Organic Process Research & Development **2010,** *14,* 417–424

Process Development of a Diacyl Glycerolacyltransferase-1 Inhibitor

Matthew M. Ravn,*,† Seble H. Wagaw,† Kenneth M. Engstrom,† Jianzhang Mei,† Brian Kotecki,† Andrew J. Souers,‡ Philip R. Kym,‡ Andrew S. Judd,‡ and Gang Zhao†

Global Pharmaceutical R&D, Process Research & Development, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064, U.S.A., and Global Pharmaceutical R&D, Discovery, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064, U.S.A.

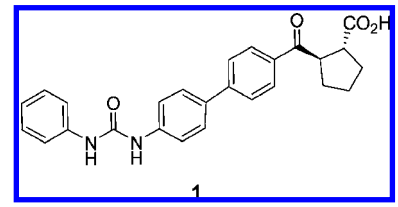
Abstract:

A synthesis of a selective diacyl glycerolacyltransferase-1 (DGAT-1) inhibitor, 1, is described. The synthesis illustrates a diketone Favorskii reaction on 9 in place of the more common ketoester variant for generation of the dicarboxycyclopentane core, the development of an efficient classical resolution of a key cyclopentyl ketoacid intermediate 4, and an ambient temperature Suzuki−Miyaura coupling which avoids epimerization of the labile aryl ketone of 1.

Introduction

Diacyl glycerolacyltransferase-1 (DGAT-1) is one of two known isoforms that catalyze the final and committed step of triglyceride biosynthesis[1] and hence could play a role in the development of obesity and insulin resistance.[2,3] Compound **1** (Figure 1), a selective DGAT-1 inhibitor, showed good potency against human and mouse DGAT-1 isoforms, good oral pharmacokinetics in animals, and good selectivity over related acyltransferases.[4] Chronic dosing of **1** in diet-induced obese (DIO) mice conferred both weight loss and a reduction in liver triglycerides and was successful in lowering serum triglyceride levels in lipid challenge models.[4] Herein is described the initial scale up and alternate route exploration of **1**.

First-Generation Route. For the initial SAR studies, a divergent synthesis of **1** was developed for our screening program which allowed for late diversification of the left-hand portion of the molecule.[4a] The core aryl bromide **4** was prepared



1

Figure 1

analogous to literature procedures (Scheme 1).[5] The Favorskii reaction[6] of 2-oxocyclohexanecarboxylate **2** followed by differentiation of the carboxyl groups provided racemic ester acid **3** which was converted to aryl bromide **4** by Friedel−Crafts acylation of bromobenzene followed by saponification with concomitant epimerization of the cyclopentane ring to predominantly the *trans*-isomer. Resolution by two recrystallizations of the (*R*)-α-methyl benzylamine salt provided >95% ee (*R*,*R*)-**4**. After esterification to simplify processing, a Suzuki−Miyaura coupling with 4-nitrophenyl brononic acid followed by and iron-catalyzed reduction provided aniline **5**. A variety of urea analogues were then prepared by coupling of the aniline with the desired isocyanate followed by saponification to regenerate the carboxylic acid.

The initial scale-up campaign used commercially available, albeit expensive, *trans*-**3** which contained 5% of the corresponding *cis*-isomer and 10−15% of the diacid impurity **6** (Scheme 2). The acid chloride could be prepared using thionyl chloride, but removal of the excess thionyl chloride by distillation with toluene resulted in >15% losses to the distillate. If the distillation was not run, the remaining thionyl chloride resulted in lower yields and the formation of numerous unidentified impurities. Instead, reaction with oxalyl chloride followed by codistillation with dichloroethane (DCE) to remove remaining oxalyl chloride provided the acid chloride along with the resulting bis-acid chloride derived from the diacid impurity **6**. Friedel−Crafts acylation of the mixture provided a 77% yield of methyl ester **7** as a mixture of *cis*- and *trans*-isomers along with diketone **8.** Diketone **8** was easily removed after saponification via a simple acid−base extraction. The three-step, one-crystallization process provided racemic ketoacid **4** in overall 73% yield.

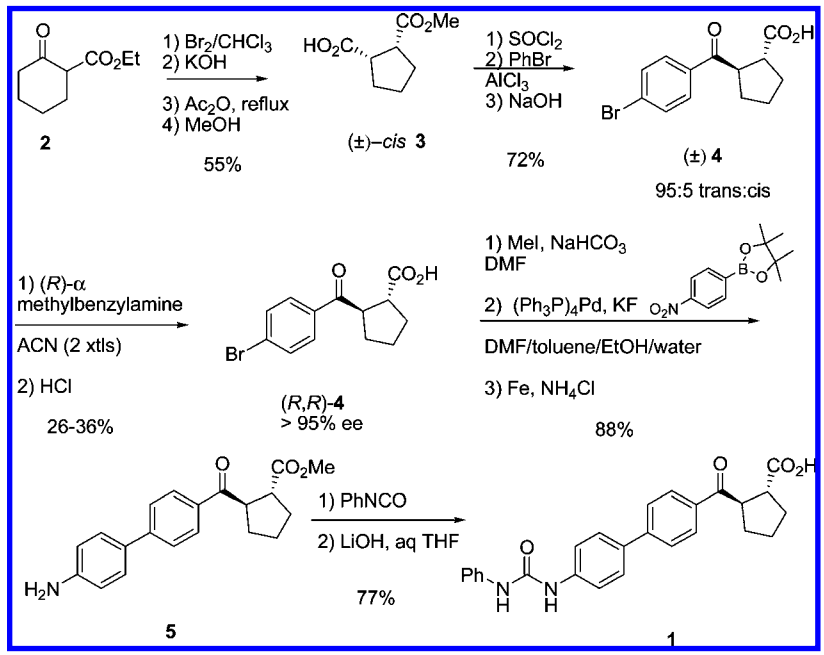
Experiments suggested the initial resolution[5] would present significant challenges to further scale-up. The narrow difference in solubilities for the diastereoisomeric salt pairs of (*R*,*R*)-**4** with

* To whom correspondence should be addressed. Phone: 857-935-4215. Fax: 847-938-2258. E-mail: matthew.ravn@abbott.com.
† Global Pharmaceutical Process R&D.
‡ Global Pharmaceutical Discovery R&D.

