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Asymmetric Phase-Transfer Catalyzed Glycolate Alkylation, Investigation of the Scope, and Application to the Synthesis of (−)-Ragaglitazar

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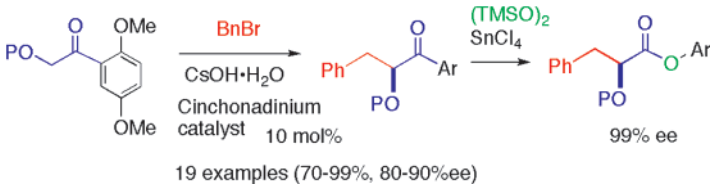
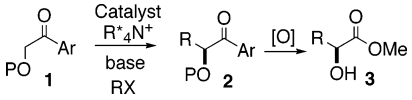


Asymmetric glycolate alkylation using a protected acetophenone surrogate under solid−liquid phase-transfer conditions is a new approach to the synthesis of 2-hydroxy esters and acids. Diphenylmethyloxy-2,5-dimethoxyacetophenone **1** with a trifluorobenzyl cinchonidinium bromide catalyst **9** (10 mol %) and cesium hydroxide provided *S*-alkylation products **2** at −35 °C in high yield (80−99%) and with excellent enantioselectivities using a wide range of electrophiles (80−90% ee). Alkylated products were elaborated to useful α-hydroxy intermediates **3** using bis-TMS peroxide Baeyer−Villiger conditions and selective transesterification reactions. The ester products have been enantioenriched by simple recrystallization from ether to give a single isomer (99% ee). A tight ion-pair model is proposed for the observed *S*-stereoinduction that includes van der Waals contacts between the extended enolate and the isoquinoline of the catalyst. To demonstrate the utility of the new methodology, the anti-diabetes drug (−)-ragaglitazar **24** was synthesized in six steps from a key 2-alkoxy-3-*p*-phenoxypropionic acid **26** that was made using PTC glycolate alkylation.

Introduction

Phase-transfer catalysis (PTC) is rapidly becoming an attractive, general approach to asymmetric synthesis. Under these conditions a reactive enolate, ion-paired with an enantiopure ammonium ion, partitions to the organic phase where it can selectively react with a variety of electrophiles. Successful methods have been developed for asymmetric glycine alkylations, enone epoxidation, conjugate additions, and other transformations that now rival auxiliary and metal-complex-based approaches.[1] PTC has numerous attractive features including the use of inexpensive, cinchona alkaloid catalysts, which are readily available in both enantiomeric antipodes, simple hydroxide bases for in situ enolate formation, and mild conditions that can be run in either liquid−liquid or liquid−solid mode over an extended temperature range. The formation of C−C bonds through direct alkylation of an enolate poses a significant synthetic problem. There are only a few successes based on catalytic methods using sp^3 hybridized electrophiles.[2] The recent report by Jacobsen is a significant advance in this area.[2a] In an effort to develop a process using glycolate intermediates, we previously reported PTC with oxygenated substrates using the novel alkoxyacetophenone **1**.[3] This method provides a route to a variety of alkylated hydroxy products **2** formed under mild conditions in high selectivity (Scheme 1). Previous to this work, known asymmetric glycolate alkylations were limited to chiral auxiliary based approaches.[4] The resultant PTC product undergoes

SCHEME 1. Glycolate Alkylation



(1) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028. (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961−998. (c) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *3*, 3−15.

(2) (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62−63. (b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451. (c) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8830.

(3) Andrus, M. B.; Hicken, E. J.; Stephens, J. S. *Org. Lett.* **2004**, *6*, 2289−2292.

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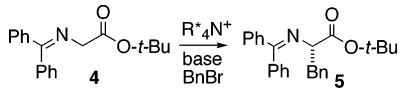
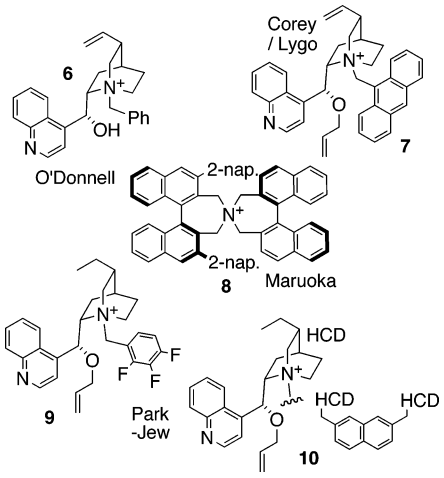
SCHEME 2. PTC Glycine Alkylation



SCHEME 3. Phase Transfer Catalysts Investigated



Baeyer−Villiger-type oxidation to give the aryl ester, which is readily transesterified to produce the useful α-hydroxy ester **3**. PTC glycolate alkylation also serves as a starting point to the design of new asymmetric, catalytic approaches to a variety of oxygenated products using other electrophiles. We now report a full account of the development of catalytic glycolate alkylation including substrate optimization, investigation of the conditions, the scope of the electrophile, elaboration to synthetic intermediates, the origin of the stereoinduction, together with a direct, efficient route to the new diabetes drug (−)-ragaglitazar.

PTC amino acid synthesis has been facilitated by the benzophenone imine *tert*-butyl glycine **4** (Scheme 2), pioneered by O'Donnell,[5] as a result of its extended enolate conjugation and relatively low pK_a value (18.7, DMSO).[1c] Cinchonidine-derived catalysts (Scheme 3, 1−10 mol %), bases, and reaction condition variations have shown steady improvement in selectivity for the production of *S*-**5** (Scheme 3). Nonnatural chiral bis-binaphthyl catalysts[1a,3f] typified by **8** have also demonstrated success. Asymmetric PTC reactions have been shown to follow an interfacial-type mechanism, where enolate formation occurs at the solvent interface boundry layer and alkylation of the ammonium-enolate ion-pair in the organic layer is the rate-limiting step (Scheme 4).[6] To extend PTC to glycolates, with oxygen now in place of nitrogen at C-2, reactivity and selectivity must be addressed in the context of an entirely new substrate. The key effect is the formation of the organic soluble glycolate enolate-cinchonidinium tight ion-pair **12** that selectively reacts with electrophiles.[1a,7] The cinchonidinium cation is free to ion exchange with additional metal enolate **11** at the interface, facilitating further phase transfer and alkylation. Liquid−solid PTC mode, which gives improved selectivity with metal hydroxide hydrates without added water at lower temperatures (−78 to −20 °C), is an important recent advance.[3c]

