Organic Process Research & Development **2004**, *8*, 897–902

A Scaleable Synthesis of Fiduxosin

Anthony R. Haight,* Anne E. Bailey,† William S. Baker, Michael H. Cain, Richard R. Copp,‡ John A. DeMattei,§ Kelley L. Ford, Rodger F. Henry, Margaret C. Hsu, Robert F. Keyes, Steven A. King, Maureen A. McLaughlin, Laura M. Melcher, William R. Nadler,|| Patricia A. Oliver,⊥ Shyamal I. Parekh, Hemant H. Patel,# Louis S. Seif, Mike A. Staeger, Gregory S. Wayne, Steven J. Wittenberger, and Weijiang Zhang▽

GPRD Process Research and Development, Abbott Laboratories, Building R8/1, 1401 Sheridan Road, North Chicago, Illinois 60064-6285, U.S.A.

Abstract:

Fiduxosin (1) has been under development at Abbott Laboratories for the treatment of benign prostatic hyperplasia. A convergent strategy required methodologies for preparation of an enantiomerically pure 3,4-*cis*-disubstituted pyrrolidine and a 2,3,5-trisubstituted thienopyrazine in a regiospecific manner. A [3+2] cycloaddition of an enantiopure azomethine ylide followed by a diastereoselective crystallization was employed to prepare the benzopyranopyrrolidine in high diastereomeric and enantiomeric purity. Conditions for reduction of an O-aryl lactone susceptible to epimerization were developed, and cyclization of the alcohol/phenol to the ether was accomplished in high yield. The thienopyrazine was prepared by condensation of methyl thioglycolate and a regiospecifically prepared 2-bromo-3-cyano-5-phenylpyrazine. Conditions for effective halogen substitutive deamination to prepare regiospecific trisubstituted pyrazines will be described.

Introduction

Benign prostatic hyperplasia (BPH), or the nonmalignant enlargement of the prostate gland, is a disorder associated with up to 80% of all males over the age of 60.[1] Typical symptoms of BPH include nocturia, increased frequency of urination, and low urine flow caused, in part, by the enlargement of the prostate gland and contraction of the smooth muscle tissue surrounding the bladder neck. The finding by Caine[2] that the smooth muscle of the prostate and bladder neck contains large numbers of α-adrenoreceptor sites led to the experimental observation that the nonselective α_2/α_1-adrenoreceptor antagonist, phentolamine, could effectively address the symptoms of BPH. Clinical evidence with the selective α_1-adrenoreceptor antagonist prazosin and further functional studies have led to the recognition that blocking of the α_1-adrenoreceptor sites can successfully treat the physiological effects of BPH.[3]

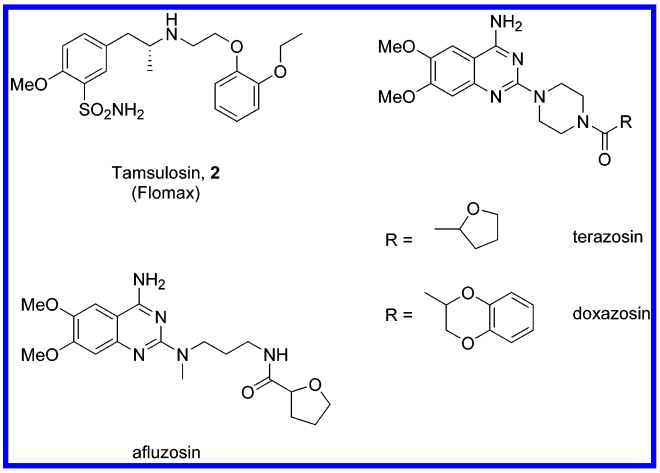


Figure 1. **BPH antagonists.**

The first α_1-antagonists approved for the treatment of BPH (terazosin,[3] prazosin,[4] and doxazosin[5]) had previously been introduced as therapies for hypertension. It is not surprising then that cardiovascular side effects limited the dosing of these agents for the treatment of BPH. Binding and functional assays have demonstrated that the α_1-adrenoreceptors are composed of at least three native subtypes: α_{1a}-, α_{1b}-, and α_{1d}-adrenoreceptor sites with the α_{1a}-site attributed to the uroselectivity.[6] Tamsulosin (Flomax), **2**,[7] was the first compound designed with improved α_{1a}/α_{1b}-selectivity for the treatment of BPH (Figure 1).

At Abbott, the α_{1a}-antagonist fiduxosin (**1**) was found to have improved uroselectivity relative to tamsulosin.[8] To further advance development of fiduxosin, a scaleable synthetic route was necessary. We describe here our efforts

* To whom correspondence should be addressed. E-mail: anthony.haight@abbott.com.

