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

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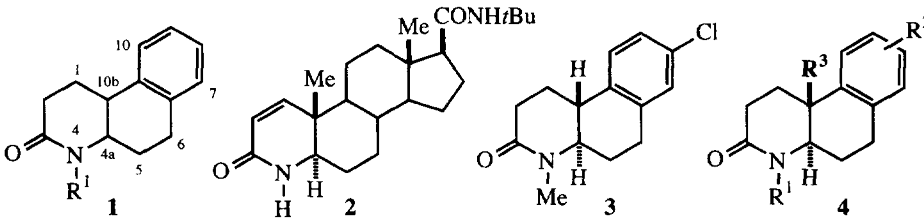
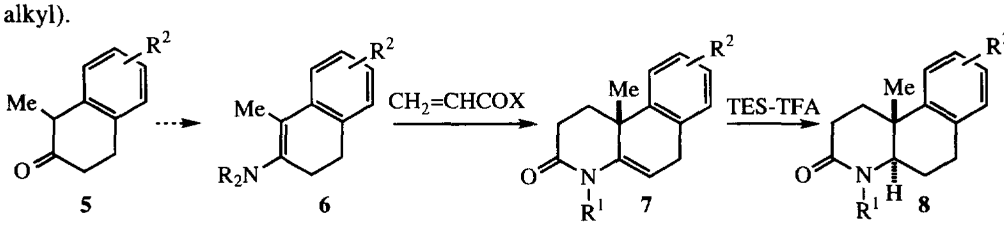
Abstract: In one operation, metalloenamines derived from *R*-phenylethylamine (PEA) and a β-tetralone were treated with an electrophile followed by acrylic anhydride. The unpurified lactams were reduced to give 10b-angular benzoquinolinones (BQs).

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**).



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).

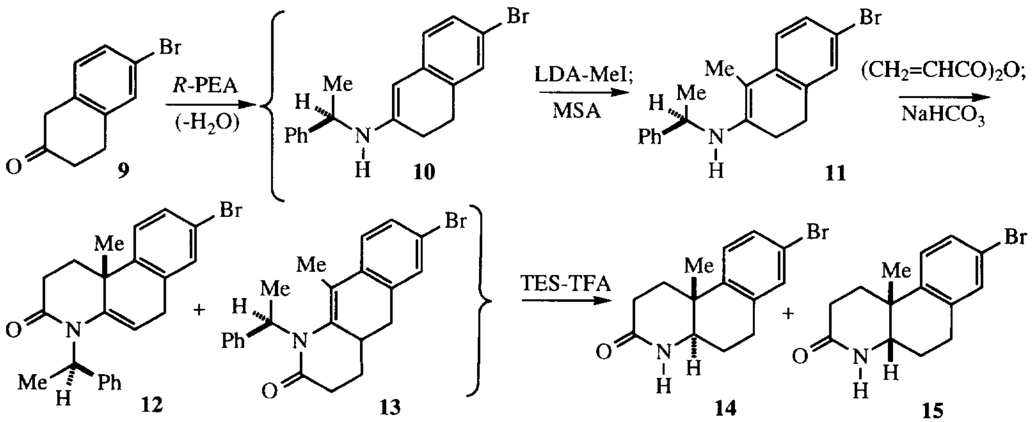


(1)

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



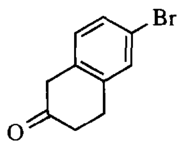
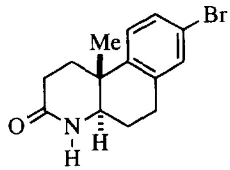
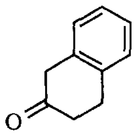
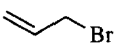
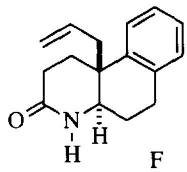
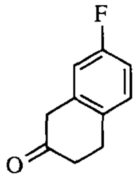
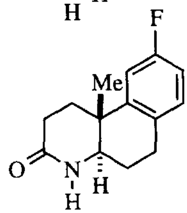
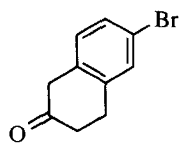
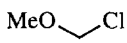
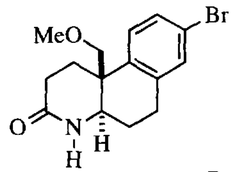
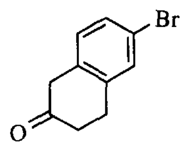
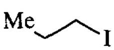
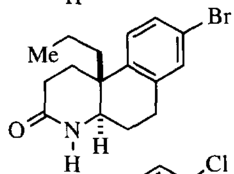
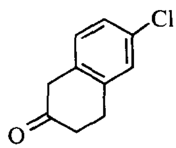
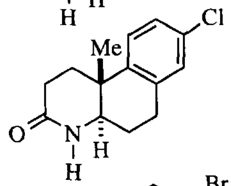
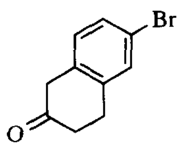
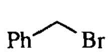
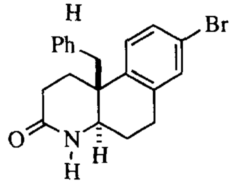
The tandem alkylation/aza-annulation method has been applied to a number of other β-tetralones with various alkylating reagents (Table 1).[13] Similar in situ ee values and *trans/cis* ratios were observed for entries 2-7.[13c,13d] In all these examples, the major by-product was the isomer analogous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

We thank Drs. John R. Stille and Charles D. Jones and Profs. Paul Wender and William Roush for suggestions. Analytical data supplied by the Lilly Molecular Structure Division, the Lilly CPR&D Analytical Group, and Joespeh Kennedy is gratefully acknowledged.

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.

References and Notes

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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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