SCHEME 4. Phase Transfer Mechanism

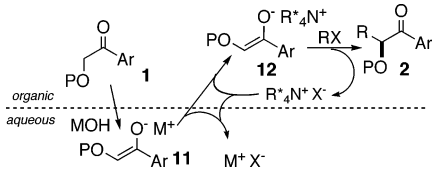
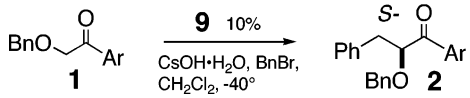


TABLE 1. PTC Benzylation of Aryl Ketone 1



aryl ketone, Ar =	time (h)	yield (%)	ee (%)
phenyl	26	74	25
p-anisyl	6	82	54
o-anisyl	8	78	66
m-anisyl	16	50	50
N,*N*-dimethylaniline	13	87	17
o-toluyl	12	72	62
2,4-xylyl	8	70	66
5-methyl-2-anisyl	11	83	60
1-naphthyl	8	78	55
2,4-dimethoxy	13	90	54
2,5-dimethoxy	7	83	71

Results and Discussion

Aryl ketone functionality, with a lower pK_a value (∼22), proved essential for PTC reactivity (Table 1). Glycolate esters (pK_a ∼25) were initially explored without success even with the use of the more potent phosphazene, Schwesinger bases BTPP and P_2-*t*-Bu under homogeneous conditions.[3b] *tert*-Butyl benzyloxyacetate (not shown) failed to give product with allyl bromide in the presence of cinchonidinium catalyst and various bases. The corresponding thioester gave low yields and selectivities

(4) Previous asymmetric glycolate alkylations are limited to chiral auxiliaries: (a) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167. (b) Schmidt, B.; Wildermann, H. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1050−1060. (c) Chappell, M. D.; Stachel, S. J.; Lee, C. B.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 1633−1636. (d) Burke, S. D.; quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (e) Cardillo, G.; Orena, M.; Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501−1508. (f) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793−1796. (g) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063−1064. (h) Davies, S. G.; Wills, M. *J. Organomet. Chem.* **1987**, *328*, C29−C33. (i) Ludwig, J. W.; Newcomb, M.; Berbreiter, D. E. *Tetrahedron Lett.* **1986**, *27*, 2731−2734. (j) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343−1344. (k) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60−61. (l) Yu, H.; Ballard, C. E.; Boyle, P. D.; Wang, B. *Tetrahedron* **2002**, *58*, 7663−7679.

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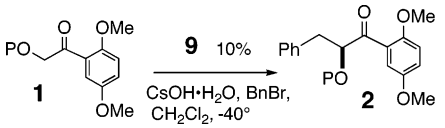
(7) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028.

TABLE 2. PTC Benzylation of 2,5-Dimethoxy Ketone 1



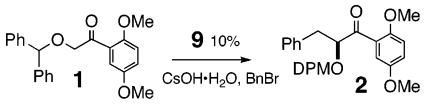
P =	time (h)	yield (%)	ee (%)
Bn	7	83	71
PMB	9	83	68
2-Nap-Me	13	80	75
p-MeO-Ph	23	70	40[a]
methyl	10	84	7[a]
DPM	7	80	80

[a] The *o*-methoxyketone **1** was used.

with catalyst **9** and $CsOH·H_2O$ (29%, 13% ee) and P_2-*t*-Bu (50 h, 41%, 8% ee). Numerous acetophenones with various protecting groups **1** were screened (Table 1). Benzyl-protected substrates **1** were made from benzyloxy acetyl chloride via the Weinreb amide and displacement with aryl Grignard reagents.[8] Benzyloxyacetophenones **1** were treated with benzyl bromide (5 equiv) and trifluorobenzyl cinchonidinium bromide **9**[3g] (10 mol %) using $CsOH·H_2O$ (5 equiv) in CH_2Cl_2 at −40°.[9] This catalyst is conveniently made in three steps from inexpensive cinchonidine and can be chromatographed prior to use. The parent acetophenone **1** (Ar = Ph) gave product **3** with 25% ee (Chiral HPLC) in 74% yield after 26 h.[10] More electron-rich aryl ketones were predicted to show higher reactivity and selectivity through enhanced ion-pairing with the catalyst.[3c] The rate of phase transfer, ion-pairing, and nonbonded interactions that control selectivity should all be improved by increasing the electrostatic interaction of the enolate with the ammonium ion of the catalyst. The *p*-methoxy variant **1** improved to 54% ee, and *o*-anisyl **1** further increased to 66% ee with much shorter reaction times and higher yields, 6 and 8 h, respectively. Dimethylaniline, tolyl, and 2,4-dimethoxy variants did not show improvement. Finally, 2,5-dimethoxyacetophenone **1** demonstrated a synergistic enhancement of reactivity and selectivity, giving product with 71% ee (83%) in 7 h.

The 2,5-dimethoxyphenyl motif was maintained and explored with various protecting groups **1** (catalyst **9**, Table 2). The benzyl-, *p*-methoxybenzyl-, and 2-naphthylmethyl-protected substrates **1** (P = Bn, PMB, 2-NPM) all reacted with good yields and selectivities (80−83%, 68−75% ee). With the C2 hydroxyl protected as a *p*-methoxyphenyl or a simple methyl ether, the rate of reaction was decreased and the selectivity was eroded. The larger benzhydryl (P = diphenylmethyl, DPM) group was found to be superior, allowing for efficient reactivity at −40 °C in CH_2Cl_2 to give **2** in 80% yield and very good selectivity of 80% ee (90:10 er). It is interesting to note that the topology of this group approximates the diphenylmethyl imine group of glycine **4**. The rate of reaction with DPM **1** was also significantly faster, being complete after 7 h at this temperature. Other modifications to DPM group, including bis(*p*-methoxyphenyl)methyl and di-2-naphthylmethyl, did not show enhanced reactivity (88% and 83%) or selectivity (85% and 84% ee).

TABLE 3. Effect of Solvent, Temperature, and Base



solvent	temp (°C)	time (h)	yield (%)	ee (%)
CH_2Cl_2	−40	7	80	80
CH_2Cl_2/Et_2O 1:1	−40	22	84	86
CH_2Cl_2/*n*-hex. 1:1	−40	13	96	86
toluene	−40	28	80	86
$CHCl_3$	−40	24	50	60
Tol/$CHCl_3$ 7:3	−40	23	68	76
CH_2Cl_2/*n*-hex. 1:1	−40	16	72	41[a]
CH_2Cl_2/*n*-hex. 1:1	−40	13	50	10[b]
CH_2Cl_2/*n*-hex. 1:1	−40	39	74	84[c]
CH_2Cl_2/*n*-hex. 1:1	−40	72	tr	*d*
CH_2Cl_2/*n*-hex. 1:1	−20	12	86	82
CH_2Cl_2/*n*-hex. 1:1	−30	12	95	85
CH_2Cl_2/*n*-hex. 1:1	−60	52	69	84

[a] Corey/Lygo catalyst **7** was used. [b] Catalyst **8** was used. [c] $RbOH·H_2O$ used as base. [d] $Ba(OH)_2$ used.

