# *Notes*

## Resolution of δ-Lactams Provides Access to Nonracemic Benzoquinolinones: The Synthesis of LY300502 and LY300503

Bret A. Astleford, James E. Audia, Jack Deeter, Perry C. Heath, Samantha K. Janisse, Thomas J. Kress, James P. Wepsiec, and Leland O. Weigel*

*Chemical Process Research and Development, Lilly Research Laboratories, A Division of Eli Lilly & Company, Indianapolis, Indiana 46285-4813*

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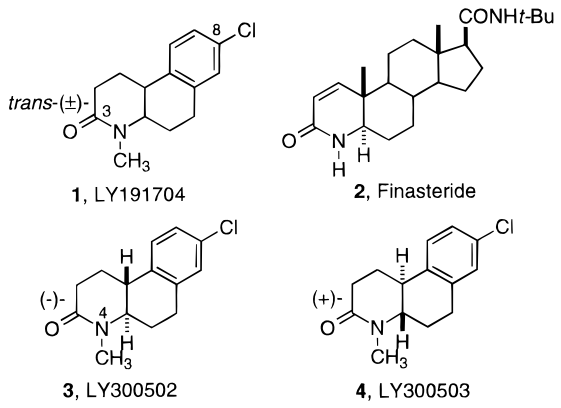
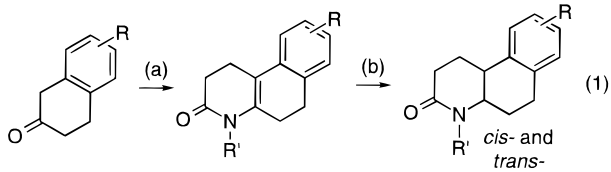
Recently, LY191704 (**1**) was synthesized[1] and identified as a selective, potent, noncompetitive type I inhibitor of 5-α-reductase in cell cultures derived from human foreskin fibroblasts.[2] This activity may be useful in the development of new drugs for the treatment of acne, male pattern baldness, benign prostatic hyperplasia, or prostatic cancer and may augment the utility of finasteride (**2**).[3] As part of the development portfolio[4] for this new drug, a reliable and efficient process for the preparation of large amounts of **1** was required. In addition, the enantiomers of **1**, LY300502 (**3**) and LY300503 (**4**), were required for preclinical evaluation and potential commercial development.




We disclose herein the synthesis of **1** with a high degree of regiochemical control and enhanced stereoselectivity. We also present a new and practical method for the resolution of **1** into **3** and **4**.

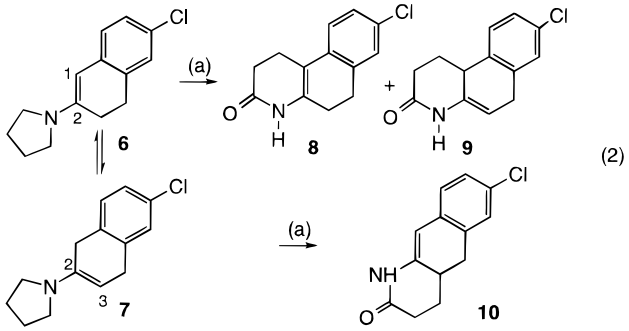
**Synthesis of LY191704.** The benzoquinolinone nucleus of **1** and related compounds were previously prepared[1] by conversion of the 2-tetralone derivative into an enamine followed by aza-annulation[5] with an acrylamide derivative. Kursanov-type reduction of the enelactam (triethylsilane−trifluoroacetic acid, TES−TFA)[6] gave mixtures of the *cis*- and *trans*-benzoquinolinones (eq 1).




(1)

(a) pyrrolidine; $CH_2$=CHNHR' (b) TES-TFA

When an aza-annulation reaction was conducted as described by Ninomiya[5c] with 6-chloro-2-tetralone[7] (**5**), problems of regioselectivity were encountered which have not been previously detailed.[8] Fusion of enamine of **6**[7a] with acrylamide[5c] (Ninomiya's protocol) gave **8**, the isomer **10**,[9] and 3−5% of the nonconjugated isomer[5d] **9** (eq 2).




(2)

(a) $CH_2$=$CH_2CONH_2$, *p*-TsOH, no solvent, 85 °C

Upon isolation, a 60:40 mixture of **8**:**10** was obtained in 75% yield.[8a] The in situ ratio of **8**:**10** was highly

(1) (a) For synthesis and SAR of LY191704, see: Jones, C. D.; Audia, J. E.; Hirsch, K. S.; Lawhorn, D. E.; McQuaid, L. A.; Neubauer, B. L.; Pike, A. J.; Pennington, P. A.; Stamm, N. B.; Toomey, R. E. *J. Med. Chem.* **1993**, *36*, 421. (b) Neubauer, B. L.; Goode, R. L.; Gray, H. M.; Hanke, C. W.; Hirsch, K. S.; Hsiao, K. C.; Jones, C. D.; Lawhorn, D. E.; McQuaid, L.; Toomey, R. E.; Valia, K.; Audia, J. E. *Drugs Future*, **1995**, *20*, 144. (c) Hirsch, K. S.; Jones, C. D. EP Appl. 531026, August 20, 1992.

(2) (a) Hirsch, K. S.; Jones, C. D.; Audia, J. E.; Anderson, S.; McQuaid, L.; Stamm, N. B.; Pennington, P.; Russell, D. W.; Neubauer, B. L.; Toomey, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5277. (b) Holt, D. A.; Levy, M. A.; Ladd, D. L.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Metcalf, B. W. *J. Med. Chem.* **1990**, *33*, 937.