† Present address: Hospira Inc., 275 N. Field Dr., Lake Forest, IL 60045.

‡ Present address: Quintessence Biosciences, 505 S. Rosa Rd., Madison, WI 53719.

§ Present address: Array Biopharma 1885 33rd St., Boulder, CO 80301.

|| Present address: Industria Farmaceutica Serono, Via Luigi Einaudi, 11, 00012 Guidonia-Montecelio, Italy.

⊥ Present address: Vertex Pharmaceuticals, Boston, MA.

Present address: Gujarat Industrial Chemicals, 388 620 Gujarat, India.

▽ Present address: Theravance Inc., 901 Gateway Blvd. South, San Francisco, CA 94080.

(1) Bock, M. G.; Patane, M. A. *Ann. Rep. Med. Chem.* **2000**, *35*, 221. Garraway, W. M.; Collins, G. N.; Lee, R. J. *Lancet* **1991**, *338*, 469.

(2) Caine, M.; Pfau, A.; Perlberg, S. *Brit. J. Urol*. **1976**, *48*, 255.

(3) Lepor, H.; Henry, D.; Laddu, A. R. *Prostate* **1991**, *18*, 345.

(4) Hedlund, H.; Andresson, K.-E.; Ek, A. *J. Urol*. **1983**, *130*, 275.

(5) Holme, J. B.; Christensen, M. M.; Rasmussen, P. C.; Jacobsen, F.; Nielsen, J.; Norgaard, J. P.; Olesen, S.; Noer, L.; Wolf, H.; Husted, S. E. *Scand. J. Urol*. **1994**, *28*, 77.

(6) Hieble, J. P.; Ruffolo, R. R. *Exp. Opin. Invest. Drugs* **1997**, *6*, 367. Meyer, M. D.; Altenbach, R. J.; Bai, H.; Basha, F. Z.; Carroll, W. A.; Kerwin, J. F.; Lebold, S. A.; Lee, E.; Pratt, J. K.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Brune, M. E.; Buckner, S. A.; Hancock, A. A.; Drizin, I. *J. Med. Chem.* **2001**, *44*, 1971 and references therein.

(7) Yamada, S.; Suzuki, M.; Tanaka, C.; Mori, R.; Kimura, R.; Inagaki, O.; Honda, K.; Asano, M.; Takenaka, T.; Kawabe, K. *Clin. Exp. Pharmacol. Physiol*. **1994**, *21*, 405.

(8) Hancock, A. A.; Buckner, S. A.; Brune, M. E.; Esbenshade, T. A.; Ireland, L. M.; Katwala, S.; Milicic, I.; Meyer, M. D.; Kerwin, J. F., Jr.; Williams, M. *J. Pharmacol. Exp. Ther*. **2002**, *300*, 478.

10.1021/op049889k CCC: $27.50
Published on Web 10/16/2004

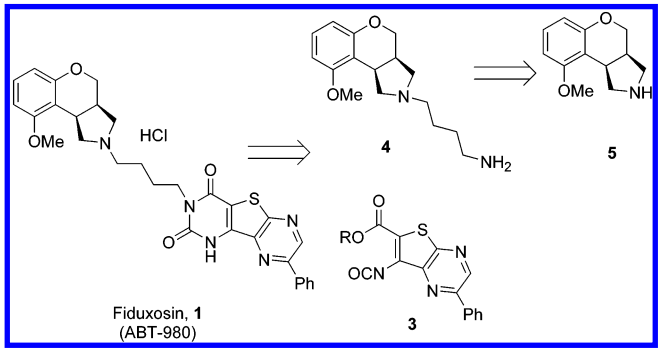


Figure 2. **Retrosynthesis of fiduxosin.**

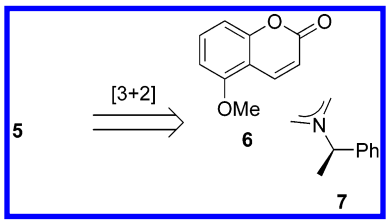


Figure 3. **[3+2] Cycloaddition strategy.**

to prepare multi-kilogram quantities of **1** through a convergent strategy.