Solvent, base, and temperature were explored to optimize the process (Table 3). Solvents and combinations 1:1 CH_2Cl_2/Et_2O, CH_2Cl_2/*n*-hexane, and toluene were explored again with trifluorobenzyl catalyst **9** and the insoluble base $CsOH·H_2O$ at −40 °C in liquid−solid mode with benzyl bromide. Product **2** was obtained with excellent selectivity using CH_2Cl_2/Et_2O, 86% ee (22 h, 93:7 er). Liquid−liquid mode, with aqueous NaOH or KOH in toluene, was inferior. The fastest rate was found in CH_2Cl_2/*n*-hexane, giving a 96% yield in 13 h with 93:7 er. Other solvents and combinations were less effective. In 1:1 CH_2Cl_2/*n*-hexane, the 9-anthracenylmethyl cinchonidine catalyst **7** gave **2** with 40% ee and the bis-binaphthyl catalyst **8** gave only 10% ee. Rubidium hydroxide with **2** showed excellent selectivity; however, the rate was slow, 39 h, and barium hydroxide failed to give product. Temperature changes had only a slight effect on the rate of the reaction. At −20 °C with $CsOH·H_2O$, the selectivity dropped slightly to 82% ee. At −30°, the selectivity improved to 85% ee. At −60 °C the rate of reaction was very slow, 52 h, and the selectivity was lowered slightly to 84% ee. Catalyst aggregation or substrate coordination are the likely causes of this nonlinear response.[13c] Changing the reaction concentration, from 0.1 to 0.05 or 0.6 M, and amount of the benzyl

(8) (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15−48. (b) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107−4110. (c) Williams, R. M. *J. Org. Chem.* **1987**, *52*, 2615−2618.

(9) TLC was used to monitor for disappearance of the starting material.

(10) Comparisons were made with racemic materials formed without added PTC catalyst at higher temperatures (chiral HPLC, Chiracel AD column, 10% EtOH/hexane, 0.5 mL/min, 170 psi, *R*-isomer t_R −15.2 min, *S*-17.0 min, UV 254 nM detection). See Supporting Information.

(11) (a) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547−1552. (b) Boyes, S. A.; Hewson, A. T. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2759−2765.

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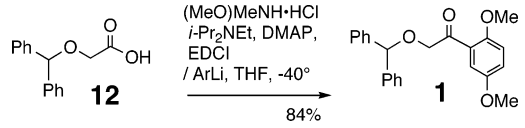
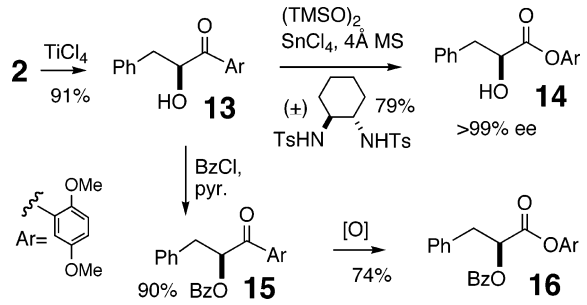
SCHEME 5. Synthesis of Aryl Ketone 1



SCHEME 6. Elaboration of PTC Product 2



halide, 2 to 10 equiv, also did not greatly effect the selectivity or reaction rate. These findings are consistent with the findings that asymmetric PTC reactions are zero order in substrate and less than first order in alkyl halide (0.6).[13a] Variations of the trifluorobenzyl catalyst **9** were also made and tested without improvement. Changing the counteranion to BF_4^-, exchanging the *O*-allyl ether for *O*-benzyl, and maintaining the vinyl group gave **2** with essentially the same selectivity (86% ee). The important factors that affect reactivity and selectivity are the substitution patterns of the acetophenone and the quinuclidine *N*-substituent of the catalyst. High reactivity and selectivity were obtained with more electron-rich, ketones consistent with the enolate-catalyst ion-pairing model. The optimal conditions with **1** and $CsOH·H_2O$ in 1:1 CH_2Cl_2/*n*-hexane have been used many times, including on a multigram scale, with reproducible results.

DPM-acetophenone **1** is conveniently made in two steps (Scheme 5). Benzhydryl alcohol reacts with ethyl bromoacetate to give **12** in 95% yield following ester hydrolysis with aqueous HCl. One-pot Weinreb amide formation, followed by treatment of the crude intermediate with lithiated 1,4-dimethoxybenzene, gives the crystalline product **1** in 84% isolated yield.

To establish synthetic utility and the absolute stereochemistry, oxidation and transesterification conditions were developed to convert the PTC product **2** to known esters (Scheme 6). The DPM group was easily removed with $TiCl_4$ (20 min, CH_2Cl_2, −78°, 91%) to give hydroxy ketone **13**. Alternatives to *m*-CPBA (*m*-chloroperbenzoic acid), the standard reagent for Baeyer−Villiger oxidation,[11] were investigated for the formation of the aryl ester. It was important to use conditions that would not give epoxidation of alkene-containing substrates. By avoiding peracids at this point, alkene products from allyl and propargyl electrophiles with **1** would provide a significant strategic advantage and expansion of the scope of the process. A variation of the oxidation conditions developed by Shibazaki[12] was developed using bis-TMS peroxide (2.5 equiv), catalytic $SnCl_4$, *dl-trans*-cyclohexanediamine bis-toluenesulfonamide (both at 0.5 equiv), and K_2CO_3 to give ester **14** in 79% yield. The reported conditions with excess bis-TMS peroxide (4 equiv) and tin-diamide complex (1.5 equiv) gave lower yields in this case (20−62%). The phenyl ester **14** was found to be crystalline, allowing for enhancement of the enantiopurity through simple recrystallization from warm ether (>99% ee). Benzoate **15** and other protecting groups also allow for production of the aryl ester **16** under the TMS peroxide conditions. This ester **16** was selectively converted to methyl esters under transesterification conditions that either maintain the benzoate ester, giving **17**, or alternatively generate the methyl ester and give a free hydroxyl at C2, **18**.[13] When treated with catalytic NaOMe (20 mol %) in MeOH, the *S*-methyl ester benzoate **17** was obtained in 81% isolated yield ($[\alpha]_D$ −35.5° (*c* 2.0, $CHCl_3$), lit.[14] −40.2° (*c* 1.85, MeOH). Alternatively, when **16** was treated with excess NaOMe (2.1 equiv) in methanol for 13 h, *S*-hydroxy ester **18** ($[\alpha]_D$ −8.8° (*c* 2.0, $CHCl_3$), lit.[15] −7.6° (*c* 2.0, $CHCl_3$) was obtained in 82% yield after 13 h without racemization. *n*-π-Interaction renders the aryl ester more labile when catalytic sodium methoxide is used, allowing for selective aryl ester transesterification in the presence of an alkyl ester.