(3) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Casccieri, M. A.; Cheeung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298.

(4) Weigel, L. O.; Astleford, B. A. *Chirality in Industry - II*; Collins, A. N., Crosby, J., Sheldrake, G. N., Ed.; Wiley: New York, 1996, in press.

(5) (a) Stork, G. *Pure Appl. Chem.* **1968**, *17*, 383. (b) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647. (c) Ninomiya, I.; Higuchi, S.; Mori, T. *J. Chem. Soc., Chem. Commun.* **1971**, 457. (d) El-Barbary, A. A.; Carlsson, S.; Lawesson, S. O. *Tetrahedron* **1982**, 405. (e) Review of enamine mediated aza-annulation: Stille, J. R.; Barta, N. S. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1996; Vol. 17, in press.

(6) (a) Cannon, J. G.; Chang, Y.; Amoo, V. E.; Walker, K. A. *Synthesis* **1986**, 494. (b) Using isomer-free **8**, we conducted a series of reductions isothermally without solvent (to increase rate) and measured the % of *cis*-**13**: temperature °C, (% *cis*): −15° (2−3%); 0° (7−9%); 34° (14%); 83° (18%).

(7) (a) Nixon, J. A.; Pioch, R. P.; Schaus, J. M.; Titus, R. D., European Pat. Appl. EP 343830 A2, November 29, 1989. (b) For the preparation of 6-chloro-2-tetralone, see Rosowsky, A.; Battiglia, J; Chen, K. K. N.; Modest, E. J. *J. Org. Chem.* **1968**, *33*, 4288. (c) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.

(8) (a) Astleford, B. A.; Deeter, J.; Kress, T. J.; Janisse, S. K.; Weigel, L. O.; Wepsiec, J. P. 206th National American Chemical Society Meeting, Chicago, IL ORGN075, August 23, 1993. (b) When the aza-annulation with β-tetralone was performed in our labs, the yield reported by Ninomiya was reproduced. The isomer distribution derived from **5** is due, in part, to the inductive/resonance effects of the 6-halogen substituent.

(9) For similar observations of regioselectivity in the alkylation of tetralone enamines due to 1-8 peri-effects, see: (a) Volpe, T.; Revial, G.; Pfau, M.; d'Angelo, J. *Tetrahedron Lett.* **1987**, *28*, 2367. (b) d'Angelo, J. *Tetrahedron Lett.* **1988**, *29*, 4427.

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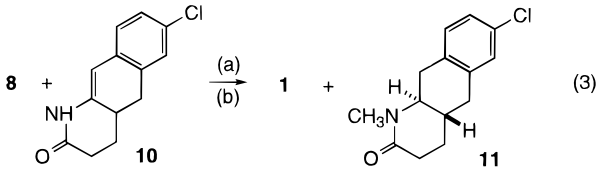
variable and ranged from approximately 60:40 to 85:15. Although we observed only the $\Delta^{1,2}$ enamine isomer **6** by $^1$H NMR, compound **10** arose[9] from the reaction of the $\Delta^{2,3}$ enamine **7**. Necessarily, the alkylation of **7** was substantially faster than reaction of **6**. Interestingly, the ratio of **8**:**10** varied[10a] during the course of the reaction, which suggested that the equilibrium and/or relative rate of alkylation of the enamine **6** and **7** changed with the changing reaction medium.[10b]

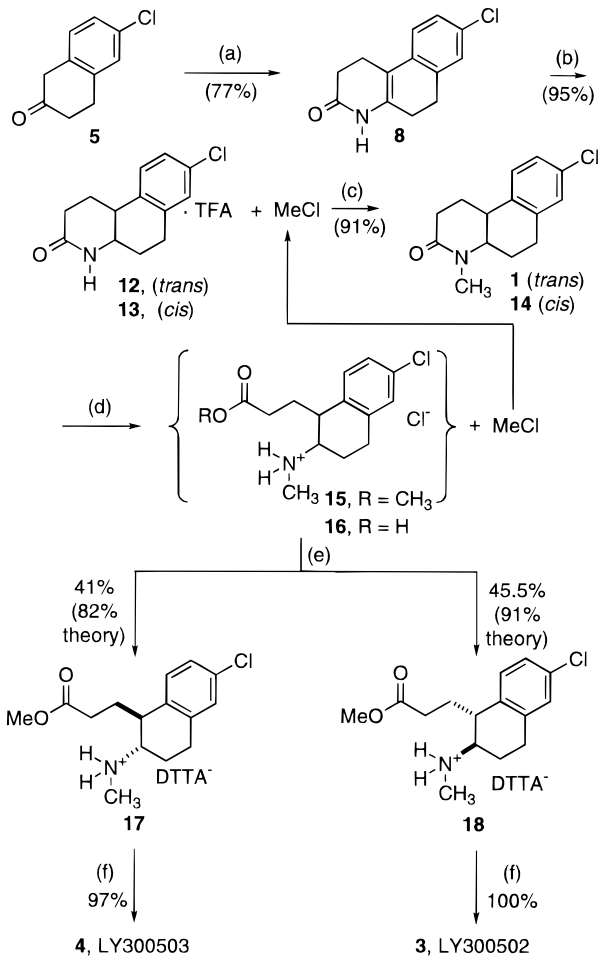
The structure assignment of **10** was in contrast to results recently reported by Cannon's group in the aza-annulation of 8-methoxy-2-tetralone.[11] Therefore, the structure of **10** was unambiguously established. The purified mixture of **8** and **10** from above was subjected to reduction (TFA-TES) and methylated (vide infra) to give a mixture of **1** and **11** (equation 3). Structure determination by single crystal X-ray analysis of a purified sample of **11**[12] corroborated our assignment of **10**. In addition, the reduction of **10** had proceeded stereospecifically[11b] to give the *trans* isomer **11**.[11c]




(a) TES-TFA (b) MeCl-NaI, THF, aqueous NaOH

In previous work we found the product distribution of the aza-annulation process with 2-tetralones could be controlled.[8] Reaction of the pyrrolidine enamine **6** proceeded well in solution with excess acrylamide. Under optimized laboratory conditions (e.g., isopropyl acetate, 89 °C, 4 mol % TsOH, 4−5 equiv of acrylamide) the in situ ratio of **8**:**10** was improved to 95:5, and **8** crystallized from the reaction medium in 77% yield (Scheme 1).