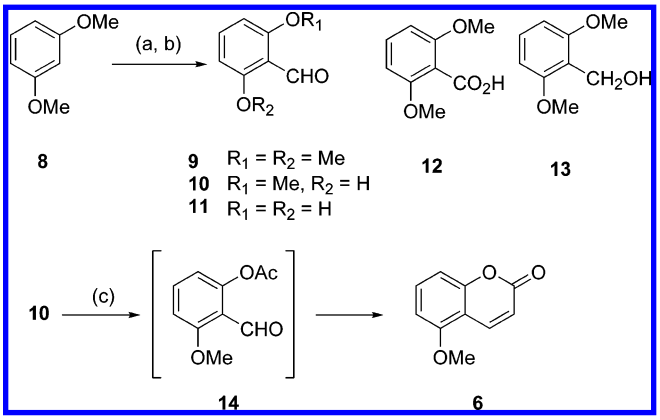
Results

Fiduxosin can be assembled via the coupling of the thienopyrazine isocyanate **3** with the benzopyranopyrrolidyl butyryl diamine, **4**. Consequently, we required a regiospecific preparation of **3** and a synthesis that would control both the relative and absolute stereochemistry in the 3,4-disubstituted pyrrolidyl ring system of **5** (Figure 2).

A diastereoselective cycloaddition between 5-methoxycoumarin, **6**, and a nonracemic azomethine ylide was envisaged as the key step in preparing the benzopyranopyrrolidine (Figure 3).[9,10] This approach offers the advantage of establishing both the relative and absolute stereochemistry in one step. In the original synthesis of **1**,[9] the use of the (*R*)-α-methylbenzylamine derived azomethine ylide **7** provided a facile means to key tricyclic amine intermediate **5** with high enantiomeric excess. The ease of isolation and the robustness of the chemistry encouraged us to use this route for the initial clinical deliveries.

Preparation of 5-methoxycoumarin **6** was accomplished in three steps from 1,3-dimethoxybenzene. Regioselective lithiation of **8** with *n*-BuLi at 0 °C in THF/TMEDA followed by treating the aryllithium with DMF gave the desired 2,6-dimethoxybenzaldehyde, **9** (Scheme 1). Although TMEDA was not necessary for the metalation, it did stabilize the DMF adduct. Without TMEDA, the tetrahedral intermediate would collapse to the aldehyde, which we had observed to dealkylate under the reaction conditions. Addition of aqueous HCl followed by distillation of the THF left an aqueous slurry

Scheme 1. **5-Methoxycoumarin synthesis**[a]



[a] Reaction conditions: (a) (1) BuLi, 0 °C, THF/TMEDA; (2) DMF; (3) 4 M HCl (68%). (b) $AlCl_3$, CH_2Cl_2 (93%). (c) (1) Ac_2O, DMF, K_2CO_3, 70 °C; (2) H_2O (10 mol%), 120 °C (68%).

of **9**. Cannizarro reaction byproducts were prevalent if the mixture was not first acidified.[11,12] Following the addition of heptane to the slurry to remove residual **8**, aldehyde **9** was isolated in 68% yield and 99.3% GC purity as an off-white solid. The mass balance was accounted for in the filtrate, which contained unreacted **8** (6%), aldehyde **9** (5%), and the Cannizarro acid **12** (8%) and alcohol **13** (8%).

Selective dealkylation was carried out by addition of **9** to a −15 °C methylene chloride slurry of 1.5 equiv of $AlCl_3$.[13] Slowly warming the reaction mixture to ambient temperature gave mono-demethylation in 4−6 h with <5% bis-demethylation as detected by GC. If the reaction was allowed to warm further to 30 °C, significant bis-dealkylation to **11** would occur. Fortunately, this undesired impurity sublimed during the drying of the product (45 °C under vacuum) giving aldehyde **10** in 93% yield and >99% GC purity.

Preparation of coumarin **6** from aldehyde **10** was carried out by the Perkin reaction.[14] Employing Cs_2CO_3 and DMF as the base and solvent, respectively, acetic anhydride condensed with **10** to yield coumarin **6** in 86% isolated yield. Although the reaction proceeded in high yield and good purity, the expense of cesium carbonate caused us to evaluate alternative bases.[15] Among these, potassium carbonate was found to be the best, but the procedure required some modifications. The reaction was carried out in a stepwise fashion by first treating **10** with 5 equiv of Ac_2O and 1.1 equiv of K_2CO_3 in DMF at 70 °C to generate the intermediate acetate **14**. Addition of a catalytic amount of water (10 mol %) then generated a more soluble mixed base system of potassium acetate and carbonate. After increasing the reaction temperature to 120 °C for 10 to 12 h, the conversion was complete and the product was precipitated by slow addition of water. Coumarin **6** was obtained in 68% isolated yield. The coumarin was isolated with up to 25% weight inorganic salts. Since no adverse consequences were found in the

(9) Meyer, M. D.; Altenbach, R. J.; Basha, F. Z.; Carroll, W. A.; Drizin, I.; Kerwin, J. F., Jr.; Wendt, M. D.; Haight, A. R.; Zhang, W. U.S. Patent 6,046,207, 2000. Lavielle, G.; Dubuffet, T.; Millan, M.; Newman-Tancredi, A., U.S. Patent 5,663,191, 1995.