Asymmetric PTC alkylation of **1** with catalyst **9** (10 mol %) was performed with a number of benzyl, allyl, and propargyl electrophiles (2−5 equiv, Table 4). All benzyl and allylic bromides (2 equiv) investigated reacted in high yield and selectivity (85−90% ee). The yields indicated and the selectivities (chiral HPLC) are again reported for isolated materials with comparisons to racemic materials. Propargyl bromides (3 equiv), including those substituted at the 3-position (entries 6 and 7), were also successful. Allyl iodides, as used with oxazolidinone auxiliary based glycolates,[4a] also reacted but with lower selectivity. Reactions with *n*-alkyl iodides (5 equiv) and tosylates were not successful. Only methyl iodide reacted at −20 °C with success to give **2** with moderate results (entry 15, R = Me, 79%, 66% ee).[12,16] *tert*-Butyl bromoacetate (entry 14), in contrast, gave product with good yield (70%) and excellent selectivity (89% ee).

The approach accommodates allylic electrophiles, leading to unsaturated products where the alkenyl functionality is maintained following Baeyer−Villiger oxidation. Hexenyl ketone, obtained from PTC alkylation with (*E*)-1-bromo-2-pentene (entry 3, Table 4) underwent TMS peroxide oxidation, following DPM removal, to give aryl ester **19** in 74% yield (Scheme 7). Epoxidation was not detected in this case. The alkenyl group can also be readily converted to an alkyl target. As an example of an indirect approach to *n*-alkylation, this PTC product was also hydrogenated and deprotected in one pot to give the 2-hydroxy product **20**.

A model, where the geometry of the enolate and the cinchonium tight ion-pair arrangement are well-defined,[3c] can be used to rationalize the stereoinduction of the glycolate process. The *Z*-enolate[17] oxygen generated from **1** (Scheme 8), tight ion-paired with the least-hindered face of the ammonium nitrogen, can adopt various conformations. This *Z*-enolate has been generated from **1** under the PTC conditions and trapped with ethyl

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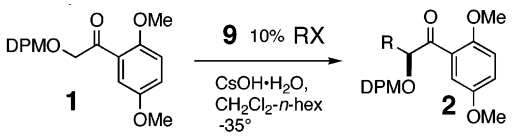
(15) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402−2404.
(16) Boeckman, R. K.; Clark, T. J.; Shook, B. C. *Org. Lett.* **2002**, *4*, 2109−2112.
(17) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081.

TABLE 4. PTC Glycolate Alkylation with Various Electrophiles



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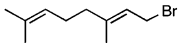
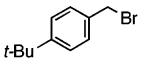
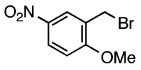
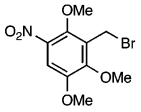
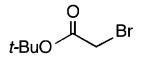
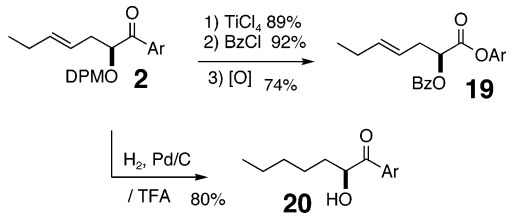
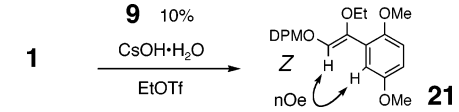
2		3	81	70
3		5	78	89
4		4	85	82
5		8	80	84
6		4	89	81
7		4	88	81
8		14	93	86
9		5	96	84
10		9	99	90
11		12	91	85
12		24	91	88
13		7	83	74
14		20	70	89
15	MeI	5	79	66[a]

[a] Reaction was performed at −20 °C.

SCHEME 7. Elaboration of Alkenyl Product 2



SCHEME 8. Formation of *Z*-Enolate



triflate to give **21**. An nOe value of 6% was observed by ^{1}H NMR to confirm the expected *Z*-geometry. Arrangements **A** and **B** with **2** are shown that expose opposite prochiral faces while maximizing π-stacking van der Waals contacts between the catalyst and the enolate from **1** with the oxygen pointing directly at the ammonium nitrogen (Figure 1). In arrangement **A**, the DPM group adopts a $\pi-\pi$ interaction with the trifluorobenzyl group

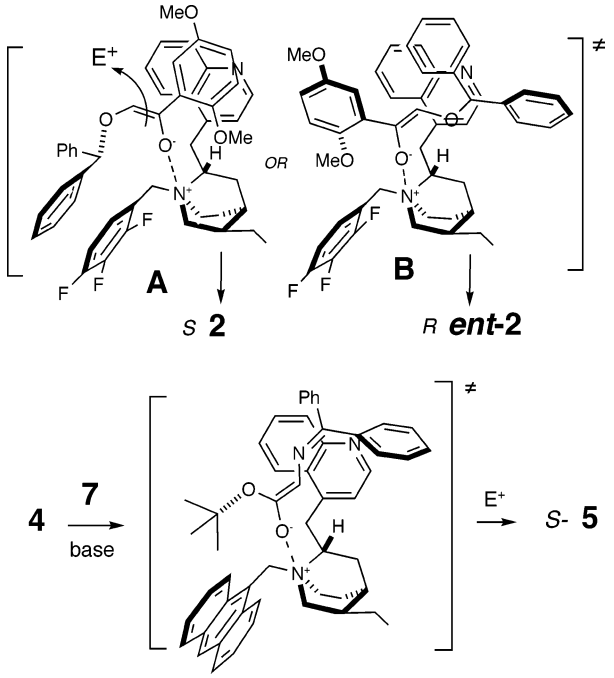


FIGURE 1. Transition-state arrangements of the *Z*-enolate from **1** ion-paired with catalyst **9** compared to the ion-pair model with glycine **4** and catalyst **7**.

of the catalyst.[18] The extended conjugation of the substrate, made up by the enolate and the dimethoxyphenyl group, then incurs a π-interaction with the quinoline of the catalyst. The front *re* face of the enolate attacks the electrophile generating the major *S*-product **2**. The electronegative trifluoro *N*-benzyl group enhances the ion-pairing with the electron-rich enolate. In arrangement **B**, the dimethoxylphenyl fits between the ligand *N*-benzyl without π-stacking and the quinoline group π-stacks with the DPM group. The electrophile alkylates from the front *si* face as shown, generating the minor *R* product. A similar model reported by Corey for glycine imine **4** invokes π-stacking with the *E*-enolate over the quinoline leading to alkylation to give *S*-product **5** (Scheme 8).[3c]