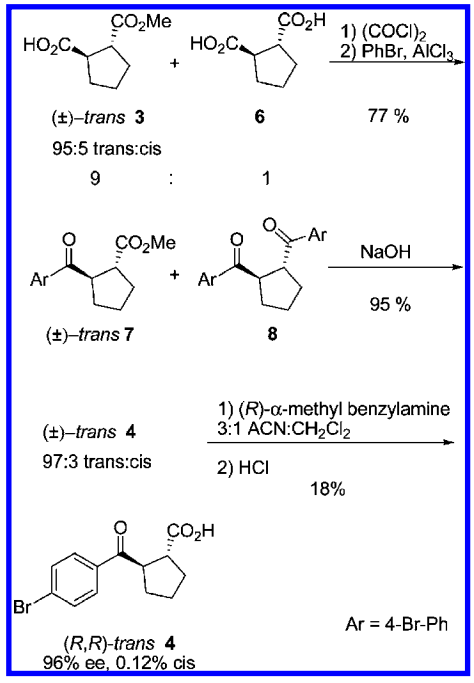
(1) (a) Cases, S.; Smith, S. J.; Zheng, Y.-W.; Myers, H. M.; Lear, S. R.; Sande, E.; Novak, S.; Collins, C.; Welch, C. B.; Lusis, A. J.; Erikson, S. K.; Farese, R. V., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13018. (b) Cases, S.; Stone, S. J.; Zhou, P.; Yen, E.; Tow, B.; Lardizabal, K. D.; Voelker, T.; Farese, R. V., Jr. *J. Biol. Chem.* **2001**, *276*, 38870.
(2) Zammit, V. A.; Buckett, L. K.; Turnbull, A. V.; Wure, H. *Pharmacol. Ther.* **2008**, *118*, 295.
(3) Hubbard, B. K.; Enyedy, I.; Gilmore, T. A.; Serrano-Wu, M. H. *Expert Opin. Ther. Patents* **2007**, *17*, 1331.
(4) (a) Zhao, G.; Souers, A. J.; Voorbach, M.; Falls, H. D.; Droz, B.; Brodjian, S.; Lau, Y. Y.; Iyengar, R. R.; Gao, J.; Judd, A. S.; Wagaw, S. H.; Ravn, M. M.; Engstrom, K. M.; Lynch, J. K.; Mulhern, M. M.; Freeman, J.; Dayton, B. D.; Wang, X.; Grihalde, N.; Fry, D.; Beno, D. W. A.; Marsh, K. C.; Su, Z.; Diaz, G. J.; Collins, C. A.; Sham, H.; Reilly, R. M.; Brune, M. E.; Kym, P. R. *J. Med. Chem.* **2008**, *51*, 380. (b) King, A. J.; Segreti, J. A.; Larson, K. J.; Souers, A. J.; Kym, P. R.; Reilly, R. M.; Zhao, G.; Mittelstadt, S. W.; Cox, B. F. *J. Pharm. Exp. Ther.* **2009**, *330*, 526.
(5) Smith, R.; Campbell, A.-M.; Coish, P.; Dai, M.; Jenkins, S.; Lowe, D.; O'Connor, S.; Su, N.; Wang, G.; Zhang; M.; Zhu, L. U.S. Patent 20040224997(A1), 2004. *Chem. Abstr.* **2004**, *141*, 41027.
(6) (a) Favorskii, A. E. *J. Russ. Phys. Chem. Soc.* **1894**, *26*, 590. (b) Yus, M.; Guijarro, D. *Curr. Org. Chem.* **2005**, *9*, 1713.

10.1021/op900310v
Published on Web 02/15/2010

Scheme 1. **Discovery synthesis of 1**[4,5]



Scheme 2. **Scale-up of ketoacid 4**



(*R*)- and (*S*)-α-methyl benzylamine in acetonitrile indicated little thermodynamic difference (Table 1). In addition, the process required heating in the presence of α-methyl benzylamine which resulted in rapid epimerization of **4** to a 93:7 mixture of *trans*- and *cis*-isomers. As the *cis*-isomer of **4** is a difficult impurity to remove in later steps of the synthesis, an ambient temperature resolution was required. Increasing the volume of aqueous ethanol for the second recrystallization of the salt such that heating was not required to dissolve the solids provided only a 10% yield of 96% ee **4** salt free of *cis*-isomer.

To identify more appropriate solvents for the resolution, solubilities of the salts of (*R*)- and (*S*)-α-methyl benzylamine with (*R*,*R*)-**4** were examined in a range of solvents (Table 1). The larger solubility differences obtained in dichloromethane were utilized to develop an improved ambient temperature resolution employing 0.5 equiv of (*R*)-α-methyl benzylamine in a mixed 3:1 acetonitrile/methylene chloride system to provide 26% recovery of 95% ee salt containing 1.7 area percent (*A*%) *cis*-isomer. An unoptimized recrystallization of the free acid from ethyl acetate/heptane to remove *cis*-isomer provided an overall 18% yield of 96.2% ee ketoacid **4** containing 0.12 *A*% *cis*-isomer.