**Scheme 1**



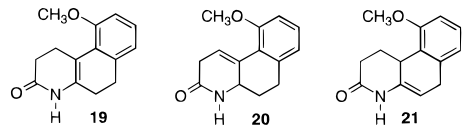

(a) pyrrolidine; acrylamide, *p*-TsOH, *iso*-PrOAc, reflux (b) TES, TFA, -10 to 35 °C (c) MeCl, NaI, NaOH, THF, 27 °C (d) HCl, MeOH, reflux; recycle MeCl to step above (e) monosodium *R,R*-DTTA; isolate **17** from MeOH; isolate **18** from methylene chloride (f) sodium bicarbonate, toluene, water

Reduction of amide **8** to the *trans* lactam **12** with excess TES−TFA[1,6a] in methylene chloride was slow due to the poor solubility of **8.** Unfortunately, the reduction also yielded 13% of the *cis* isomer **13** (Scheme 1). This amount of isomer proved difficult to remove and substantially reduced the recovery of **12** upon crystallization. However, reduction of **8** at (-10 °C with slow warming to 35 °C) without solvent under triphasic conditions (solid **8** + TFA + TES)[8] reduced the in situ amount of the *cis* isomer **13** to 6−7%. Moreover, the isolation and purification was facilitated by the direct isolation of the TFA complex **12**.[13] The complex **12** (containing 4% of **13**) was isolated in 95% yield after trituration with hot heptane (Scheme 1). Recrystallization(s) of **12** (or the free amide) from various solvents afforded pure **12**. However, removal of low levels of **13** by selective methanolysis in a subsequent step proved more efficient (vide infra).

Methylation of the free amide of **12** using sodium hydride−methyl iodide has been reported.[1] For larger preparations, a novel water-based methylation of **12** was

(10) (a) The ratio of **8** to **10** was measured throughout the reaction (10 mmol, 5 equiv of acrylamide and 3 mol % of TsOH, 87 °C): time h, (**8**:**10**); 2.5 (94:6); 6 (92:8); 144 (85:15). (b) The pyrrolidine released underwent Michael addition to acrylamide (exothermic) at a faster rate than aza-annulation. These results suggest that use of 1.75 equiv of acrylamide as recommended by Ninomiya (see ref 5c) represents 88% of theory for complete conversion. A patent reported that 2.4 equiv of acrylamide was optimal: Tanabe Seiyaku KK JP-48023779, March 27, 1973.

(11) (a) Cannon reported three isomers from aza-annulation with 8-methoxy-2-tetralone and acrylamide (total yield 30%, ratio of **19**:**20**:**21**, 77:17:6). Reduction (TES−TFA) of **19** and **21** reportedly gave the *trans* isomer but **20** gave the *cis* isomer. Cannon, J. G.; Kirschbaum, K. S. *Synthesis* **1993**, 1151. (b) Mellin reported the mixture from ref 11a gave 65:35 *cis*/*trans* mixture upon reduction with TES−TFA: Mellin, C.; Vallagrda, J.; Nelson, D. L.; Bjork, L.; Yu, H.; Anden, N. E.; Csoregh, L.; Arvidsson, L. E.; Hacksell, U. J. *J. Med. Chem.* **1991**, *34*, 497. (c) The spectral data of **6** was similar to the data for structure II in reference 11a. We are exploring the results of the aza-annulation and reduction sequence reported by Cannon (ref 11a) and Mellin (ref 11b).

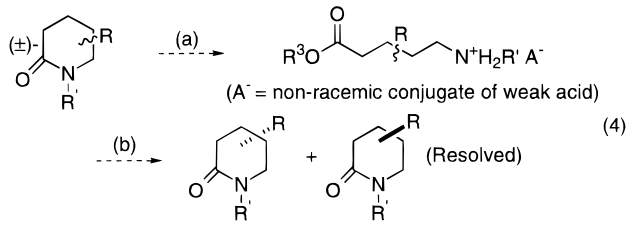



(12) Compound **11** crystallized in the monoclinic space group $P2_1/n$ with a unit cell having the dimensions $a$ = 13.442(2) Å, $b$ = 6.851(1) Å, $c$ = 13.700(3) Å, and $\beta$ = 94.25° (2) with a calculated density of 1.318 g/cm$^{-3}$. The data was collected on an automated four-circle diffractomer using monochromatic copper radiation. The structure was solved with the use of direct methods and was refined by least-squares with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included at calculated positions. The final R-factor was 0.05. An ORTEP plot of *trans*-(±)-**11** is included in the supporting information. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(13) The formation of TFA complexes provided a useful method for isolation and purification of a number of related benzoquinolinone derivatives. Unpublished observations, L. Weigel.

developed.[14] Reaction of **12** with methyl chloride in THF−$H_2O$ in the presence of sodium iodide and 50% sodium hydroxide gave **1** in 91% yield mixed with 2% of the *cis* isomer **14** (Scheme 1). The methyl chloride used for this step had been generated and trapped in the next step of the synthesis sequence. By using methyl chloride in this manner, some potential environmental concerns regarding the transport and utilization of large amounts of methyl iodide were obviated.