The utility of PTC alkylation is demonstrated by a direct seven-step synthesis of the important new anti-diabetes drug ragaglitazar **24**, a potent inhibitor of peroxisome proliferator receptor (PPAr).[19] Previous routes, which all go through a key 2-alkoxy-3-phenylpropionate **23**, have relied on hydrolase kinetic resolution catalysis, a strain of which was found only after screening 80 hydrolases, with racemic materials **22** (Scheme 9). Asymmetric approaches to α-hydroxy carboxylic acids including chiral oxaziridines reacted with preformed enolates and hydrogenation of α-ketoesters were unsuitable for this target.[20] The 2-alkoxy-3-phenylpropionate can be considered a privileged structure that is common to many new drugs and current lead compounds in this therapeutic area.[19c]

(18) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497.

(19) (a) Ebdrup, S.; Pettersson, I.; Rasmusse, H. B.; Deussen, H.-J.; Jense, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. *J. Med. Chem.* **2003**, *46*, 1306−1317. (b) Saad, M. F.; Osel, K.; Lewin, A. J.; Patel. N.; Edwards, C. R.; Greco, S.; Nunez, M.; Huang, W. C.; Reinhardt, R. R. *Diabetes* **2002**, *51* (suppl 2), A35−A36. (c) Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118−4127.

SCHEME 9. Previous Route to Ragaglitazar

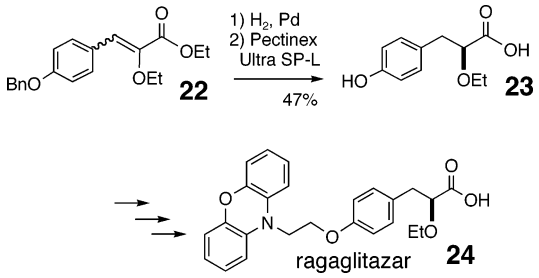
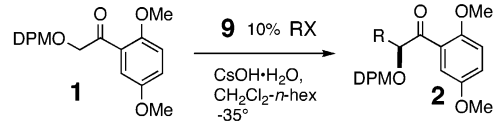
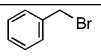
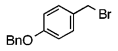
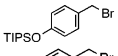
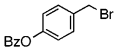
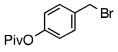


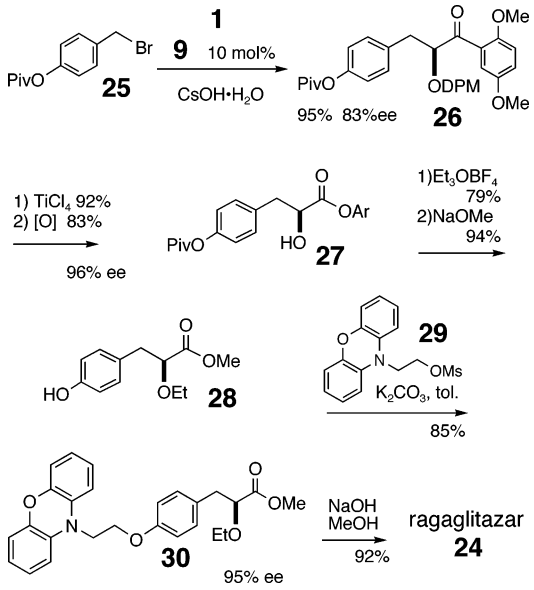
TABLE 5. Effect of Equivalents and *p*-Substitution



entry	RX	equiv.	time (h)	%yield	%ee
1		2	14	86	84
2	"	5	13	93	86
3	"	10	8	93	86
4		1.25	14	80	40
5	"	2	9	88	74
6	"	5	11	88	40
7		2	24	77	70
8		3	39	73	69
9	"	5	24	66	67
10		3	24	88	80
11	"	5	24	95	83

The requisite *p*-alkoxybenzyl electrophile was investigated as a prelude to the PTC synthesis of (−)-ragaglitazar (Table 5). This seemingly straightforward variation was shown to be highly dependent on the nature of the *p*-alkoxy protecting group and the stoichiometry of the electrophile. Benzyl bromide (entries 1−3) used at 2, 5, and 10 equiv gave product **2** with consistently high selectivities. Use of 2 equiv slightly increased the reaction time and the yield was only slightly lowered. *p*-Benzyloxybenzyl bromide used at 1.25 and 5 equiv gave **2** with greatly reduced selectivity, 40% ee. Surprisingly, use of 2 equiv (entry 5) improved the selectivity (74% ee). The TIPS (triisopropylsilyl) ether (entry 7) reacted at a slower rate with only moderate selectivity (70% ee). 4-Benzoate benzyl bromide (entries 8 and 9) also reacted with slow rates and moderate selectivities. The electronically deactivated *p*-pivalate benzyl bromide (entries 10 and 11) finally was found to generate PTC product in both high yield and selectivity. This electrophile was conveniently produced from *p*-hydroxybenzyl alcohol reacted with pivaloyl chloride followed by treatment with lithium bromide in the presence of mesyl chloride. With 5 equiv of this electrophile, product was obtained in 95% yield (83% ee) and the excess benzyl bromide was readily recovered (94%).

SCHEME 10. PTC Route to Ragaglitazar



Pivaloate-protected benzyl bromide **25** (5 equiv) was used under the optimized PTC conditions with catalyst **9** (10 mol %) and ketone **1** to give **26**, 95%, 83% ee (Scheme 10). Excess halide **25** was recovered (94%) and reused on large scale (1 g). The DPM group was removed and TMS peroxide oxidation gave the aryl ester **27** in high yield with 96% ee selectivity after a single recrystallization (Et_2O). The ethyl ether was formed using triethyloxonium tetrafluoroborate in chloroform and transesterification with NaOMe was performed to give **28**. No racemation was observed at this point even when using 3 equiv of base. Ethylation performed using NaH or silver oxide and EtI or amine bases with ethyl triflate produced multiple products. Treatment with phenoxazine mesylate **29** with K_2CO_3 in warm toluene produced **30** in excellent yield (95% ee). Use of $CsCO_3$ as base also gave **30** in excellent yield (98%); however, significant racemization was observed (110 °C), 85% ee. Hydrolysis with aqueous NaOH, without racemization, completed the PTC route to this important compound. Each step from **27** to ragaglitazar in this sequence was shown by chiral HPLC to maintain high enantiopurity.