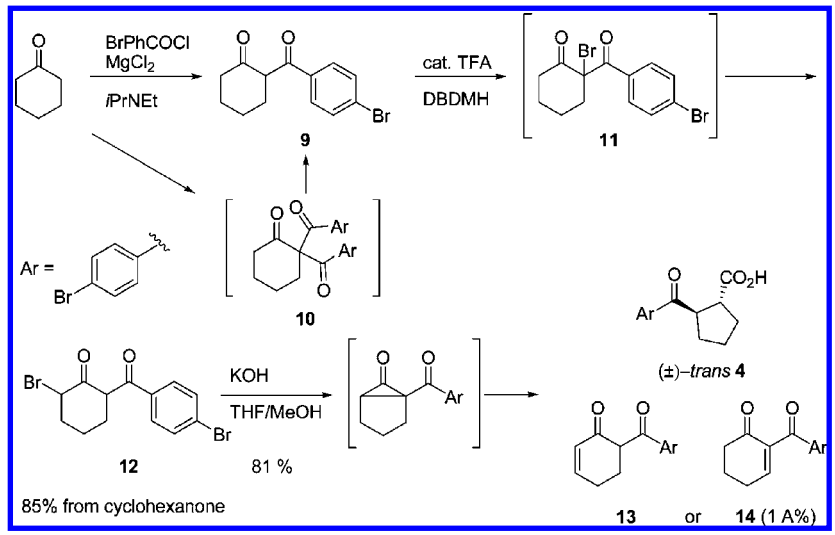
While this synthesis offered rapid access to optically pure ketoacid **4**, significant shortcomings can be noted. The cost and lead time of *trans*-**3** would have been problematic on larger scale, and the late placement and poor recovery of the resolution required significant resources be spent carrying through the undesired enantiomer, thus limiting throughput. In addition, we had little success during the time frame of the project finding a suitable replacement for the environmentally hazardous DCE in the Friedel−Crafts acylation. With these deficiencies, a second-generation route was sought that targeted reducing the number of steps to ketoacid **4** and improving the recovery from the resolution.

Second-Generation Route: Diketo Favorskii. To address the aforementioned issues, we began to explore an alternate synthesis of **4** which would reduce the number of steps and use more readily available starting materials. One potential solution was the attachment of the arylbromide prior to the Favorskii reaction, providing direct access to the ketoacid **4** from diketone **9** (Scheme 3). However, the literature covering the utilization of diketones in the Favorskii reaction is limited to a small selection of total synthesis and single reactions.[6−8]

Preparation of diketone **9** from cyclohexanone and 4-bromobenzoyl chloride gave poor conversion using inorganic bases such as potassium or cesium carbonate, but proceeded smoothly

(7) Rubinov, D. B.; Rubinova, I. L.; Chernyavskaya, Zh. V.; Lakhvich, F. A.; Akhrem, A. A. *Dokl. Chem. (Engl.)* **1991**, *1*−*3*, 182.
(8) Dang Vu, B.; Ba, D.; Bourdon, S.; Vuilhorgne, M.; Dhaleine, F.; Bourdon, R. *Bull. Soc. Chim. Fr.* **1986**, *4*, 613.

Scheme 3. **Alternate route to ketoacid 4**



under soft enolization conditions catalyzed by magnesium salts.[9] Under all conditions tested, a doubly acylated intermediate **10** was observed at a maximum of 7 *A*% by HPLC. However, when dichloromethane was used intermediate **10** acted as a competent acyl donor, reacting with cyclohexanone to provide two moles of **9** and consume **10.** Interestingly, this was not the case in polar aprotic solvents, such as acetonitrile, where significant levels of intermediate **10** were observed even with longer reaction times.

Bromination of the diketone was possible using either elemental bromine or dibromodimethylhydantoin (DBDMH) with either catalytic acid or base (K_2CO_3, TFA, HBr or Amberlyst 15). Initial bromination occurs at the tertiary position, and is most cleanly generated using DBDMH and potassium carbonate in acetonitrile. Unfortunately, bromide **11** was not a competent substrate for the Favorskii reaction and isomerization to the secondary bromide **12** was necessary. Equilibration of **11** to **12** was accomplished by isomerization of **11** with HBr in acetic acid. However, since the equilibration occurs under acidic conditions, we surmised that a one pot bromination/equilibration should be feasible. The use of DBDMH and catalytic TFA in acetonitrile provided the cleanest reaction profile, where tertiary bromide **11** was observed at ambient temperatures but could be equilibrated to >95 *A*% of the desired secondary bromide **12** on heating. Remaining **11** was subsequently removed by crystallization of **12**.

Treatment of secondary bromide **12** with methanolic aqueous hydroxide resulted in the efficient conversion to ketoacid **4** as a 95:5 mixture of *trans*- and *cis*-isomers. The major reaction related impurities included 1 *A*% bromobenzoic acid resulting from hydrolysis of the diketone and 1 *A*% of an enone **13** or **14** as suggested by LC/MS analysis. Minimal counterion effects were observed and all aqueous hydroxides performed similarly (LiOH ≈ NaOH ≈ KOH). Mildly basic conditions employing aqueous carbonates or dibasic phosphate were not effective. The choice of solvents showed marked effects on the reactivity.[10] Removal of MeOH or substitution with higher alcohols such as EtOH and IPA resulted in poor yields. In fact, the methyl ester of **4** is observed at >20 *A*% as an intermediate in the reaction mixture. This suggests that MeOH plays a key role in the transformation, potentially as a nucleophile for opening of the proposed cyclopropanone intermediate before being hydrolyzed to **4**.[6b]

Resolution. Due to the poor yield in the initial resolution of racemic ketoacid **4**, evaluation of alternate chiral bases was undertaken to develop a more robust process. Diastereomeric salt pairs of a range of chiral amines were prepared and their relative solubilities were examined (Table 1). The highest selectivities of >40 to 1 were observed for salts of α-methylnapthylamine and isopinocamphenylamine. However, salts of *N*-methyl-α-methylbenzylamine provided significant solubility differences across a range of solvents, and *N*-methyl-α-methylbenzylamine was preferred with regard to cost and availability. Use of (*S*)-(−)-*N*-methyl-α-methylbenzylamine for the resolution of racemic ketoacid **4** provided salt in 98.3% ee and 41.5% yield, and had the additional benefit of reducing the *cis*-ketoacid **4** from 3 *A*% to 0.7 *A*% in the salt (Scheme 4). Subsequent crystallization of the free acid gave (*R*,*R*)-ketoacid **4** in 99.9% ee and 36.2% overall yield containing only 0.15 *A*% *cis*-isomer.

Suzuki−Miyaura Coupling. A late-stage Suzuki−Miyaura coupling utilizing the free acid **4**, rather than the methyl ester, with boronate **17** provided the most convergent access to **1** (Scheme 5). The key challenge for this coupling was achieving a sufficient reaction rate while avoiding the facile epimerization of the aryl ketone. The boronate coupling partner **17** was prepared in one step from commercially available aniline **16** and phenyl isocyanate **15** in good yield.