**Resolution of LY191704.** LY300502 (**3**) and LY-300503 (**4**) have been resolved by the separation of the diastereomeric derivatives (2-*R*-phenethyl auxiliary on the nitrogen of the free amide of **12**)[15] or by direct chromatographic separation of **1**.[16] Production of large quantities of **3** and **4** by these methods was not deemed feasible. Classical acid−base type resolutions of *δ*-lactams similar to **1** are not generally possible. We envisioned that one tenable strategy might be defined by a sequence involving *δ*-lactam alcoholysis to the ester[17] and an appropriate resolution[18] of the amine with a nonracemic acid (HA) followed by lactamization (eq 4). This simple approach for the resolution of lactams has not been previously described.[19]




(a) HX, ROH; $Na^+A^-$ (-NaX) (b) Separate diastereomers; base

In the event, the tricyclic lactam **1** (containing 2% of the *cis* isomer **14**) underwent direct acid-catalyzed methanolysis (3−6 d) to **15** in high yields.[17a,b] The methanolysis was faster in the presence of water. When **1** was heated to reflux with methanol and excess concentrated hydrochloric acid for 9 h, complete consumption of the lactam was observed (Scheme 1).[20] Some amino acid (**16**) was observed but this byproduct was simply esterified by codistillation of methanol and water during workup. (During this stage, methyl chloride was trapped in THF and used in the methylation step above, Scheme 1). The *cis* amide **13** proved inert to methanolysis and remained soluble throughout the subsequent operations. Without isolation, **15** was converted into a diastereomeric mixture of salts **17** and **18** by reaction with the monosodium salt of *R,R*-di-*p*-toluoyl-L-tartaric acid (DTTA, inexpensive form)[18] and enough $NaHCO_3$ to neutralize any residual HCl (Scheme 1). Solutions of monoprotic salts **17** and **18** remained acidic during crystallization. Therefore, closure of the free amine to the lactam was less problematic.[18b] Appropriate handling of this mixture (see Experimental Section) and crystallization from methanol gave pure **17** (41% yield, 82% of theory; 98% de). The filtrates of **17** were evaporated, and **18** was purified by crystallization from $CH_2Cl_2$-$H_2O$ (45.5% yield; 91% of theory; 98% de[9c]). If required, the chemical and the diastereomeric purity of both **17** and **18** were upgraded by repeating the simple solvent slurries (high temperatures promote lactamization). Neutralization of **18** (or **17**) under mild biphasic conditions with toluene−aqueous $NaHCO_3$ produced **3** (or **4**) in high yields (Scheme 1).[18]

**Conclusion.** In summary, we have demonstrated control of regioselectivity in the aza-annulation of **5** to **8**, defined a protocol for enhanced stereoselectivity in the reduction of **8** to **12**, and presented a new resolution protocol of benzoquinolinones (**1** resolved into **3** and **4**). In addition, the synthesis route generated methyl chloride (utilized in the alkylation step), provided an effective purification method of benzoquinolinones via TFA complex formation, and allowed resolution of both antipodes of LY191704 (**1**) with the use of only *R,R*-di-*p*-toluoyl-L-tartaric acid. The overall process is straightforward and yields (30% for **3** and 25% for **4** from **5**) have allowed the preparation of suitable quantities for clinical development. These observations have alreday proved useful in the synthesis of related systems.[21,22]

## Experimental Section[23]

**8-Chloro-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3-one (8).** A solution of the 6-chloro-2-tetralone[7b] (**5**, 107 g, 591 mmol), pyrrolidine (56 mL, 1.13 equiv), and *p*-TsOH (0.17 g, 0.15 mol %) in toluene (900 mL) was heated to reflux under nitrogen for 2 h during which time water was collected with a Dean-Stark trap. This solution was concentrated *in vacuo* and the enamine **6**[7a] was triturated with heptane (350 mL). The heptane was removed by cannula and the resulting solid dried under vacuum (yield, 125 g). A portion (2.88 g) of the air-sensitive enamine was heated to reflux with acrylamide (3.51 g, 4 equiv; 85−87 °C, 72 h) in isopropyl acetate (50 mL) containing *p*-TsOH (0.11 g). The mixture was cooled in an ice bath and filtered to give 2.44 g of pure **8** (85% from **6**, 77% from **5**) after vacuum drying: TLC $R_f$ 0.36; mp 227−230 °C (lit.[1c] mp 229−230 °C); IR (KBr) $\nu$ 1695, 1665 $cm^{-1}$; MS *m/z* 233 ($M^+$), 235 (34%, $M^+ + 2$); HPLC (system A) 10.9 min (>99%); (system B) 4.37 min (>99%); GC, 6.8 min; $^1H$ NMR (DMSO-$d_6$) $\delta$ 9.43 (1H, s), 7.2−7.3 (3H, m), 2.83 (2H, m), 2.6−2.4 (4H, m), 2.28 (2 H, m); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 169.68, 134.89, 134.63, 133.69, 128.47, 126.75, 126.11,

(14) Kress, T. J. Unpublished material.

(15) Audia, J. E.; Lawhorn, D. E.; Deeter, J. B. *Tetrahedron Lett.* **1993** *34*, 7001.