In summary, a general approach to catalytic asymmetric alkylation has been developed. A surrogate benzhydryloxy acetophenone reacts with a variety of electrophiles under phase tranfer conditions to give enantioenriched products (80−90% ee). TMS-peroxide generates the aryl ester, which can be recrystallized to give a single enantiomeric product (99% ee). Transesterification readily provides methyl esters that are suitable for multistep applications. A tight ion-pair model between the enolate and the cinchonidinium catalyst, which maximizes van der Waals contacts, can be used to rationalize the observed *S*-enantioselectivity. The diabetes drug ragaglitazar was made in seven direct steps using a substituted benzyl bromide electrophile. This success within the demanding constraints of catalytic alkylation provides a sound precedent for extending the process further to include other electrophiles, i.e., aldehydes and unsatur-

(20) (a) Davis, F. A. Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934. (b) DeSantis, G.; Zhu, Z.; Greenberg, W. A.; Wong, K.; Chaplin, J.; Hanson, S. R.; Farwell, B.; Nicholson, L. W.; Rand, C. L.; Weiner, D. P.; Robertson, D. E.; Burk, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9024−9025. (c) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870−2871. (d) LeBlond, C.; Wang, J.; Liu, J.; Andrews, A. T.; Sun, Y.-K. *J. Am. Chem. Soc.* **1999**, *121*, 4920−4921.

ated carbonyl compounds, and will aid in the design of new catalysts for improved selectivity and reactivity.

Experimental Section

Benzhydryloxy-acetic Acid (12). To an oven-dried round-bottom flask were added benzhydrol (5.07 g, 27.5 mmol) and 270 mL of benzene. Then tetrabutylammonium hydrogensulfate (0.465 g, 1.37 mmol) was added with stirring followed by 50 mL of a 50% aqueous (w/w) NaOH solution. The reaction was stirred for 30 min then ethyl bromoacetate (4.6 mL, 41.3 mmol) was added dropwise. The solution was allowed to stir at ambient temperature for 24 h. The resulting thick white solution was then diluted with H_2O and hexanes, the layers were mixed and then separated. The aqueous layer was then carefully acidified, while stirring vigorously, with 6 M HCl until a pH of ~7 was obtained. Then 1 M HCl was added until the pH was ~1.4, as monitored by pH 0−2.5 indicator strips. Next, the resulting white, cloudy solution was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to provide 6.32 g (95%) of the title compound as a white powder. Observations by TLC and ^{1}H NMR concluded that the product was analytically pure and it was carried on to the next step. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.76 (bs, 1H), 7.40−7.22 (m, 10H), 5.60 (s, 1H), 3.99 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.3, 141.7, 128.4, 127.5, 126.8, 82.1, 65.2.

2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone (1). To a flame-dried round-bottom flask were added benzhydryloxy-acetic acid **12** (1.95 g, 8.07 mmol) and 32 mL of CH_2Cl_2. The solution was cooled to 0 °C and *N*,*O*-dimethylhydroxylamine hydrochloride (1.20 g, 12.3 mmol) was added in one portion followed by *N*,*N*-diisopropylethylamine (2.10 mL, 12.1 mmol). Then 4-(dimethylamino)pyridine (0.156 g, 1.27 mmol) was added followed by 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (1.56 g, 8.12 mmol). The reaction was stirred at 0 °C for 1 h and then warmed to ambient temperature where it stirred for an additional 24 h. The solution was then diluted with CH_2Cl_2 (80 mL) and H_2O (80 mL). The layers were mixed and separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with an aqueous 1 M H_3PO_4 solution, then with a saturated aqueous $NaHCO_3$ solution, and finally with a saturated aqueous NaCl solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude amide was filtered through a silica gel plug, eluting with EtOAc, and the filtrate was then concentrated and thoroughly dried in vacuo, resulting in the isolation of a pale yellow solid. Dry THF (40.0 mL) was added to the crude mixture followed by cooling to −40 °C. To a separate flame-dried round-bottom flask were added 1,4-dimethoxybenzene (1.46 g, 10.6 mmol) and 18.0 mL of THF. The solution was cooled to 0 °C, and then, with stirring, *n*-BuLi (6.3 mL, 1.6 M in hexanes, 10.1 mmol) was added dropwise over 30 min to produce a faint yellow solution. The solution was allowed to stir for 3 h at 0 °C then added via cannula to the previously described, precooled solution of the crude 2-benzhydryloxy-*N*-methoxy-*N*-methyl-acetamide solution. The resulting solution was allowed to stir for 15 min at −40 °C and then quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL). The reaction was warmed to ambient temperature, and the solution was partitioned between a saturated aqueous NaCl solution and a 1:1 mixture of Et_2O/CH_2Cl_2. The layers were separated and the aqueous layer extracted with (1:1) Et_2O/CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified via column chromatography (20% EtOAc/hexanes) to produce 2.24 g (84%) of the desired compound as an off-white crystalline solid. TLC R_f = 0.23 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.20 (m, 11H), 7.00 (dd, J = 3, 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 5.62 (s, 1H), 4.71 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.7, 153.7, 141.8, 128.5, 127.7, 127.5, 125.9, 121.1, 113.7, 113.1, 83.4, 75.1, 56.0, 55.9; mp = 70−72 °C; HRMS (FAB$^+$) found 385.1412 [M + Na]$^+$, calcd 385.1410 for $C_{23}H_{22}O_4Na$. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 75.98; H, 6.09.

Representative Procedure for Phase-Transfer Alkylation (Table 4, entry 8). (2*S*)-2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-4-methyl-pent-4-en-1-one. To a flame-dried round-bottom flask were added 2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone **1** (0.10 g, 0.276 mmol), *O*(9)-allyl-*N*-2′,3′,4′-triflurorbenzylhydrocinchonidinium bromide (15.7 mg, 0.028 mmol), CH_2Cl_2 (1.4 mL) and hexane (1.4 mL). The solution was cooled to −35 °C and then CsOH·H_2O (0.232 g, 1.38 mmol) was added in one portion. The mixture stirred for 10 min at which time benzyl bromide (0.165 mL, 1.38 mmol) was added dropwise. The mixture stirred at −35 °C for 14 h at which time the reaction was diluted with Et_2O (40 mL) and H_2O (15 mL). The layers were mixed and then separated and the organic layer was washed with H_2O (2 × 15 mL) followed by a saturated aqueous solution of NaCl and then dried over $MgSO_4$. The mixture was filtered, the solvent removed in vacuo and the crude residue purified by column chromatography (15% EtOAc/hexane) to afford 0.116 g (93%) of the desired compound as a colorless oil. TLC R_f = 0.35 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ −6.7° (*c* 2.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.07 (m, 14H), 7.00 (dd, J = 3.0, 9.0 Hz, 1H), 6.88−6.80 (m, 3H), 5.41 (s, 1H), 5.14 (dd, J = 3.0, 9.6 Hz, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 3.06 (dd, J = 2.7, 13.8 Hz, 1H), 2.88 (dd, J = 9.6, 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.2, 153.9, 152.7, 142.7, 141.4, 138.5, 129.9, 128.29, 128.27, 127.8, 127.5, 127.4, 127.3, 127.2, 126.5, 120.5, 114.3, 113.4, 82.8, 82.5, 56.1, 56.0, 39.1; HRMS (EI$^+$) found 452.1982 M$^+$, calcd 452.1988 for $C_{30}H_{28}O_4$. Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.59; H, 6.24. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 7.3 min, *R* (minor) 6.4 min, 86% ee). The absolute configuration was determined by elaboration of the product to known compounds described below.

