtained as a solid after flash chromatography (95:5 hexane−EtOAc): mp 81−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 0.85−0.93 (m, 1H, H-4), 1.07 (d, J=7.2 Hz, 3H, CH_3), 1.19−1.34 (m, 3H, H-6, H-8), 1.45 (s, 9H, ^{t}Bu), 1.58−2.06 (m, 8H, H-3, H-4, H-4a, H-5, H-7, H-8), 2.56 (ddd, J=16.0, 7.5, 2.1 Hz, 1H, H-1′), 2.78 (ddd, J=16.0, 5.7, 2.1 Hz, 1H, H-1′), 3.94 (dt, J=12.0, 4.5 Hz, 1H, H-8a), 4.28−4.35 (m, 1H, H-2), 9.75 (t, J =2.1 Hz, 1H, H-2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.0 (CH_3), 19.7 (C-4), 20.3 (C-7), 25.7 (C-3), 25.9 (C-6), 28.4 (3CH_3-^{t}Bu), 29.4 (C-8), 33.2 (C-5), 37.1 (C-4a), 46.0 (C-2), 50.1 (C-1′), 50.4 (C-8a), 79.6 (C-^{t}Bu), 154.9 (NCO), 200.7 (CO); IR (NaCl) 1725, 1686 cm^{-1}; $[\alpha]^{22}_D$ −5.2 (*c* 0.9, MeOH); HRMS calcd for $[C_{17}H_{29}NO_3 + Na]$ 318.2045, found 318.2040. Operating as in the previous series, from the above aldehyde (100 mg, 0.34 mmol), BuLi (0.4 mL of a 1.6 M solution in hexane, 0.63 mmol), and methyltriphenylphosphonium bromide (243 mg, 0.68 mmol) in THF (2.7 mL), (2*R*,4a*R*,5*S*,8a*S*)-2-allyl-1-(*tert*-butoxycarbonyl)-5-methyldecahydroquinoline (70 mg, 70%) was obtained as an oil after flash chromatography (95:5 hexane−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 0.81−0.84 (m, 1H, H-4), 0.99 (d, J =7.2 Hz, 3H, CH_3), 1.03−1.19 (m, 3H, H-6, H-8), 1.40 (s, 9H, ^{t}Bu), 1.42−1.88 (m, 8H, H-3, H-4, H-4a, H-5, H-7, H-8), 2.03−2.22 (m, 1H, H-1′), 2.32−2.40 (m, 1H, H-1′), 3.66 (m, 1H, H-2), 3.82 (dt, J=12.3, 4.5 Hz, 1H, H-8a), 4.92−5.01 (m, 2H, H-3′), 5.62−5.76 (m, 1H, H-2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.1 (CH_3), 19.6 (C-4), 19.7 (C-7), 22.1 (C-3), 25.9 (C-6), 28.5 (3CH_3-^{t}Bu), 29.9 (C-8), 33.2 (C-5), 36.6 (C-4a), 39.9 (C-1′), 49.9 (C-8a), 50.8 (C-2), 78.9 (C-^{t}Bu), 116.4 (C-3′), 136.2 (C-2′), 155.0 (NCO); IR (NaCl) 1688 cm^{-1}; $[\alpha]^{22}_D$ −2.1 (*c* 1.0, MeOH); HRMS calcd for $[C_{18}H_{31}NO_2 + Na]$ 316.2247, found 316.2236. A solution of the above alkene (60 mg, 0.2 mmol) in MeOH (7 mL) containing 40% Pd−C (25 mg) was stirred under hydrogen at rt for 1 h. After the usual workup, flash chromatography (98:2 hexane−Et_2O) afforded pure (2*S*,4a*R*,5*S*,8a*S*)-1-(*tert*-butoxycarbonyl)-5-methyl-2-propyldecahydroquinoline (57 mg, 97%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.92 (t, J=7.2 Hz, 4H, CH_3, H-4), 1.05 (d, J=7.2 Hz, 3H, CH_3), 1.17−1.38 (m, 5H, H-6, H-8, H-2′), 1.42−1.52 (m, 3H, H-4, H-7, H-1′), 1.46 (s, 9H, ^{t}Bu), 1.53−1.94 (m, 7H, H-3, H-4a, H-5, H-7, H-8, H-1′), 3.70−3.76 (m, 1H, H-2), 3.88 (dt, J=12.0, 4.4 Hz, 1H, H-8a); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3), 19.1 (CH_3), 19.8 (C-4), 19.9 (C-7), 20.4 (C-2′), 22.6 (C-3), 26.0 (C-6), 28.6 (3CH_3-^{t}Bu), 29.9 (C-8), 33.1 (C-5), 36.5 (C-4a), 37.6 (C-1′), 49.9 (C-2), 50.9 (C-8a), 78.6 (C-^{t}Bu), 155.1 (NCO); IR (NaCl) 1688 cm^{-1}; $[\alpha]^{22}_D$ +14.7 (*c* 0.9, MeOH). Anal. Calcd for $C_{18}H_{33}NO_2$: C 73.17, H 11.26, N 4.74. Found: C 72.84, H 11.65, N 4.74. To a solution of the above saturated compound (100 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (2 mL) was added TFA (0.5 mL, 26 mmol), and the mixture was stirred at rt for 15 min. Then, CH_2Cl_2 (3 mL) was added, and the solution was washed with 10% aqueous KOH, dried, and concentrated to give *ent*-2-epi-pumiliotoxin C (65 mg, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.88−0.92 (t, J =6.8 Hz, 3H, H-3′), 0.98−1.00 (d, J = 7.2 Hz, 3H, CH_3), 1.06−2.05 (m, 16H), 2.79−2.82 (m, 1H, H-2), 3.10−3.15 (dt, J=10.8, 4.1 Hz, 1H, H-8a); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.2 (C-3′), 19.2 (C-4), 19.3 (CH_3), 20.5 (C-7), 25.2 (C-3), 28.3 (C-8), 29.7 (CH_2), 31.4 (CH_2), 32.5 (C-5), 38.3 (C-1′), 41.8 (C-4a), 49.6 (C-2), 50.0 (C-8a); IR (NaCl) 2859 cm^{-1}; $[\alpha]^{22}_D$ −22.2 (*c* 0.6, MeOH). For the hydrochloride: mp 230−235 °C; $[\alpha]^{22}_D$ −13.3 (*c* 1.1, MeOH).

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Supporting Information Available: Experimental procedures for compounds **14**−**17**, copies of the ^{1}H and ^{13}C NMR spectra of all compounds, and X-ray crystallographic data for compounds **5b**, **6**, and *ent*-2-epi-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.