(16) Abel, A. D.; Erhard, K. F.; Yen, H. K.; Yamashita, D. S.; Brandt, M.; Mohammed, H.; Levey, M. A.; Holt, D. A. *Bioorg. Med. Chem. Lett.***1994**, 1365.

(17) (a) Audia, J. E.; Jones, C. D.; McQuaid, L.; Weigel, L. US 5 334 767 August 2, 1994. (b) For methanolysis of N-BOC-*δ*-lactams under basic conditions, see: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424. (c) For ring-opening of *N*-tosyl lactams, see: Bon, E.; Bigg, D. C. H.; Betrand, G. *J. Org. Chem.* **1994**, *59*, 1904 and references therein. (d) For acid-catalyzed methanolysis of *N*-acyl lactams see Dixit, N. A.; Tandel, S. K.; Rajappa, S. *Tetrahedron Lett.* **1994** *35*, 6133. (e) For reversal of the selectivity in reference 17b, see: Wei, Z. Y.; Knaus, E. E. *Tetrahedron Lett.* **1994** *35*, 847.

(18) (a) Astleford, B. A.; Audia, J. E.; Dunigan, J. M.; Janisse, S. K.; Kennedy, J.; Kress, T. J.; Waggoner, R.; Wepsiec, J. P.; Weigel, L. O. 206th National American Chemical Society Meeting, Chicago, IL ORGN76, August 23, 1993. (b) Attempted resolution of the nonmethylated **12** using the resolution sequence shown in eq 4 was problematic due to facile lactamization.

(19) For a similar approach involving enzymatically mediated closure of amino esters to lactams, see Gutman, A. L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* **1992**, *33*, 3943.

(20) Other strong acids ($H_2SO_4$, TsOH, $MeSO_3H$, etc.) catalyzed the methanolysis but gave nonvolatile sulfonic acid esters (e.g. TsOMe) which are toxic and problematic during purification of intermediates.

(21) Kuo, F.; Wheeler, W. J. *J. Labeled Compd. Radiopharm.* **1994**, *34*, 915.

(22) Weigel, L. O. 12th Process Development Symposium, Robinson College, Cambridge, England, December 12, 1994.

(23) Physical data was gathered as reported previously, see: Weigel, L. O.; Dunigan, J. *J. Org. Chem.* **1991**, *56*, 6225. The de's of **17** and **18** were determined by closure to **4** and **3** (Scheme 1, step 5) and HPLC on a Chiralcel OD column with 10% *i*-PrOH-hexane at 2.0 mL min at 40 °C and 220 nm. (**3**, $t_r$ = 16.1 min; **4**, $t_r$ = 14.0 min); RP HPLC, System A: Waters Nova-Pak C-18 column at 2.0 mL/min with acetonitrile−water (27:73 + 0.67% $NH_4OAc$ w/v); System B: Zorbax RX C-8 with acetonitrile−water (1:1) + 0.50% $NH_4OAc$ w/v at 2.0 mL/min. Capillary GC: DB1 column 30 m x 0.25 $\mu$m isothermal at 250 °C; TLC, silica gel 60 $F_{254}$ (0.25 mm) using ethyl acetate−hexane−methanol (50:50:1) with a Shimadzu CS-930 Scanner 255 nm or 520 nm after development with phosphomolybdic acid.

122.36, 105.73, 30.21, 26.91, 24.36, 20.14. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18, N, 5.99. Found: C, 66.54; H, 5.34; N, 6.27.

**7-Chloro-1,2,3,4,4a,5-hexahydrobenzo[*g*]quinolin-2-one (10).** Tetralone **5** (201 g, 1.11 mol), pyrrolidine (81.8 g, 1.03 equiv), and *p*-TsOH (0.44 g) were converted to the enamine as described above. The enamine was immediately treated with molten acrylamide (237 g, 3.33 mol) at 95 °C for 22 h. This mixture was poured into water (70 °C, 3.5 L) with good mechanical stirring and cooled to 0 °C after which the supernatant was decanted. The solid was then stirred for 25 h with methanol (350 mL) and filtered to provide 196 g (75%) of a 60:40 mixture of **8**:**10** (HPLC and $^1$H NMR assay). A portion of this mixture was slurried with three portions of diethyl ether to give pure **10**: TLC, $R_f$ 0.35; mp 238−241 °C; IR $\nu$ 3388, 1676, 1646 cm$^{-1}$; UV, $\lambda$ ($\epsilon$): 297 (27000), 226 (16000), 215 (14000); MS *m*/*z* 233 ($M^+$), 235 (33%, $M^+ + 2$); HPLC (system A), 16.2 min (97%); HPLC (system B), 4.4 min ; GC: 6.4 min; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.53 (1H, s), 6.91−7.2 (3H, m), 5.86 (1H, s), 2.91 (1H, m), 2.7−2.2 (4H, m), 2.03−1.85 (2H, m), 1.57 (2H, m); $^{13}$C NMR $\delta$ 169.45, 141.41, 134.05, 133.61, 128.32, 126.54, 126.26, 125.64, 101.09, 33.97, 31.40, 30.99, 26.10. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.63; H, 5.13; N, 5.91.