For the initial development of the coupling, mild bases (KF and K_2HPO_4) and a selection of catalysts were compared (Table 2, entries 1−6).[11] Of these, reactions employing di-*tert*-butylphosphenyl ferrocene palladium(II) dichloride[11,12] **22** (entry 6) exhibited the highest conversions, cleanest reaction profiles, and lowest levels of protodeboronation. Unfortunately, even

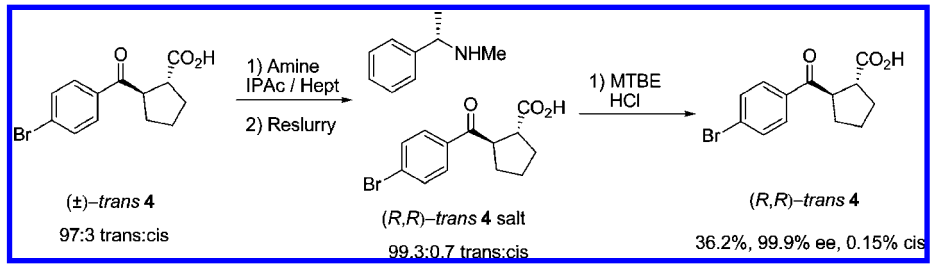
(9) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139.
(10) Only aqueous mixed solvent systems were expolored in the context of this work.
(11) (a) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.
(12) Purchased from Johnson-Matthey.

Table 1. **Solubilities (in mg/mL) and relative ratios of the diastereomeric amine salts of (*R*,*R*)-4 with chiral amines**

	α-methylbenzylamine			*N*-Me-α-methylbenzylamine			*N*-Bn-α-methylbenzylamine			α-methylnaphthylamine		
	R	*S*	ratio	*R*	*S*	ratio	*R*	*S*	ratio	*R*	*S*	ratio
EtOH	39.2	91.2	2.3	>200	50.5	>4.0	61.4	>200	>3.3	24.5	113	4.6
*i*PrOH	11.8	27.4	2.3	>200	17.1	>11.7	22.8	94.3	4.1	6.9	33.8	4.9
H_2O	4.8	8.5	1.8	>40	6.4	>6.2	0.9	1.8	2.0	0.9	2.1	2.3
EtOAc	3.8	7	1.8	>115	9.3	>12.4	66.4	>200	>3.0	4.2	17.8	4.2
IPAc	2.7	4.6	1.7	**95.7**	**6.4**	**15.0**	38.9	174	4.5	2.9	8.9	3.1
MeCN	**2.1**	**3.5**	**1.7**	40.4	4.2	9.6	17	73.4	4.2	1.7	5	2.9
MTBE	2.7	3.8	1.4	42.9	5.6	7.7	35.2	133	3.8	2.8	6.9	2.5
CH_2Cl_2	**16.6**	**140**	**8.4**	>200	>200	N/A	>200	>200	N/A	29.8	>200	>6.7
PhMe	1.2	5.1	4.3	>200	15.1	>13.2	100	>200	>2.0	**1.7**	**67.6**	**39.8**
Hpt	ND	ND	ND	**1.5**	**0.22**	**6.8**	1	12.6	12.6	0.036	0.098	2.7

	cyclohexylethylamine			isopinocampheylamine			norephedrine			ephedrine		
	R	*S*	ratio	+	−	ratio	+	−	ratio	+	−	ratio
EtOH	>200	16.7	>12.0	58	>200	>3.4	>200	>200	N/A	27.2	30.1	1.1
*i*PrOH	60.2	20.8	2.9	18.9	76	4.0	96.7	54.1	1.8	7.4	8.7	1.2
H_2O	7.8	4.3	1.8	1.8	3.6	2.0	11.9	7	1.7	4.9	5.4	1.1
EtOAc	4.3	1.6	2.7	1.7	6.6	3.9	8.4	17.3	2.1	2.5	2.8	1.1
IPAc	2.6	1.1	2.4	1.1	4.1	3.7	4.2	5.6	1.3	1.5	1.6	1.1
MeCN	1	0.5	2.0	0.6	1.3	2.2	3	6.2	2.1	1.3	1.5	1.2
MTBE	2.7	1.4	1.9	1.3	4.4	3.4	2.6	3.6	1.4	1.3	1.4	1.1
CH_2Cl_2	>400	56.5	>7.1	51	>400	>7.8	167	28.4	5.9	22.2	27.2	1.2
PhMe	43.9	2.1	20.9	**2**	**83**	**41.5**	2	9.7	4.9	0.9	0.9	1.0
Hpt	0.097	0.045	2.2	0.048	0.14	2.9	ND	ND	ND	0.015	0.009	1.7

Scheme 4. **Resolution of ketoacid 4**

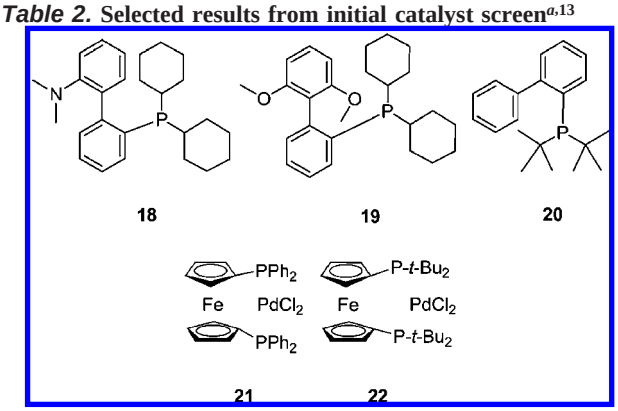


under the relatively mild conditions used for this coupling, a purified mixture of bromide **4** (99:1 trans:cis) exhibited complete equilibration to the thermodynamic mixture of **1** (95:5 trans:cis) by completion of the coupling (Table 3, entry 7). This epimerization could be partially controlled by lowering the reaction temperature to 35 °C where 0.9% *cis*-isomer in the starting aryl bromide **4** translated to 1.7% *cis*-isomer in the coupled product (Table 3, entry 8). However, further reductions in temperature, while minimizing the isomerization, lead to sluggish reaction rates requiring more than 3 days to reach completion (Table 3, entry 9). Testing alternate bases such as dibasic sodium phosphate, potassium bicarbonate, and potassium fluoride did not substantially reduce epimerization, and the rate of coupling was substantially slower in the case of bicarbonate. However, further screening of solvent combinations identified conditions which allowed the coupling to robustly proceed at ambient temperatures (Table 3, entry 10). Together, these modifications served to minimize both impurities and catalyst loading, thus simplifying the final purification. Notable reaction impurities included protodeboronation (0.15 *A*%), aryl bromide homodimer (0.8 *A*%), and excess boronate (1.1 *A*%).