(10) Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529. Negron, G.; Roussi, G.; Zhang, J. *Heterocycles* **1992**, *34*, 293. Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc., Perkin Trans 1* **1991**, (5), 1091.

(11) Geissman, T. A. *Org. Reactions* **1944**, *2*, 94.

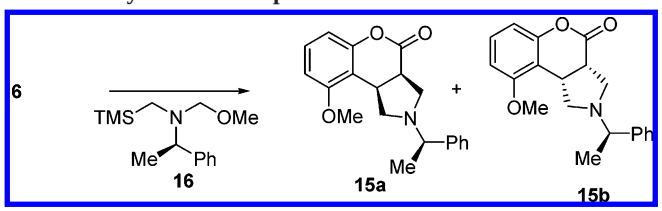
(12) Cannizarro type products were still seen with the pH < 2; however they were greatly reduced: >80% conversion to **12** and **13** without HCl versus <20% conversion after neutralization to pH <2.

(13) Horie, T.; Tominaga, H.; Kawamura, Y.; Yamada, T. *J. Org. Chem.* **1992**, *57*, 3343.

(14) Johnson, J. R. *Org. React.* **1942**, *1*, 210.

(15) The cost of cesium carbonate is 20 times the cost of potassium carbonate.

Table 1. **Cycloaddition optimization**



entry[a]	solvent	additive	temp (°C)	conversion[b]	dr (**15a**/**15b**)
1	THF	TFA (10%)	8 to 10	>90%	1.7/1
2	toluene	TFA (10%)	8 to 10	>90%	1.8/1
3	EtOAc	TFA (10%)	8 to 10	>90%	1.6/1
4	MtBE/ THF	TFA (10%)	8 to 10	>90%	1.7/1
5	THF	BF_3-Et_2O (10%)	8 to 10	<50%	1.7/1
6	MtBE	$AlCl_3$ (10%)	8 to 10	10%	2.1/1
7	THF	TBAF (10%)	−1 to 23	<50%	1.9/1
8	THF	TFA (10%)	−10 to −9	36%[c]	1.5/1
9	THF	TFA (10%)	55	<25%	1.7/1

[a] Reaction conditions: **16** (2 equiv) added over 30 to 60 min to the mixture of **6**, additive, and solvent. [b] HPLC ratio (**15a** + **15b**)/(**6** + **15a** + **15b**) at 220 nm. [c] Ylide (1.3 equiv) added.

subsequent steps due to the inorganics, the crude solid was used as obtained.[16]

The original synthesis of **1** utilized a [3+2] cycloaddition of the ylide derived from **16** and coumarin **6**.[9] Although there was practically no diastereoselectivity observed, the cycloadducts **15a** and **15b** could easily be separated by crystallization. The poor selectivity observed was not suprising,[10] because the preferred exo-transition state of the cycloaddition precludes efficient stereodifferentiating interactions between the chiral auxiliary and the developing stereocenters.[17] Nonetheless, we were attracted by the efficient separation of the diastereomers **15a** and **15b**. Practically, this cycloaddition can be thought of as a classical resolution. Any enhancement in diastereoselectivity would result in a yield improvement, so we first embarked on an investigation to improve the reaction selectivity and yield.

Solvent, azomethine ylide activation methods, and temperature were all evaluated for their influence on the diastereoselectivity and efficiency of the cycloaddition. Dilution with MtBE or replacement of the THF with toluene or ethyl acetate did not greatly influence either the diastereomeric ratio or the product assay (Table 1, entries 1−4). Alternative methods of activating the ylide precursor **16** failed to give good conversion and, additionally, offered little promise for improving the diastereoselectivity (entries 5−7). Changing the temperature from −10 °C to 55 °C did affect the amount of product observed with little influence on the stereoselectivity (entries 8 and 9).

Given the poor diastereoselectivity, it was important to optimize the isolation of the desired diastereomer, **15a**. EtOAc and 50/50 MtBE/EtOAc slurry mixtures of **15a** and **15b** were analyzed by HPLC for the diastereomeric ratio in the supernatant. The minor lactone **15b** proved more soluble than **15a** in both solvent systems, where, at 0−5 °C, the ratio of **15a** to **15b** was 1:5 and 1:6, respectively. Using the concentration of **15b** in these crystallization solvents (60 mg/mL in EtOAc; 47 mg/mL in EtOAc/MtBE 50/50), we were able to determine the minimum amount of solvent required to remove isomer **15b** in a single crystallization.