**8-Chloro-1,2,3,4,4a,5,6,10b-*trans*-octahydrobenzo[*f*]quinolin-3-one−Trifluoroacetic Acid (1:1) (12).** The lactam **8** (43.7 g, 187 mmol) was charged into a three-neck RB flask with dry triethylsilane (130 mL, 94.6 g, 814 mmol, 4.35 equiv). The reaction flask was placed in a cooling bath (−10 °C) and with good mechanical stirring, trifluoroacetic acid (130 mL, 192 g, 1.69 mol, 9.0 equiv) was added over 20 min. The mixture was stirred (−10 °C, 7 h; 0 °C, 14 h; 25 °C, 20 h; 35−37 °C, 1 h) and monitored by HPLC analysis (time h/% conversion/% *cis* **13**; 7/38/3.5; 24/76/4.8; 44/99/6). The mixture was then concentrated under vacuum and the solid residue digested in heptane (200 mL, 55 °C, 1 h), cooled (ice bath), and filtered. The solid was treated with heptane again (300 mL, 60 °C, 1 h; 25 °C) and filtered to give **12** (62.2 g, 95% yield) mixed with 4.5% of **13**. This material was suitable for use in the next step: TLC , $R_f$ 0.12; mp: 138−141 °C (lit.[1c] mp 230−231 °C for free amide of **12**); HPLC (system B), 3.84 min; IR $\nu$ 1635 cm$^{-1}$; UV $\lambda$ ($\epsilon$): 204 (21,600); MS *m*/*z* 235($M^+$, 100%), 237 (M + 2, 34%); $^1$H NMR $\delta$ 8.17 (1H, s), 7.27−7.05 (3H, m), 3.38 (1H, m), 2.93 (2H, m), 2.53−2.8 (4H, m), 2.18 (1H, m), 1.95−1.4 (2H, m); $^{13}$C NMR $\delta$ 170.44, 138.31, 135.75, 130.76, 128.18, 127.54, 125.67, 54.05, 39.47, 31.14, 28.57, 27.46, 24.61. Anal. Calcd for $C_{15}H_{15}ClF_3NO_3$: C, 51.52; H, 4.32; N, 4.01, F, 16.30. Found: C, 51.82; H, 4.41; N, 4.04; F, 16.07.

**8-Chloro-1,2,3,4,4a,5,6,10b-*cis*-octahydrobenzo[*f*]quinolin-3-one (free amide of 13).** The heptane washes from the preparation of **12** (1:1 of **12**:**13**) were neutralized with aqueous sodium bicarbonate and evaporated. The solid was purified by preparative HPLC on silica gel with 20% THF in $CH_2Cl_2$ to give the free amide of **13**: TLC $R_f$ 0.10; mp 185−187 °C; IR $\nu$ 1635 cm$^{-1}$; UV $\lambda$ ($\epsilon$): 204 (21600); MS *m*/*z* 235 ($M^+$, 100%), 237 ($M^+ + 2$, 38%); HPLC (system B), 3.57 min; $^1$H NMR $\delta$ 7.3−7.1 (3H, m), 6.47 (1H, s), 3.36 (1H, m), 2.95−2.83 (2H, m), 2.74−2.3 (4H, m), 2.12−2.03 (1H, m), 1.93−1.60 (2H, m); $^{13}$C NMR $\delta$ 172.51, 137.67, 135.35, 132.02, 129.89, 128.72, 126.61, 51.11, 35.57, 30.04, 27.45, 26.81, 26.67. Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04; N, 5.94. Found: C, 66.20; H, 6.10; Cl, 15.49; N, 5.98.

**8-Chloro-4-methyl-1,2,3,4,4a,5,6,10b-*trans*-octahydrobenzo[*f*]quinolin-3-one (1, LY191704).** The TFA complex **12** (33.2 g, 95 mmol) in warm THF (125 mL) was washed with aqueous sodium hydroxide (2 × 25 mL, 2 N). The THF layer was treated with sodium iodide (23.5 g, 158 mmol), aqueous sodium hydroxide (50% w/w, 47 mL), and a solution of methyl chloride in THF (15% w/v, 125 mL; 18.7 g, 3.9 equiv, obtained from the methanolysis below) in a pressure reactor for 33 h at 26−27 °C. The mixture was then cooled in an ice bath and neutralized with 12 N HCl (pH 2-3), and enough water was added to dissolve the inorganic salts. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (200 mL) after which the organic extracts were combined, washed twice with saturated brine and dried (4 Å molecular sieves, 33.2 g), filtered, and concentrated under vacuum to 50 mL. Heptane (100 mL) was added to a cloud point, and the mixture was seeded with **1**. After crystallization ensued, more heptane (200 mL) was added with stirring and the mixture was concentrated (over 3 h, 15−20 °C) under vacuum to 75 mL, cooled, and filtered to provide **1** (21.6 g, 91%): TLC, $R_f$ 0.16; mp[24] 90−93 °C (Lit[1c] mp 82 °C); GC, 5.6 min; HPLC (system B), 5.54 min.; IR $\nu$ 1630, 1487, 1397, 1260 cm$^{-1}$; UV, $\lambda$ ($\epsilon$): 279 (600), 272 (600); MS *m*/*z* 249 ($M^+$), 251 ($M^+ + 2$); HPLC, min (97.5% **1** + 2% **9**); $^1$H NMR $\delta$ 7.24−7.15 (3H, m), 3.21 (1H, m), 3.03 (3H, s), 3.12−2.9 (2H, m), 2.8−2.4 (5H, m), 1.68 (2H, m); $^{13}$C NMR $\delta$ 170.31, 137.30, 135.58, 132.44, 128.38, 126.31, 126.26, 60.77, 40.95, 32.32, 3047, 28.16, 27.77, 23.89. Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61; Cl, 14.20. Found: C, 67.36; H, 6.55; N, 5.67; Cl, 14.64.

