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A Diastereoselective Tandem Metalloenamine Alkylation/Aza-annulation of β–Tetralones Expedites the Synthesis of Benzoquinolinones

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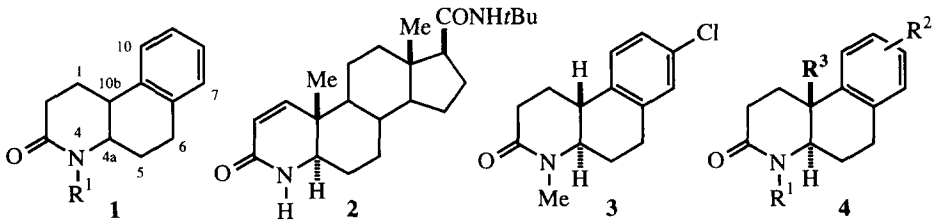
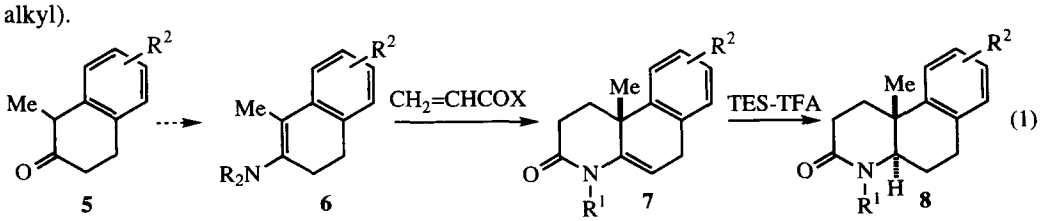
Abstract: In one operation, metalloenamines derived from *R*-phenylethylamine (PEA) and a β-tetralone were treated with an electrophile followed by acrylic anhydride. The unpurified lactams were reduced to give 10b-angular benzoquinolinones (BQs).

Several years ago, some benzo[f]quinolinones (BQs) were identified as selective and potent non-competitive type I inhibitors of 5-α-reductase in cell cultures derived from human foreskin fibroblasts.[1] Inhibitors of this isozyme may have utility in the treatment of acne, male pattern baldness, benign prostatic hyperplasia, or prostatic cancer. Moreover, BQs (**1**) may enhance the effectiveness of type II selective inhibitors (e. g. azasteroids such as finasteride, **2**)[2] in disorders requiring more complete suppression of dihydrotestosterone (DHT) formation. A prototype BQ (LY300502, **3**) is currently in clinical development.[3] For the development of the emerging portfolio of these drugs, we required an efficient asymmetric synthesis of 10b-**R**^{3}-benzo[f]quinolinones (**4**).



1 **2** **3** **4**

The first syntheses[1,3] of this class of BQ's (**4**; R^1 = H, alkyl; **R**^{3}= Me) required a 1-methyltetralone[4] derivative (**5**) as starting material. Conversion of **5** to the enamine **6** [R_2N = pyrrolidino or *R*-PhCH(Me)NH] and treatment with an acrylate derivative (X = NH_2, Cl, NHR^1) gave the lactam **7** (equation 1). Ionic reduction with triethylsilane/trifluoroacetic acid (TES-TFA)[5] provided the *trans* BQ (**8**; R^1 = H, alkyl).



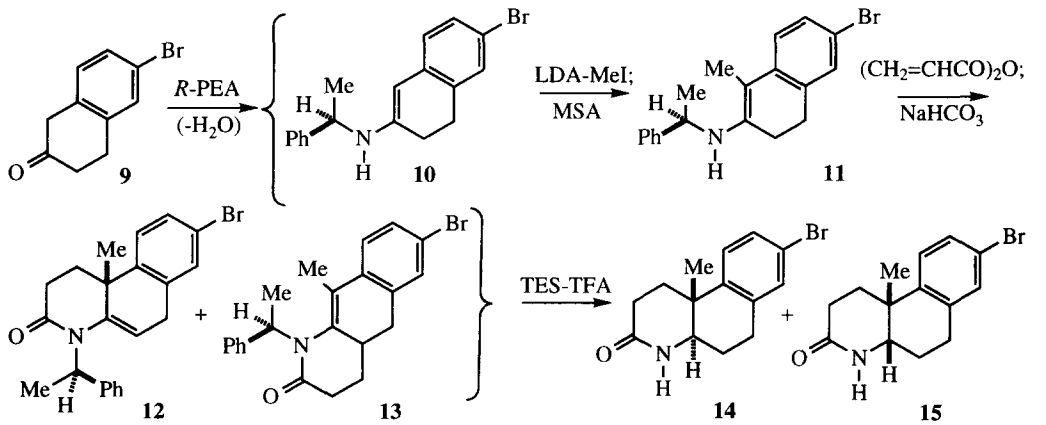
5 **6** **7** **8** (1)