(2*S*)-2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-pent-4-en-1-one (Table 4, entries 1 and 2). Following purification via chromatography the product was obtained in 83% yield as a colorless oil. TLC R_f = 0.31 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ −10.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.16 (m, 10H), 7.12 (d, J = 3.0 Hz, 1H), 6.98 (dd, J = 3.0, 9.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 5.95−5.81 (m, 1H), 5.53 (s, 1H), 5.05−4.97 (m, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 2.55−2.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 153.8, 152.6, 142.7, 141.8, 134.5, 128.6, 128.5, 128.2, 128.1, 127.8, 127.7, 127.4, 127.3, 126.7, 120.1, 117.3, 114.2, 113.2, 82.3, 81.4, 56.0, 55.9, 37.2; HRMS (FAB$^+$) found 425.1715 [M + Na]$^+$, calcd 425.1723 for $C_{26}H_{26}O_4Na$. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.61; H, 6.57. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 12.6 min, *R* (minor) 11.2 min, 83% ee).

(2*S*)-2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-4-methyl-pent-4-en-1-one (Table 4, entry 3). Following purification via chromatography the product was obtained in 78% yield as a colorless oil. TLC R_f = 0.36 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ −26.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.16 (m, 11H), 6.98 (dd, J = 3.3, 9.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 5.52 (s, 1H), 5.12 (dd, J = 4.8, 7.5 Hz, 1H), 4.82−4.77 (m, 2H), 3.75 (s, 3H), 3.55 (s, 3H), 2.40−2.35 (m, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 153.8, 152.6, 144.0, 142.8, 141.8, 141.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 127.3, 127.2, 126.7, 120.3, 114.3, 113.9, 113.2, 82.2, 80.1, 56.0, 55.9, 41.1, 22.5; HRMS (FAB$^+$) found 439.1878 [M + Na]$^+$, calcd 439.1880 for $C_{27}H_{28}O_4Na$. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 5.9 min, *R* (minor) 5.4 min, 89% ee).

(*S*)-1-(2,5-Dimethoxyphenyl)-2-hydroxyheptan-1-one (20). To a 100-mL round-bottom flask containing (*S*)-2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-hept-4-en-1-one (**2**, Table 4, entry 4) (0.150 g, 0.348 mmol) was added dry toluene. Then 10% Pd on activated carbon (0.030 g) was carefully added to the solution and the mixture stirred at ambient temperature under a H_2 atmosphere (balloon pressure). After 30 h the mixture was filtered through a silica gel plug, eluting with EtOAc. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (3.5 mL). Then trifluoroacetic acid (0.060 mL, 0.70 mmol) was added dropwise. The reaction was stirred at ambient temperature for 30 min and then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, then dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatography (radial, 1 mm plate, 20% EtOAc/hexanes) afforded the title compound, 0.074 g (80%), as a colorless oil. TLC $R_f = 0.26$ (20% EtOAc/hexanes); $[\alpha]^{23}_D$ −51.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, J = 2.5 Hz, 1H), 7.09 (dd, J = 3.5, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.12−5.09 (m, 1H), 3.87 (s, 3H), 3.81 (obs s, 1H), 3.80 (s, 3H), 1.80−1.73 (m, 1H), 1.52−1.18 (m, 7H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.5, 153.8, 153.4, 124.6, 121.5, 114.5, 113.3, 56.1, 56.0, 34.7, 31.8, 25.4, 22.7, 14.2; HRMS (EI$^+$) found 266.1531 M$^+$, calcd 266.1518 for $C_{15}H_{22}O_4$.

4-(Hydroxymethyl)phenyl Pivalate. To a flame-dried 500-mL round-bottom flask were added NaH (dry 95%, 2.13 g, 88.9 mmol) and 400 mL of THF. The suspension was cooled to 0 °C under N_2. Then 4-hydroxybenzyl alcohol (10.06 g, 80.9 mmol) was added in one portion. The mixture stirred at 0 °C until bubbling ceased at which time the reaction was warmed to ambient temperature and stirred for an additional 30 min. The mixture was again cooled to 0 °C and trimethylacetyl chloride (10.95 mL, 88.9 mmol) was added slowly. After stirring for 30 min at 0°C the mixture was warmed to ambient temperature and stirred for 2 h. Then 100 mL of a saturated aqueous $NaHCO_3$ solution was added followed by 300 mL of H_2O. The mixture was extracted with EtOAc (3 × 100 mL), the combined organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified via column chromatography (40% EtOAc/hex) to afford 13.40 g (80%) of the title compound as a pale yellow oil which solidified in cold storage. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.36 (m, 2H), 7.06−7.03 (m, 2H), 4.67 (s, 2H), 1.84 (bs, 1H), 1.37 (s, 9H).

4-(Bromomethyl)phenyl Pivalate (25). To an oven-dried 500-mL round-bottom flask was added LiBr (55.84 g, 643 mmol), THF (120 mL), and NEt_3 (22.4 mL, 160.8 mmol). Then 4-(hydroxymethyl)phenyl pivalate (13.4 g, 64.3 mmol) was added as a THF solution (200 mL). The mixture was cooled to 0 °C and methanesulfonyl chloride (10.45 mL, 135 mmol) was added dropwise. The solution stirred at 0 °C for 2 h at which time H_2O (200 mL) was added. The solution was warmed to ambient temperature and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified via column chromatography (10% EtOAc/hex) to provide 14.15 g (81%) of the desired compound as a white solid. Mp = 58−60 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.40 (m, 2H), 7.05−7.03 (m, 2H), 4.50 (s, 2H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.1, 151.2, 135.3, 130.4, 122.1, 39.3, 33.0, 27.3; HRMS (EI$^+$) found 270.0255 M$^+$, calcd 270.0255 for $C_{12}H_{15}O_2Br$.