**7-Chloro-1-methyl-1,2,3,4,4a,5,10,10a-*trans*-octahydrobenzo[*g*]quinolin-2-one (11).** A portion of the mixture of **8**:**10** from the aza-annulation reaction above was reduced (TES−TFA) and methylated as described above. The mother liquors from the crystallization of **1** were concentrated under vacuum, digested in refluxing hexane (20 mL/g), and decanted. The solid was recrystallized three times from hexane to afford **11**: TLC, $R_f$ 0.15; HPLC (system B), 5.7 min; mp 134−136 °C; IR $\nu$ 1630 cm$^{-1}$; UV $\lambda$ ($\epsilon$): 204 (21,600), 271 (600), 274 (600); MS *m*/*z* 249 ($M^+$, 100%), 251 ($M^+ + 2$, 32%); GC, 5.8 min; $^1$H NMR $\delta$ 7.15 (3H, M), 3.34 (2H, M), 3.03 (3H, s), 2.75 (1H, m) 1.87 2.73−2.37 (4H, m) (2H, m), 1.63 (1H, m); $^{13}$C NMR $\delta$ 137.2, 132.3, 131.7, 131.3, 128.2, 122.7, 60.6, 36.7, 36.2, 36.1, 32.6, 31.2, 26.8. Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61; Cl, 14.20. Found: C, 67.37; H, 6.31; N, 6.03.

Crystals of **11** for single crystal X-ray analysis[12] were grown by isothermal evaporation of solvent (270 mg **11** with 17 mL hexane and 3 mL of EtOAc, 24 h).

**6-Chloro-1,2,3,4-tetrahydro-2(*S*)-(methylamino)-1(*S*)-naphthalenepropanoic Acid Methyl Ester−(2*R*,3*R*)-Bis[(4-methylbenzoyl)oxy]butanedioic Acid (1:1) (17).** Lactam **1** (LY191704, 24.9 g, 100 mmol, containing 2% **14**) was refluxed with methanol (12.5 mL) and hydrochloric acid (12 N, 16.2 mL) for 4 h. Fresh HCl (4 mL) and methanol (3.5 mL) were added, and the mixture was heated another 5 h. The MeCl evolved during this portion of the process was entrained in THF at −78 °C and employed in the conversion of **12** into **1** above. The mixture was cooled and concentrated to 45 g at 40−43 °C . Analysis at this point by HPLC showed 97% conversion (based upon formation **15** and the amino acid **16**). Three portions of methanol (150 mL) were added, and the reaction mixture was concentrated under vacuum at 45 °C. The mixture was diluted to 240 mL with methanol and heated at 50 °C for 1 h (HPLC analysis showed >97% of **15**). The mixture was diluted in a 500.0 mL volumetric flask with MeOH and titrated (0.224 mequiv acid/mL, 0.12 equiv of excess HCl). In a separate vessel, (*R*,*R*)-di-*p*-toluoyl-L-tartaric acid monohydrate (DTTA, 40.4 g, 100 mmol) was dissolved in methanol (600 mL) at 45 °C and treated with $NaHCO_3$ (9.41 g dissolved in 44 mL of warm water, 112 mmol). The solution containing **15** was added at 15 °C over 10 min with good stirring to the sodium DTTA solution. The mixture was cooled to 4 °C for 1 h and filtered to give **17** (92% de; the methanol filtrate was set aside for the isolation of **18**, see below). In turn, the $CH_2Cl_2$ filtrate from the isolation of **18** from below was concentrated *in vacuo*, and the residue (mostly **17**) was triturated with methanol (100 mL). The two solid portions of **17** were combined and stirred with methanol (600 mL, 35 °C to −10 °C) affording **17** as a monohydrate (28.0 g, 82% of theory); mp 120−130 °C dec; IR $\nu$ 3800−2500, 1725, 1612 cm$^{-1}$; UV, $\lambda$ ($\epsilon$): 270 (2200), 239 (28000), 204 (46200); MS *m*/*z* 282 ($M^+$ for amine), 284 ($M^+ + 2$ for amine), 386 ($M^+$ for DTTA); KF, 2.4% water; HPLC (system A), 0.50 min (DTTA, 49%), 1.3 min (amino ester of **17**, 49%); HPLC (system B), 1.71 min (amino ester of **17**); Chiral HPLC; 14.0 min (98% de); $[\alpha]_D$ −66.6°, $[\alpha]_{365}$ −343° (*c* = 1.00, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.0−8.0 (1H, b s), 7.85 (4H, d), 7.37 (4H, d), 7.2−7.0 (3H, m), 5.63 (2H, s), 3.58 (3H, s), 3.38 (1H, m), 2.75 (1H, m), 2.88 (2H, m), 2.45 (3H, s), 2.37 (6H, s), 2.35 (2H, m), 1.8−1.53 (4 H, m); $^{13}$C NMR (DMSO-$d_6$, partial) $\delta$ 130.90, 129.41, 129.33, 128.30, 127.94, 127.07, 126.83, 126.83, 126.11, 125.75, 72.14, 59.93, 55.28, 51.41, 51.36, 40.24, 38.65, 32.09, 31.08, 30.70, 30.35, 27.72, 23.06, 21.23, 19.20. Anal. Calcd for $C_{15}H_{20}ClNO_2-C_{20}H_{18}O_8\cdot H_2O$. C, 61.22; H, 5.84;

(24) Compounds **1**, **3**, and **4** (although chemically pure) often exhibit poor melting point and DSC behavior due to polymorphism. Unpublished data of M. Kearns, C. Pasini, and L. Weigel.

N, 2.04; O, 25.61; Cl, 5.17. Found: C, 61.49; H, 6.14; N, 1.87; O, 25.06; Cl, 5.47.