As the final step involves a metal mediated coupling, control of the residual metal levels in the isolated product became

(13) Full screening results are available in the Supporting Information.

Table 2. **Selected results from initial catalyst screen[a,13]**



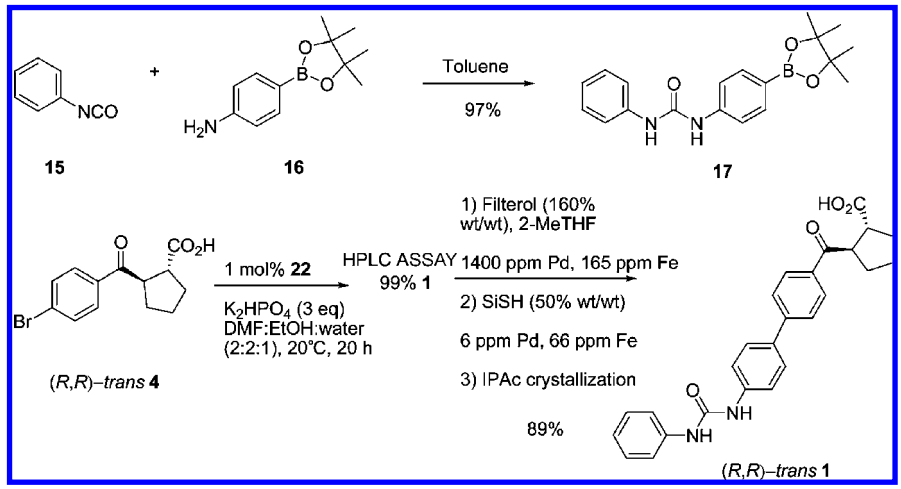
entry	catalyst	HPLC area % **4**	HPLC area % **1**	HPLC area % protodeboronation
1	(t-Bu_3P)$_2$ Pd, 3 mol %	5.2	48.1	1.9
2	$Pd(OAc)_2$ (3 mol %) + **18** (4.5 mol %)	19.3	32.5	22.7
3	$Pd(OAc)_2$ (3 mol %) + **19** (4.5 mol %)	17.4	28.2	2.9
4	$Pd(OAc)_2$ (3 mol %) + **20** (4.5 mol %)	1.0	53.7	5.4
5	**21** (3 mol %)	10.1	44.9	0.9
6	**22** (3 mol %)	**<0.1**	**56.1**	**0.7**

[a] Reaction conditions: THF/EtOH/water (2.5:5:2.5 v/v/v), 50 °C, 3 equiv of K_2HPO_4, 20 h.

Table 3. **Optimization of Suzuki reaction**

entry	conditions	catalyst	*trans*-/*cis*-bromide 4	% assay yield of **1**	*trans*-/*cis*-product **1**
7	1:2:1 THF/EtOH/water (10 vol), 50 °C, K_2HPO_4 (3 equiv), 16 h	3 mol % **22**	99/1	97	95/5
8	1:2:1 THF/EtOH/water (10 vol), 35 °C, K_2HPO_4 (3 equiv), 18 h	3 mol % **22**	99.1/0.9	96	98.7/1.7
9	1:2:1 THF/EtOH/water (10 vol), 30 °C, K_2HPO_4 (3 equiv), 72 h	3 mol % **22**	99.1/0.9	96	98.3/1.3
10	2:2:1 DMF/EtOH/water (15 vol), 20 °C, K_2HPO_4 (3 equiv), 24 h	3 mol % **22**	99.85/0.15	99	99.85/0.15

Scheme 5. **Endgame chemistry and isolation**



necessary. A short screen of metal scavenging agents showed a wide range of behaviors in terms of metals removal and product absorption. A selection of carbons[14] showed modest removal of palladium (20−60%) but excessive absorption of product (5−20%) while functionalized silicates and polymeric resins gave lower losses (1−3%) and efficient removal of palladium (80−95%). For early scale ups we relied on a two stage approach to metal removal where the product solution was first treated with an acid washed clay (Filterol grade F4,[15] 160 wt % relative to **1**, 24 h, 99% recovery) which served to reduce metals and improve color. This was followed by treatment with a functionalized silicate (Silicycle, 3-mercaptopropyl, 50 wt % relative to **1**, 99% recovery) and isolation by crystallization. The final process provided biaryl ketoacid **1** in 89% yield with >99.5 *A*% purity by HPLC.

As the project was discontinued shortly after finishing the preparation of racemic **4** in our kilo lab, the remaining portions of the synthesis were only demonstrated on 5−100 g lab scale. In a general sense, there appears to be few issues which would preclude the scale up of the resolution, boronate preparation and Suzuki coupling based on the observations in lab. However, the chemistry detailed for the second generation preparation of **4** via the diketo Favorskii reaction would likely need some additional optimization prior to scale up. Specifically, the three steps all possess significant exotherms (∼10−40 °C) which would require control via slow addition or other process controls. This along with some additional streamlining of the extraction and isolation sequences would have provided a robust process. Overall, the demonstrated chemistry would have been capable of delivering the necessary supplies of **1** with some further development had it been required.

(14) Carbons tested at 10 wt % loading in 2-MeTHF realtive to product: Darco G60, Ceca Acticarbone ENO-PC, 5SC-G, CPL and L3S grades.