The optimized procedure entailed addition of a 2-fold molar excess of the ylide precursor **16** to a cooled THF solution containing **6** and catalytic TFA which resulted in the formation of a 1.5:1 ratio of the lactones **15a**/**15b** with high conversion (Scheme 2). The isolation was carried out by concentrating the reaction mixture and solvent switching to EtOAc for crystallization to give **15a** in >99:1 diastereomeric purity and in 40−43% isolated yield from 5-methoxycoumarin. The mother liquors had 10 mg/mL of **15a** (15−20 wt % of product) and 60 mg/mL of the undesired **15b** isomer.

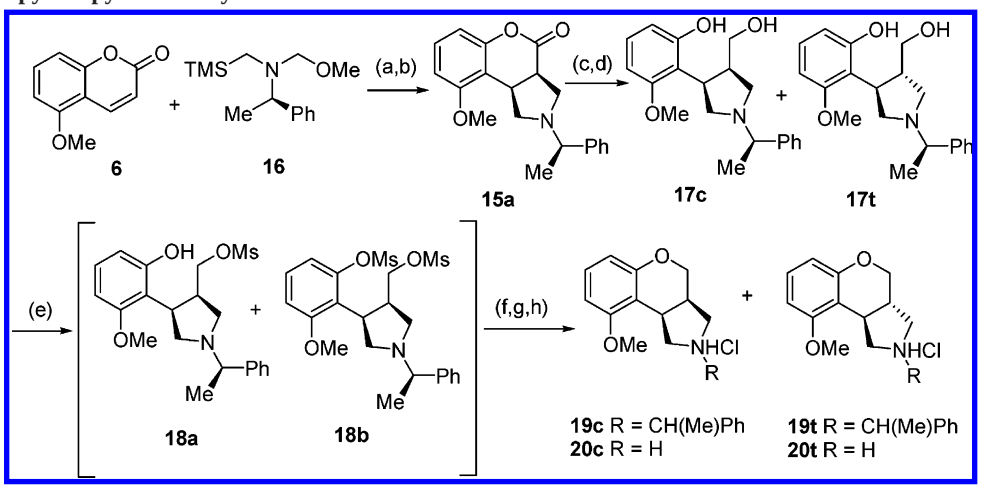
The carbonyl group was removed by a reduction/cyclization sequence. Addition of a THF solution of lithium borohydride to lactone **15a** resulted in formation of diols **17c** and **17t** in a 9:1 ratio. The epimerization results from enolization of the intermediate aldehyde (**21a**/**21b**) generated during the reduction (Scheme 3).[18] Epimer **17t** could be minimized by reversing the order of addition to maintain an excess of the reducing agent. On multi-kilogram scale, controlled inverse addition was successful in minimizing the amount of **17t** observed (55:1 for **17c**/**17t**).

Further improvement on the selectivity was realized after the preparation of the phenol/alcohol on a large scale. The alternative reduction methodology involved slowly adding methanol to a mixture of lactone **15a** and excess $NaBH_4$ in toluene at 0 °C. As the methanol is added, the reduction initiates to cleanly give **17c** with less than 0.2% of the epimer **17t**.[19] Quenching of the reduction with methanol followed by refluxing and distillation effectively hydrolyzed the boronate ester and removed residual boron as trimethyl borate[19,20] to give the desired diol in >95% yield and >98% purity. Although this methodology is superior to the $LiBH_4$ reduction protocol, it was not employed in the initial scale-up as the conditions were not optimized prior to the first delivery of fiduxosin.

To complete the cyclization, crude diol prepared from the $LiBH_4$ reduction sequence was treated with excess MsCl and TEA. Reaction with 1 equiv of MsCl gave a mixture of **17c**, **18a**, and **18b** (5:92:2 respectively). We were unable to selectively react the primary alcohol in the presence of the phenol. To consume the diol completely required 1.3 equiv of MsCl which resulted in a mixture of mono- and bis-mesylates, **18a** and **18b** in ∼7:1 ratio. On exposure to potassium *tert*-butoxide, **18b** undergoes aryl deprotection,[21] and in one pot, the mesylate mixture was cleanly converted to the tricyclic freebase of **19c** in >98% assay yield.