On a practical scale, this approach proved somewhat problematic. The tetralones **5** were typically obtained from methylation of the parent β-tetralone. Small amounts of impurities, derived from incomplete methylation (**4**, **R**^{3} = H),

proved very difficult to remove. Therefore, assiduous purification of **5** was typically required.

As a solution to this problem, we envisioned that an enamine derived from *R*-PEA could mediate a metalloenamine alkylation as well as the asymmetric aza-annulation. This approach ensured a high degree of monoalkylation, set the stereogenic center at C-10b and eliminated the need to prepare **5**.[6] To this end, we utilized a combination of observations of Evans,[7] Fraser,[8] d'Angelo,[9] Audia,[3] Stille,[10] and Pollack[11] in the development of a useful sequence. As an illustrative example, 6-bromo-2-tetralone (**9**)[12,13a] was converted into the enamine[3] (**10**) with *R*-PEA and treated sequentially with lithium diisopropylamide (LDA), methyl iodide, and methanesulfonic acid (MSA) to give **11** (Scheme 1). The solution of **11** was immediately treated with acrylic anhydride to afford **12** and the isomer **13** (10-12%). Although **12** could be purified, this intermediate was not stable. Without purification, **12** and **13** were subjected to reductive cleavage with TES in TFA.[15] Analysis of this reaction solution indicated 86-88% ee for **14**[13b] in addition to the reduction product of **13**[14] and 1% of the *cis* isomer **15**. Crystallization of **14** gave pure BQ in 78% yield with 98% ee.

Scheme 1



The tandem alkylation/aza-annulation method has been applied to a number of other β-tetralones with various alkylating reagents (Table 1).[13] Similar in situ ee values and *trans/cis* ratios were observed for entries 2-7.[13c,13d] In all these examples, the major by-product was the isomer analogous to **13**.

In conclusion, we have developed a diastereoselective tandem metalloenamine/aza-annulation sequence for the expedient preparation of benzo[f]quinolinones. The salient features of this sequence are: (a) the dual utilization of the chiral enamine to mediate the alkylation and set the stereogenic centers, (b) a high degree of mono-alkylation, (c) an expedient protocol, and (d) an expanded scope for the preparation of angularly substituted BQs.

Acknowledgments

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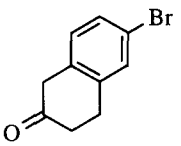
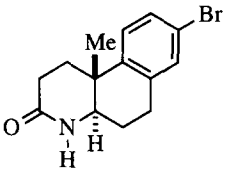
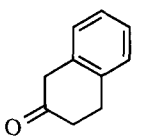
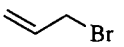
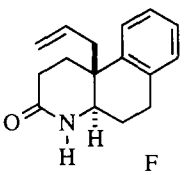
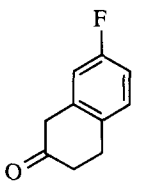
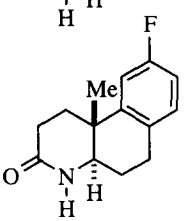
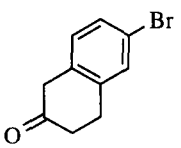
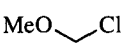
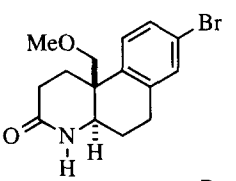
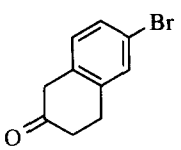
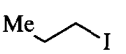
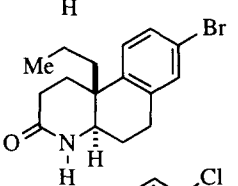
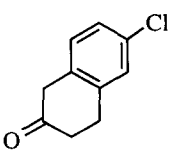
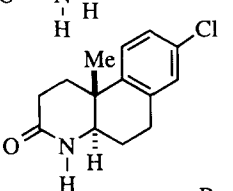
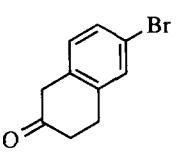
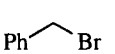
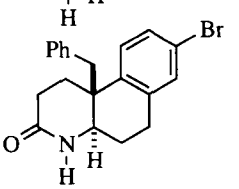
Table 1. Benzo[f]quinolinones Prepared by Metalloenamine/Aza-annulation of β-Tetralones[13a]