(15) Purchased from BASF Catalysts LLC, 100 Campus Drive, Florham Park, NJ 07932. Grade F4 is no longer manufactured but has been substituted with Grade F1. The performance of Grade F1 has not been verified in this system.

Conclusion

In summary, the selective DGAT-1 inhibitor **1** was prepared in six steps in 22% overall yield from cyclohexanone with a longest linear sequence of five steps. An alternate preparation of intermediate ketoacid **4** was demonstrated which had the advantage over literature methods of reducing the number of steps from seven to two and increasing the yield from 40% to 69%. A classic resolution of ketoacid **4** was systematically developed using relative solubility data of the diastereoisomeric salt pairs to provide a robust process and key purification for the penultimate intermediate. The development of conditions for the room temperature Suzuki−Miyaura coupling provided a convergent synthesis of **1** that avoided generation of problematic impurities.

Experimental Section

General Methods. Analytical HPLC was carried out using an Agilent 1100 or 1200 system.

(±)-Methyl 2-(4-bromobenzoyl)cyclopentanecarboxylate (7). A suspension of (±)-*trans*-2-(methoxycarbonyl)cyclopentanecarboxylic acid **3** (1.15 kg, 6.68 mol) in 1,2-dichloroethane (12.0 L) at <30 °C was treated with oxalyl chloride (1.81 kg, 14.3 mmol, 2.1 equiv) over 1 h. After 15 h at 22 °C, the solution was concentrated to ∼1/3 the total volume (∼5 L) followed by two chase distillations with 1,2-dichloroethane (2 × 6.0 L) to

the same volume. The resulting solution of acid chloride was utilized in the next step with no purification.

A suspension of aluminum chloride (1.88 kg, 14.1 mol, 2.1 equiv) in 1,2-dichloroethane (6.0 L) was cooled to 3 °C. The above solution of acid chloride was diluted with bromobenzene (4.42 kg, 28.2 mmol, 4.2 equiv) and then added over 45 min at <12 °C with a rinse of 1,2-dichloroethane (0.4 L). The resulting dark-red solution was maintained at 2 °C for 2 h, warmed to 20 °C over 3 h, and maintained at 22 °C for 15 h. The reaction solution was quenched into a mixture of water and ice (18 kg) slowly over 35 min at <10 °C using 1,2-dichloroethane (1 L) as a rinse. The quenched reaction mixture was acidified with concd HCl (600 mL) and mixed rapidly for 4 h while warming to 20 °C. The bottom organic layer was separated, and the upper aqueous layer was extracted with MTBE (4.5 kg). The combined organic layers were washed with water (6 kg), and concentrated under reduced pressure to ~6 L followed by two chase distillations with EtOH (2 × 6 L) to the same volume. The resulting solution of ester **7** (77% assay yield by HPLC, 1.60 kg as a mixture of *trans*- and *cis*-isomers, 5.14 mol, 10.65 kg solution) was used without further purification. An analytical sample was prepared by column chromatography and isolated as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.83 (m, 2H), 7.63−7.58 (m, 2H), 4.05 (dt, J = 9.3, 6.9 Hz, 1H), 3.65 (s, 3H), 3.43 (q, J = 8.1 Hz, 1H), 2.22−2.07 (m, 2H), 1.97−1.85 (m, 1H), 1.85−1.70 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.56, 175.35, 134.99, 131.82, 130.06, 128.21, 52.29, 49.78, 46.39, 31.97, 31.07, 26.30. HR-MS calculated for $C_{14}H_{15}BrO_3$: 310.02046, found: 310.02047 $[M]^+$.

***trans*-(±)-2-(4-Bromobenzoyl)cyclopentanecarboxylic acid (4).** The solution of (±)-methyl 2-(4-bromobenzoyl)cyclopentanecarboxylate (**7**) (1.60 kg, 5.14 mol) in EtOH (10.65 kg total) was diluted with a solution of NaOH (815 g, 20.4 mol, 4 equiv) in water (6 L) and heated to 46 °C. After 2.5 h, the reaction solution was cooled to 25 °C, diluted with additional water (6 L), and concentrated under reduced pressure to ~12 L to remove the majority of the EtOH. The aqueous solution was washed with MTBE (4 × 6 L) to remove organic extractable impurities. The pH of the resulting aqueous solution was adjusted to ~4 using 36% HCl (1.63 kg) and extracted twice with EtOAc (12 L, 6 L). The combined organic layers were concentrated under reduced pressure to an oil and chase distilled with MeOH (12 L) to a thick, yellow slurry. The resulting slurry was dissolved in MeOH (6 L) at 40 °C and maintained at 40 °C while water (12 L) was added over 4 h. The slurry was cooled to 22 °C, mixed for 19 h, filtered, washed with water (3 × 6 L), and dried under vacuum to give **4** as a light-yellow solid (1.49 kg, 97.5 wt %, 95% potency adjusted yield, 97:3 mixture of trans:cis). Mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 7.90−7.76 (m, 2H), 7.67−7.50 (m, 2H), 4.04 (dt, J = 9.2, 6.9 Hz, 1H), 3.51 (q, J = 7.9 Hz, 1H), 2.23−2.10 (m, 2H), 2.03−1.93 (m, 1H), 1.87−1.66 (m, 3H). ^{13}C NMR (101 MHz, $CDCL_3$) δ 199.24, 181.02, 134.76, 131.83, 130.04, 128.30, 49.59, 46.12, 32.02, 30.76, 26.24. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41; Br, 26.89. Found: C, 52.62; H, 4.29; Br, 26.85.

***trans*-(1*R*,2*R*)-2-(4-Bromobenzoyl)cyclopentanecarboxylic Acid (4).** A slurry of racemic acid **4** (126 g, 0.425 mol, 1.0 equiv) in isopropylacetate (IPAc) (945 mL) was stirred as (*S*)-(−)-*N*-methyl-α-methylbenzylamine (31.6 g, 0.234 mol, 0.55 equiv) was added, resulting in a mild exotherm from 20 to 23 °C and giving a homogeneous solution. After several minutes, solids crystallized from the mixture. After one hour, heptane (2835 mL) was added over one hour. The slurry was stirred at 23 °C for 17 h and −10 °C for 24 h. The solids were filtered and washed twice with heptane (2 × 250 mL) to give product of 94.7% ee with a 7.6% loss of the desired enantiomer to the combined filtrate and washes.