**6-Chloro-1,2,3,4-tetrahydro-2(*R*)-(methylamino)-1(*R*)-naphthalenepropanoic Acid Methyl Ester−(2*R*,3*R*)-Bis[(4-methylbenzoyl)oxy]butandioic Acid (1:1) (18).** The methanol filtrates from the isolation of **17** were immediately concentrated under vacuum to 125 g (<30 °C) and diluted with $CH_2Cl_2$−water (1:1, 550 mL). This mixture was concentrated and fresh $CH_2Cl_2$ (275 mL) was added. The mixture was cooled (−4 °C, 0.5 h) and filtered under slight positive pressure to give **18** (33.6 g, 92% de). The $CH_2Cl_2$ portion of the filtrate was utilized in the isolation of **17** (see above). A portion of **18** (5.00 g of 33.6 g) was stirred with 5:1 $CH_2Cl_2$−water (60 mL) at 35 °C. The mixture was cooled to −10 °C for 1.5 h and filtered to give **18** (4.63 g, 91% of theory): mp 140−145 °C dec; KF, 0.43% water; IR (KBr) $\nu$ 3800−2500, 1725, 1612 $cm^{-1}$; UV $\lambda$ ($\epsilon$): 270 (2200), 239 (28000), 204 (46200); MS $m/z$ 282 ($M^+$ for amine), 284 ($M^+ + 2$ for amine), 386 ($M^+$ for DTTA), 668 ($M^+$); HPLC (system A) 0.48 min (>49% DTTA), 1.28 min (amino ester of **18**, >49%); HPLC (system B), 1.71 min (amino ester of **18**); enantiospecific HPLC: 16.1 min (98% de); $[\alpha]_D$ −94.5°; $[\alpha]_{365}$ −445.5° ($c$ = 1.00, MeOH); $^1$H NMR (DMSO-$d_6$), identical to the spectrum of **17**; $^{13}$C NMR ($CDCl_3$−DMSO-$d_6$) $\delta$ 170.57, 165.75, 144.03, 136.81, 133.32, 132.44, 131.10, 130.03, 129.12, 128.62, 128.38, 126.78, 12666, 126.28, 72.98, 60.74, 57.50, 51.70, 40.72, 39.33, 30.92, 30.87, 30.67, 28.10, 27.58, 23.77, 21.66, 20.54. Anal. Calcd for $C_{35}H_{38}ClNO_{10}$: C, 62.92; H, 5.73; N, 2.10; Cl, 5.31. Found: C, 62.89 H, 5.58; N, 1.94; Cl, 5.34.

**(−)-(4a*R*,10b*R*)-4-Methyl-8-chloro-1,2,3,4,4a,5,6,10b-*trans*-octahydrobenzo[*f*]quinolin-3-one (3, LY300502).** A mixture of **18** (40.0 g, 99.8% de, anhydrous), toluene (800 mL), and 5% aqueous sodium bicarbonate (800 mL) was stirred (30 min, 25 °C). The water layer was separated and washed with toluene (200 mL). The combined organic extracts were washed with water (100 mL) and saturated sodium chloride (100 mL) and warmed to 60−80 °C until analysis by HPLC indicated complete lactamization. The mixture was filtered over 4 Å molecular sieves and evaporated in vacuo to afford **3** (14.9 g, 100%): TLC, $R_f$ 0.16; DSC[24] 76 °C (lit[15,17b] mp 71.5−73 °C); IR $\nu$ 3005, 1627, 1485 $cm^{-1}$; UV $\lambda$ ($\epsilon$): 279 (600), 271 (640), 205 (20700); MS $m/z$ 249 ($M^+$), 251 ($M^+ + 2$, 33%); HPLC (system A) 3.4 min (>99%); HPLC (system B), 5.54 min (99%); enantiospecific HPLC: 32.3 min (99.8% ee); GC, 5.6 min; $[\alpha]_D$ −86° $[\alpha]_{365}$ −289° ($c$ = 1.00, MeOH); $^1$H NMR $\delta$ 7.29 (3H, m), 3.22 (1H, m), 3.03 (3H, s), 3.0−2.4 (7H, m), 2.8−2.6 (2H, m); $^1$H NMR (benzene-$d_6$) $\delta$ 2.47 (3H, s); $^{13}$C NMR $\delta$ 185.34, 162.96, 137.28, 135.53, 132.53, 128.43, 126.32, 60.84, 40.96, 32.26, 30.57, 28.18, 27.78, 23.86. Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61; O, 6.41; Cl, 14.20. Found: C, 67.12; H, 6.54; N, 5.80; O, 6.21; Cl, 13.96.

**(+)-(4a*S*,10b*S*)-4-Methyl-8-chloro-1,2,3,4,4a,5,6,10b-*trans*-octahydrobenzo[*f*]quinolin-3-one (4, LY300503).** Conversion of **17** (50.0 g, 98% de) as described above provided **4** (18.0 g, 97%). TLC, IR, UV, MS, GC and HPLC (systems A and B) identical to **3** above; DSC[24] 73 °(lit.[15,17b] mp 71−73 °C); chiral HPLC 14.0 min (98% ee); $[\alpha]_D$ +84.5° $[\alpha]_{365}$ +300° ($c$ = 1.00, MeOH). Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61; O, 6.41; Cl, 14.20. Found: C, 67.12; H, 6.54; N, 5.80; O, 6.21; Cl, 13.96.

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**Supporting Information Available:** $^1$H NMR for compounds **1**, **3**, **4**, **6**, and **8**−**12**, **13** (free amide), **17**, **18**, HETCOR data for **11**, and an ORTEP plot of **11** (15 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.

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