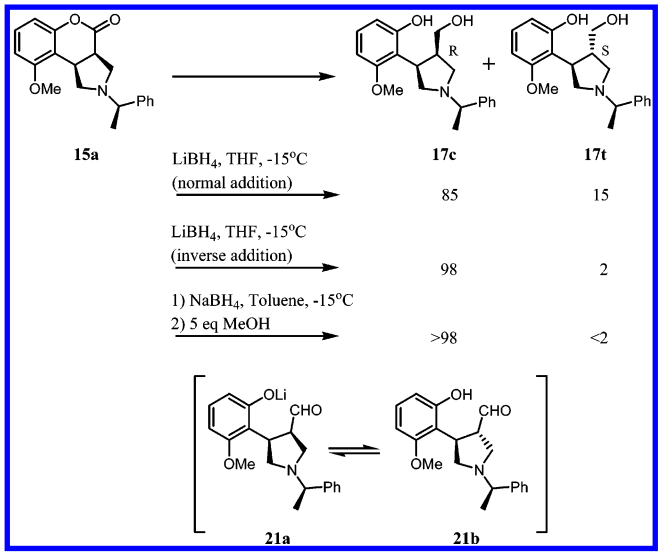
(16) Latter scale-up syntheses employed steam distillation to remove inorganics from **6**.
(17) Padwa, A.; Chen, Y. Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529.
(18) Caille, J.-C.; Govindan, C. K.; Junga, H.; Lalonde, J.; Yao, Y. *Org. Proc. Res. Dev.* **2002**, *6*, 471.
(19) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley: New York, 1998; pp 72, 89−93.
(20) Trimethyl borate forms an azeotrope with methanol: Cunningham, G. L. U.S. Patent 3004058.
(21) Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **1999**, *40*, 3989.

Scheme 2. **Benzopyranopyrollidine synthesis**[a]



[a] Reaction conditions: (a) TFA (10 mol%), THF/MtBE, 15 °C, **16** (2.0 equiv). (b) EtOAc x'tal (2 mL/g **6**) (43%). (c) $LiBH_4$, THF. (d) MeOH, reflux (95%). (e) THF/toluene, 0 °C, TEA (2.4 equiv), MsCl (1.3 equiv), 1 h. (f) KOtBu (3 equiv), 10 °C, 1 h (98%). (g) HCl, *i*PrOH (76% from **6**). (h) Pd/C, H_2, MeOH (92%).

Scheme 3. **Lactone reduction**



The low melting waxy freebase ether of **19c** proved difficult to purify by crystallization. We turned to preparing the hydrochloride salt **19c** by crystallization from 2-propanol, which provided the compound in greater than 98.0% purity with the trans isomer **19t** as the largest impurity (<1% by HPLC) in 76% yield from **6**.

The relative and absolute stereochemistry was confirmed by a single-crystal X-ray structure of **19c** (Figure 4). Hydrogenolysis of **19c** over $Pd(OH)_2/C$ at 50 °C in ethanol was uneventful in yielding tricycle **20c** in 92% isolated yield and >99.5% purity (>500:1 **20c**/**20t**).

Phenyl-Thieno[2,3-*b*]pyrazine. The most general method of synthesizing thieno[2,3-*b*]pyrazines has been to treat 3-cyano-2-chloropyrazines with thioglycolates.[22] We were acutely aware that one of the more troublesome aspects of the original synthesis of **1** was the separation of the regioisomers of **28**.[23] With this in mind, we sought efficient methods for the regiospecific preparation of 2-halo-3-cyano-