Chiral HPLC method: Chiralpak AD-H, 4.6 mm × 150 mm, 5:95:0.5 2-propanol/hexane/trifluoroacetic acid isocratic, 40 °C, 1.0 mL/min, 254 nm. (*S*,*S*)-**4** (undesired) - 16.1 min; (*R*,*R*)-**4** - 17.8 min.

The wet cake was suspended in IPAc (125 mL) and heptane (500 mL), mixed at 0 °C for 3 h, and filtered. The wet cake was washed twice with heptane (2 × 125 mL) to give product of 98.3% ee with a 0.9% loss of the desired enantiomer to the combined filtrate and washes.

The wet cake was slurried in MTBE (500 mL) and dissolved by adding 1 M HCl (500 mL). The layers were separated, and the organic layer was washed with 1 M HCl (500 mL). The organic layer was concentrated to an oil and dissolved in MTBE (60 mL). Heptane (1140 mL) was added over 30 min. The resulting slurry was stirred at −5 °C for 18 h and then filtered. The wet cake was washed once with heptane (120 mL) to give product of greater than 99.9% ee with a 2.1% loss of the desired enantiomer to the combined filtrate and washes. The wet cake was dried at 50 °C and 20 in Hg to afford the product (45.6 g, 36.2%) as a white crystalline solid. Mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.82 (m, 2H), 7.64−7.59 (m, 2H), 4.04 (dt, J = 9.3, 6.9 Hz, 1H), 3.52 (q, J = 7.9 Hz, 1H), 2.23−2.13 (m, 2H), 2.03−1.92 (m, 1H), 1.89−1.70 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.28, 180.10, 134.81, 131.88, 130.07, 128.35, 49.68, 46.01, 32.07, 30.80, 26.27. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41; Br, 26.89. Found: C, 52.59; H, 4.24, Br, 27.01.

1-Phenyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (17). A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **16** (40.0 g, 183 mmol, 1 equiv) in toluene (650 mL) was stirred at ambient temperature as phenyl isocyanate **15** (22.8 g, 20.8 mL, 192 mmol, 1.05 equiv) was added in a single portion, and the subsequent solution was warmed to 50 °C. After 16 h, during which time the product crystallized from the reaction mixture, the suspension was cooled to 20 °C. After 5 h (filtrate concentration 1 mg/mL of **17**), the solids were filtered, washed with toluene (2 × 200 mL), and dried in vacuo to give **17** (60.1 g, 97%) as a light-tan solid. Mp 245−247 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.68 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.41−7.53 (m, 4H), 7.27 (t, J = 7.5 Hz, 2 H), 6.96 (t, J = 7.4 Hz, 1 H), 1.27 (s, 12 H).^{13}C NMR (126 MHz, DMSO-d_6) δ 152.31, 142.73, 139.54, 135.46, 128.79, 121.99, 118.31, 117.08, 83.30, 24.65. Anal. Calcd for $C_{19}H_{23}BN_2O_3$: C, 67.47; H, 6.85; N, 8.28. Found: C, 67.41; H, 6.92; N, 8.25.

***trans*-(1*R*,2*R*)-2-(4′-(3-Phenylureido)biphenylcarbonyl)-cyclopentanecarboxylic Acid (1).** *trans*-(1*R*,2*R*)-2-(4-Bromobenzoyl)cyclopentanecarboxylic acid **4** (10.0 g, 33.8 mmol, 1 equiv), 1-phenyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea **17** (11.8 g, 34.9 mmol, 1.03 equiv), K_2HPO_4 (17.6 g, 101 mmol, 3 equiv), and catalyst **22** (220 mg, 0.34 mmol, 1%) were combined in a flask and purged well with nitrogen. In a separate flask, a mixture of DMF, EtOH, and water (2:2:1 v/v/v, 150 mL total) was prepared and sparged with nitrogen for 15 min before transferring by canula to the solids. After 25 h, HPLC indicated reaction completion (<0.2 *A*% **4**), and the reaction mixture was diluted with 2-methyltetrahydrofuran (2-MeTHF, 250 mL) and 1 M HCl (200 mL). The layers were separated, and the aqueous layer was extracted with 2-MeTHF (150 mL). The combined organic layers were washed three times with water (2 × 100 mL, 50 mL). The organic layer (293 g) was treated with Filterol GR[15] (25 g) and $MgSO_4$ (4 g) for 24 h and filtered using 2-MeTHF (100 mL) as a rinse (99% recovery, 1400 ppm Pd, 165 ppm Fe). The organic layer was then treated with Silicycle 3-mercaptopropyl-functionalized silica (8 g) for 25 h and filtered using 2-MeTHF (20 mL) as a rinse (99% recovery, 6 ppm Pd, 66 ppm Fe). The product solution was concentrated under reduced pressure to ∼150 mL (129 g) and chase distilled with four portions of IPAc (4 × 150 mL) concentrating to the same approximate volume each time (∼150 mL) during which time crystallization began. The final slurry (165 g) was heated to 50 °C for 3 h, then cooled over 3 h to 20 °C. After 12 h (filtrate 6 mg/mL), the slurry was filtered, washed with IPAc (3 × 25 mL), and dried under vacuum at 50 °C to give **1** as an off-white solid (12.84 g, 89%, 100 wt %, 99 *A*%). Mp 187−189 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.86 (s, 1H), 8.72 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 8.2 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 4.09 (q, J = 7.6 Hz, 1H), 3.24 (q, J = 8.2 Hz, 1H), 2.24−2.09 (m, 1H), 2.08−1.93 (m, 1H), 1.89−1.52 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 200.15, 175.98, 152.50, 144.38, 140.31, 139.66, 134.26, 132.06, 129.18, 128.85, 127.49, 126.23, 122.01, 118.59, 118.37, 49.10, 45.98, 31.12, 29.87, 25.41. Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.55; H, 5.51; N, 6.51.