Entry	Tetralone	Electrophile	Product[13b]	% Yield	% ee[13c]
1		MeI		78[13d]	98[a]
2				74	>98[a]
3		MeI		50	95[a]
4				21	91[b]
5				64	98[c]
6		MeI		62[3]	85[b]
7				76	97[c]

(a) Purified by crystallization. (b) Purified by chromatography on silica gel. (c) Purified by chromatography on silica gel and recrystallization.

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13. (a) As a representative example, purified **9** (11.2 g, 50 mmol), (*R*)-PEA (6.65 g), *p*-TsOH (40 mg) and toluene (150 mL) were heated to reflux and then slowly concentrated to approx 50 mL (110 °C, 3 h). The toluene solution of enamine **10** was diluted with THF (137 mL) and added to LDA in THF (224 mL, 0.257 M, -50 to -60 °C then 0 °C, 20 min). The resulting lithioenamine of **10** was sequentially treated with: (a) MeI (3.60 mL, 57.5 mmol, -75 to -70 °C then -5 °C for 20 min); (b) MSA (4.2 mL, -5 °C); (c) acrylic anhydride (15.1 g, 120 mmol; -75 °C to 15 °C, 13 h); and (d) solid $NaHCO_3$ and water (22 °C, 2 h). The solution was concentrated (25 °C) and the resulting residue was dissolved in 250 mL of ether and washed with (a) 3x100 mL of 1.0 N aq NaOH (b) 3x100 mL aq HCl (c) 50 mL saturated aq $NaHCO_3$ and (d) 150 mL saturated brine. The ether solution was evaporated to give **12** and **13** (white foam) which was immediately treated with TES (86 mL) and TFA (108 mL, -15 to 35 °C over 40 h then 2 h at 72 °C). The excess TES and TFA were evaporated under vacuum and the resulting oil was dissolved in CH_2Cl_2 (250 mL) and washed with $NaHCO_3$ (3x40 mL). This solution was concentrated and crystallization induced by slow addition of ether (165 mL) to give **14** (11.4 g, 78%): HPLC (Chiracel® OD-H at 220 nm, 1.0 mL/min, 40 °C) t_r **14** (8.9 min), *ent*-**14** (10.2 min, 1%); HPLC (Zorbax® RX-C18 at 220 nm, 2 mL/min 1:1 ACN-water + 1% NH_4OAc) t_r **14** (2.08 min, 99.1%); $[\alpha]_D$ 66° (*c* = 1.00, MeOH); ^1H NMR ($CDCl_3$, 500 MHz, partial) δ 3.42 (1H, dd, *J* = 2, 9 Hz), 1.18 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 172.7, 142.5, 136.7, 132.1, 129.3, 126.6, 120.2, 56.5, 36.1, 32.4, 28.8, 27.4, 23.8, 20.8; IR ($CHCl_3$) 1662 cm^{-1}; MS (FD) *m/z*: 293, 295 (M^+, $M^+ + 2$); Anal. Calcd for $C_{14}H_{16}NOBr$: C, 57.16; H, 5.48; Br, 27.16; N, 4.76. Found: C, 57.35; H, 5.69; N, 4.69. (b) All new compounds in Table 1 exhibited satisfactory ^1H NMR, ^{13}C NMR, MS, IR and combustion analyses. (c) The stereochemistry of **14** and several related BQs prepared by similar methods were proven by single crystal X-ray determination (L. O. Weigel, et al., submitted to The 212th National ACS Meeting, August 25, 1996, Orlando, FL). The stereochemical assignments of entries 2-7 (Table 1) were based upon these findings and the diastereoselectivity described in references 3 and 9. (d) The use of (*S*)-PEA in Scheme 1 afforded a reference sample of *ent*-**14**. The ee values of entries 2-7 in Table 1 were based upon the relative retentions by chiral HPLC.
14. For characterization of BQs similar to **13**, see: Weigel, L. O. et al., in press *J. Org. Chem.*, **1996**.
15. (a) The olefin of **12** was reduced approx 10x faster than cleavage of the auxiliary. (b) Reduction of **12** at 72 °C afforded 7% of **15**.

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