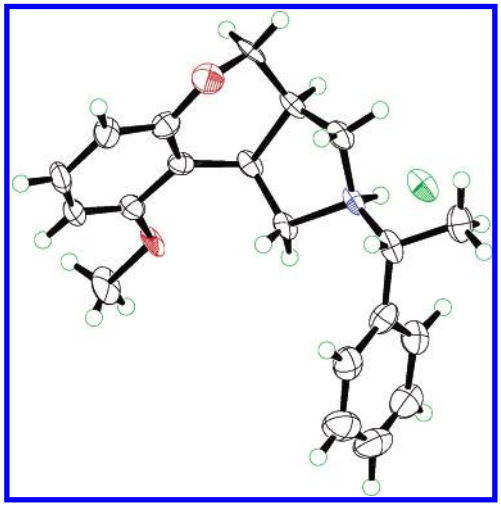


Figure 4. **X-ray structure of 19c.**

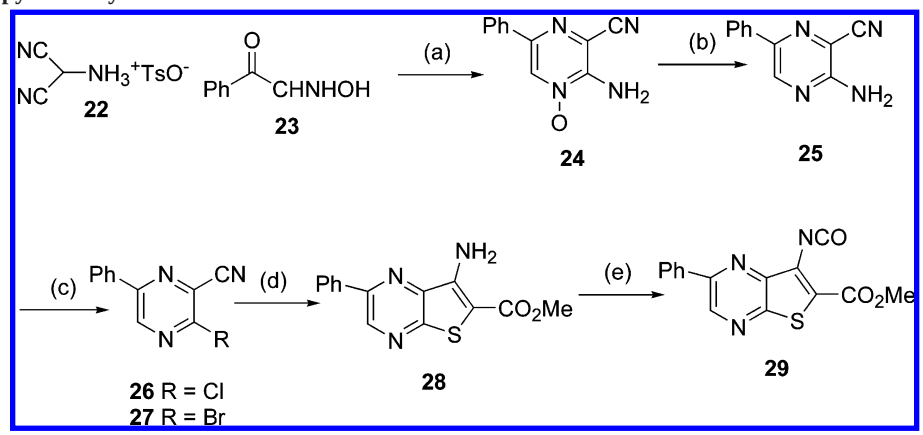
5-phenylpyrazine. We made use of chemistry by E. C. Taylor involving the condensation of aminomalononitrile **22** with phenylglyoxal oxime **23** in 2-propanol to give **24** in 95% isolated yield by simply cooling the reaction to 0 °C and collecting the solid (Scheme 4).[24] 2-Amino-3-cyano-5-phenylpyrazine *N*-oxide **24** could be reduced by treatment with $(EtO)_3P$ at 100 °C. Calorimetry of the reaction showed the presence of two large exotherms; the first initiating at 115 °C and the second at 210 °C. To alleviate safety concerns, the reaction was carried out by slowly adding **24** to neat $(EtO)_3P$ at 100 °C. Upon completion, the reaction was quenched with water to hydrolyze unreacted triethyl phosphite and precipitate **25** in 92% yield and 98% HPLC purity. As an alternative to the slow addition of **24** to the $(EtO)_3P$, it was found that the reaction could be run in refluxing ethanol. This was considered safer to scale-up as the ethanol provided an effective heat sink and assured the temperature would remain sufficiently below the onset of the observed exothermic events. Residual $(EtO)_3P$ in the ethanol was then quenched with water, and the product isolated, as before, by filtration.

(22) Taylor, E. C.; Reiter, L. C. *J. Org. Chem.* **1982**, *47*, 528. Bourguignon, J.; Lemarchand, M.; Quequiner, G. *J. Heterocycl. Chem.* **1980**, *17*, 257.

(23) Attempts to separate at regioisomeric mixtures of pyrazine intermediates were not successful. See ref 9.

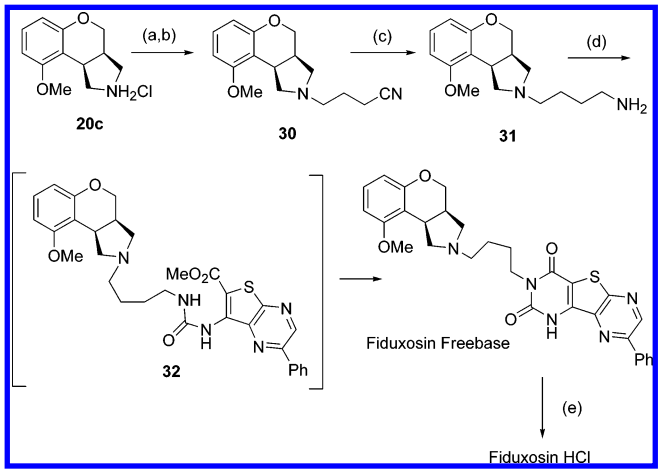
(24) Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1973**, *38*, 2817.

Scheme 4. **Thienopyrazine synthesis**[a]



[a] Reaction conditions: (a) *i*PrOH, rt, 24 h (95%). (b) $P(OEt)_3$, EtOH, 78 °C (92%). (c) See text (73%). (d) $HSCH_2CO_2Me$, Na_2CO_3, MeOH (92%). (e) Triphosgene, THF, 68 °C (95%).

Scheme 5. **Final assembly steps**[a]



[a] Reaction conditions: (a) $NaHCO_3$, CH_2Cl_2. (b) $Br(CH_2)_3CN$, iPr_2NEt, CH_3CN (95%). (c) Ra−Ni, $MeOH/NH_3$, H_2 (93%). (d) (1) **29** (0.98 equiv), toluene, rt, 2 h; (2) reflux 2 h. (e) Toluene/EtOH, HCl (70−85% from **29**).