2-(4-Bromobenzoyl)cyclohexanone (9). A suspension of $MgCl_2$ (42.4 g, 456 mmol, 2 equiv) in CH_2Cl_2 (500 mL) and 4-bromobenzoyl chloride (50.0 g, 228 mmol, 1 equiv) were mixed at 20 °C in a cold water bath as cyclohexanone (23.6 mL, 22.4 g, 228 mmol, 1 equiv) followed by *i*Pr_2NEt (79 mL, 59 g, 456 mmol, 2 equiv) was added slowly. (Note: exothermic!) The resulting solution was mixed at 22 °C for 24 h. After 24 h at 22 °C, the reaction was quenched with 3 M HCl (250 mL) and mixed at 20 °C for 1 h before separating the layers. The organic layer was washed with water (250 mL), 10% K_2HPO_4 (250 mL), and water (250 mL) and dried over $MgSO_4$ to give a crude solution of **9** (61.2 g assay yield by HPLC, 96%) which was carried directly into the next reaction. An analytical sample of **9** was prepared by crystallization from 5:1 (v/v) heptane/IPA. Mp 105−106 °C; NMR spectra are a 1:1 mixture of enol and keto tautomers, integrals are reported as relative values, ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.65 (s, 0.5H, enol), 7.77−7.72 (m, 1H), 7.60−7.53 (m, 2H), 7.44−7.39 (m, 1H), 4.31 (ddd, J = 8.6, 5.6, 1.0 Hz, 0.5H, keto), 2.59−2.44 (m, 1H), 2.49 (t, J = 6.7 Hz, 1H), 2.39 (t, J = 6.1 Hz, 1H), 2.35−2.24 (m, 0.5H), 2.17−2.06 (m, 0.5H), 2.06−1.96 (m, 1H), 1.96−1.84 (m, 0.5H), 1.83−1.72 (m, 1.5H), 1.62 (dtd, J = 8.9, 6.0, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.72, 195.98, 189.56, 189.37, 136.03, 135.16, 131.78, 131.20, 129.85, 129.18, 128.34, 124.82, 107.03, 59.06, 42.63, 33.14, 30.24, 27.71, 26.87, 23.85, 23.61, 22.26. Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66; Br, 28.42. Found: C, 55.30; H, 4.44; Br, 28.62.

2-Bromo-6-(4-bromobenzoyl)cyclohexanone (12). One-half of the above product solution containing 2-(4-bromobenzoyl)cyclohexanone **9** (30.6 g, 109 mmol, 1 equiv) was concentrated under reduced pressure to a slurry, chase distilled with two portions of ACN (2 × 150 mL), and diluted to a final volume of 150 mL with ACN (5 volumes relative to starting material). The resulting slurry was stirred as dibromodimethylhydantoin (18.7 g, 65.5 mmol, 0.6 equiv) followed by trifluoroacetic acid (842 uL, 1.24 g, 11 mmol, 0.1 equiv) was added over 5 min. (Note: exotherm to 32 °C!) The reaction was heated to 60 °C. After 17 h, the solution was cooled to 20 °C and 2:1 water/IPA (225 mL) was slowly added, during which time crystallization was observed. The resulting slurry was stirred at 20 °C for 1 h and 0 °C for 1 h. The product was filtered, washed with 1:1 water/IPA (2 × 60 mL), and dried at 20 °C for 3 days under vacuum to give **12** as a white solid (35.1 g, 94 wt %, 85% potency adjusted yield). Mp 164−166 °C; NMR spectra are a 99:1 mixture of keto and enol tautomers, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 4.71 (dd, J = 9.7, 5.4 Hz, 1H), 4.34 (dd, J = 9.5, 5.4 Hz, 1H), 2.70−2.55 (m, 1H), 2.49−2.34 (m, 1H), 2.31−2.06 (m, 3H), 1.94−1.80 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.82, 193.62, 135.12, 131.87, 131.44, 129.88, 129.00, 128.49, 57.95, 55.15, 38.95, 29.49, 23.32. Anal. Calcd for $C_{13}H_{12}Br_2O_2$: C, 43.37; H, 3.36; Br, 44.39. Found: C, 43.26; H, 3.25; Br, 44.49.

***trans*-(±)-2-(4-Bromobenzoyl)cyclopentanecarboxylic Acid (4).** A cooled suspension of 2-bromo-6-(4-bromobenzoyl)cyclohexanone **12** (5.0 g, 13.9 mmol, 1 equiv) in THF (50 mL) and MeOH (50 mL) at 2 °C was rapidly mixed as 2 M KOH (50 mL, 7.2 equiv) was added in a single portion. The reaction was exothermic and rapidly rose to 20 °C and became a homogeneous solution, and the cooling bath was removed after 4 min. After 46 h, the reaction was complete by HPLC (<1 *A*% starting bromide and methyl ester, 87% assay yield by HPLC). The reaction was concentrated under reduced pressure to remove most of the organic solvents, diluted with water (50 mL), and extracted with MTBE (50 mL) to remove some organic soluble impurities. The resulting aqueous layer was acidified with concd HCl (8 mL) and extracted twice with EtOAc (70 mL, 30 mL). The combined EtOAc layers were washed with water (50 mL) and concentrated to an oil. The oil was dissolved in MeOH (20 mL) and stirred at 20 °C as water (10 mL) was added slowly, during which time crystallization initiated. After 1 h, an additional portion of water (10 mL) was slowly added over 2 h. After 1 h, the resulting slurry was

filtered, washed with 1:1 aqueous MeOH (2 × 10 mL), and dried under reduced pressure at 40 °C to give an off-white solid (3.43 g, 97 wt %, 97 *A*%, 81% potency adjusted yield). NMR matched previously described **4**. Mp 114−116 °C; Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41; Br, 26.89. Found: C, 52.61; H, 4.27; Br, 27.26.

Acknowledgment

We thank Dr. Michael Rozema for his insightful suggestions to try the Favorskii reaction on diketone **9**.

Supporting Information Available

Full screening results for the Suzuki coupling, NMR spectra, and HPLC methods and retention times. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review December 2, 2009.

OP900310V