In our attempts to convert the 2-amino substituent of **25** to a leaving group, Sandmeyer conditions (CuCl, aqHCl, $NaNO_2$)[25] failed to give the desired chloride **26**. Careful analysis of in-process HPLC chromatograms showed a new component (thought to be the diazonium intermediate) forming rapidly and then slowly decomposing during the course of the reaction to give low yields of 2-hydroxypyrazine as the only identified component. Preparation of the diazonium salt under anhydrous conditions using *t*-BuONO as the oxidant still resulted in poor conversion with cuprous chloride. However, formation of the diazonium species in the presence of cupric chloride ($CuCl_2$, *t*-BuONO, CH_3CN) gave chloride **26** as the major component of the reaction mixture.[26] Byproducts such as the hydroxypyrazine and the acetamide resulting from a Stetter reaction with the solvent (acetonitrile) suggested chloride was not reactive enough. Switching to DMF as the solvent and cupric bromide as the halide source resulted in consumption of the diazonium salt in less than 30 min at 50−60 °C. Unfortunately, HPLC assay indicated that the bromopyrazine **27** was unstable in the reaction media at 50−60 °C, while lower temperatures resulted in higher levels of competitive reaction byproducts such as the hydroxypyrazine. To ameliorate this, immediately upon completion, the reaction mixture was rapidly quenched into a −20 °C acidic solution to precipitate the product. The crude product was dissolved in CH_2Cl_2 and clarified through a pad of Celite. Crystallization from heptane/CH_2Cl_2 gave **27** in 73% yield and >98% purity.

Coupling of **27** with methyl thioglycolate in methanol with sodium carbonate as the base proceeded uneventfully. Crude **28** was purified by filtering through a pad of alumina or silica with either methylene chloride or toluene to yield **28** as a bright yellow solid in 92% yield and >99% purity. Conversion of thienopyrazine **28** to isocyanate **29** was accomplished by heating a THF solution of **28** in the presence of 3 equiv of triphosgene followed by precipitation of **29** with heptane. This gave **29** in 90−95% yield and >99.0% purity.

Final Assembly. Hydrochloride salt **20c** was neutralized in methylene chloride with aqueous $NaHCO_3$. The solution was solvent exchanged into acetonitrile, and the freebase was *N*-alkylated with 4-bromobutyronitrile in the presence of Hunig's base. The reaction mixture was concentrated and diluted with toluene. Aqueous extraction removed unreacted freebase and a bis-alkylated ammonium salt to give nitrile **30** in >95% yield and >98% purity. The nitrile was reduced with Raney nickel in a mixture of methanol and ammonia.[27] The catalyst was filtered, and the solvent exchanged into toluene. Treatment of the toluene solution with aqueous NaOH precipitated residual nickel from the green-tinted biphasic mixture as a flocculant white solid which could be removed by filtration.[28] This yielded a toluene solution of the primary amine **31** in 93% assay yield with less than 5 ppm of residual nickel by ICP (Scheme 5).

Amine **31** was reacted with isocyanate **29** in toluene to generate fiduxosin via the transient urea **32**. Temperature control during the stages of the reaction was important. If the intermediate urea was allowed to cyclize in the presence

(25) For examples of Sandmeyer reactions with similar compounds, see: Taylor, E. C.; Reiter, L. A. *J. Am. Chem. Soc*. **1989**, *111*, 285. Favini, G.; Simonetta, M. *Gazz. Chim. Ital.* **1959**, *89*, 2222.

(26) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem*. **1977**, *42*, 2426. Doyle, M. P.; Van Lente, M. A.; Mowat, R.; Fobare, W. F. *J. Org. Chem*. **1980**, *45*, 2570. Taylor, E. C.; Reiter, L. A. *J. Am. Chem. Soc*. **1989**, *111*, 285.

(27) Freifelder, M.; Ng, Y. H. *J. Pharm. Sci*. **1965**, *54*, 1204.

(28) Svehla, G. *Vogel's Qualitative Inorganic Analysis*; Svehla, G., Ed.; p 132.

of unreacted **29**, the methanol produced would compete with **31** and generate the methyl carbamate of **29**. To inhibit the generation of this impurity, the reaction was kept at ambient temperature until the isocyanate was consumed (2 h). The mixture was then heated to reflux to drive the cyclization reaction to completion. Precipitation with heptane gave fiduxosin freebase as a free flowing solid. The free base was dissolved in 50% ethanolic toluene solution and treated with concentrated HCl (1.75 equivalents) to give fiduxosin HCl in 70−85% isolated yield from **29**.

The unusual solubility characteristics of the freebase precluded formation of the hydrochloride salt directly from either an ethanol or a toluene solution. While the freebase showed only limited solubility in either ethanol or toluene (<10 mg/mL in either), a 50/50 mixture of the solvents improved the solubility immensely (>65 mg/mL at 65 °C).

In conclusion, a convergent synthesis of fiduxosin HCl has been demonstrated. A robust and scaleable chiral azomethine ylide [3+2] cycloaddition strategy was developed as a means of generating the 3,4-*cis*-disubstituted pyrrolidine in high enantiomeric excess. We have also described methodology to regiospecifically prepare the trisubstituted bromopyrazine and its conversion to thienopyrazine.

Acknowledgment

We thank Alicia Kuckkan and James Morley for analytical support.

Supporting Information Available

Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review June 2, 2004.

OP049889K