Ethyl 2-(10*H*-Phenoxazin-10-yl)acetate. To a flame-dried 25-mL round-bottom flask was added phenoxazine (0.300 g, 1.64 mmol) followed by 1-methyl-2-pyrrolidinone (5.50 mL). Ethyl bromoacetate (0.910 mL, 8.20 mmol) was then added and the reaction warmed to 70 °C where it stirred for 20 h. The reaction mixture was then purified directly by column chromatography (10% Et_2O/hex) to afford 0.343 g (78%) of the title compound as an off-white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89−6.76 (m, 6H), 6.42 (d, J = 7.5 Hz, 2H), 4.30 (obs q, J = 6.9, 14.1 Hz, 2H), 4.26 (s, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 145.3, 133.4, 123.6, 121.7, 115.5, 111.7, 61.5, 46.8, 14.2; HRMS (EI$^+$) found 269.1053 M$^+$, calcd 269.1052 for $C_{16}H_{15}O_3N$.

2-(10*H*-Phenoxazin-10-yl)ethanol. To a flame-dried 50-mL round-bottom flask was added lithium aluminum hydride (95% powder, 0.120 g, 3.15 mmol) and THF (5 mL). Then ethyl 2-(10*H*-phenoxazin-10-yl)acetate was added as a THF solution (10 mL + 3 mL rinse) and the mixture stirred at ambient temperature for 2 h. Then additional lithium aluminum hydride (95% powder, 0.050 g, 1.32 mmol) was added and the reaction stirred for 1 h. H_2O (50 mL) was then added followed by 1 M HCl aqueous solution (5 mL). Then mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O, a saturated aqueous NaCl solution then dried over Na_2SO_4, filtered, and concentrated. The crude title compound (0.279 g, 97%) was isolated as a pale orange/brown solid and carried on to the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83−6.77 (m, 2H), 6.71−6.59 (m, 6H), 3.89 (t, J = 6.3 Hz, 2H), 3.73 (t, J = 6.0 Hz, 2H), 2.07 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 133.6, 123.8, 121.4, 115.6, 112.0, 59.3, 46.9.

(*S*)-4-(2-(Benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxopropyl)phenyl Pivalate (26). To a flame-dried round-bottom flask were added 2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone **1** (1.0 g, 2.76 mmol), *O*(9)-allyl-*N*-2′,3′,4′-triflurorbenzyl hydrocinchonidinium bromide **9** (0.157 g, 0.28 mmol), CH_2Cl_2 (14 mL) and hexane (14 mL). The solution was cooled to −35 °C and then $CsOH{\cdot}H_2O$ (2.32 g, 13.8 mmol) was added in one portion. The mixture stirred for 10 min at which time 4-(bromomethyl) phenyl pivalate **25** (3.74 g, 13.8 mmol) was added. The mixture stirred at −35 °C for 24 h at which time the reaction was diluted with Et_2O (400 mL) and H_2O (150 mL). The layers were mixed and then separated and the organic layer was washed with H_2O (2 × 50 mL) followed by a saturated aqueous solution of NaCl, then dried over $MgSO_4$. The mixture was filtered, the solvent removed in vacuo and the crude residue purified by column chromatography (10−20% EtOAc/hexane gradient) to afford 1.45 g (95%) of the desired compound as a colorless oil. Early column fractions were collected and concentrated to produce 2.82 g (94% recovery) of analytically pure 4-(bromomethyl)phenyl pivalate. $[\alpha]^{23}_D$ +14.0° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32−6.81 (m's, 17H), 5.42 (s, 1H), 5.12 (dd, J = 3.0, 10.0 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 3.03 (dd, J = 3.0, 14.0 Hz, 1H), 2.86 (dd, J = 10.0, 13.5 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.0, 177.4, 154.0, 152.8, 150.0, 142.7, 141.3, 135.9, 130.8, 128.5, 128.4, 127.9, 127.7, 127.4, 127.3, 121.4, 120.7, 114.3, 113.6, 82.7, 82.6, 56.1, 56.0, 39.3, 38.5, 27.5; HRMS (FAB$^+$) found 575.2420 [M + Na]$^+$, calcd 575.2404 for $C_{35}H_{36}O_6Na$; The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 7.9 min, *R* (minor) 6.1 min, 91.4:8.6 er, 83% ee). The absolute configuration was determined by elaboration of the product to known compounds described below.

(*S*)-4-(3-(2,5-Dimethoxyphenyl)-2-hydroxy-3-oxopropyl)phenyl Pivalate. To a 250 mL-round-bottom flask containing (*S*)-4-(2-(benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxopropyl)phenyl pivalate **26** (1.315 g, 2.38 mmol) was added CH_2Cl_2 (48 mL) and the solution was cooled to −78 °C. Then $TiCl_4$ (1.0 M in CH_2Cl_2, 2.38 mL) was added dropwise over 5 min and the reaction stirred at −78 °C for 20 min. Then a saturated aqueous $NaHCO_3$ solution was added (50 mL) and the mixture warmed to ambient temperature. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via radial chromatography (4 mm plate, 20% EtOAc/hex) to afford 0.843

g (92%) of the title compound as a colorless viscous oil. $[\alpha]^{23}_D$ −34.4° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, *J* = 3.5 Hz, 1H), 7.17−7.11 (m, 3H), 6.97−6.94 (m, 3H), 5.38−5.37 (m, 1H), 3.89 (s, 3H), 3.87 (obs m, 1H), 3.81 (s, 3H), 3.13 (dd, *J* = 3.0, 14.0 Hz, 1H), 2.73 (dd, *J* = 7.0, 14.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.9, 177.2, 154.0, 153.5, 149.9, 135.2, 130.5, 124.4, 122.1, 121.2, 114.7, 113.4, 77.5, 56.2, 56.0, 40.3, 39.2, 27.3; HRMS (FAB^+) found 409.1613 $[M + Na]^+$, calcd 409.1622 for $C_{22}H_{26}O_6Na$.

(*S*)-2,5-Dimethoxyphenyl 2-Hydroxy-3-(4-phenylpivalate)propanoate (27). To a flame-dried round-bottom flask were added activated 4 Å molecular sieves (0.500 g), *trans*-*N*,*N*-bis(*p*-toluenesulfonyl)-1,2-cyclohexanediamine (0.840 g, 1.99 mmol), K_2CO_3 (0.550 g, 3.98 mmol) and 15.0 mL of CH_2Cl_2. The mixture was cooled to 0 °C and $SnCl_4$ (2.0 mL, 1.0 M in CH_2Cl_2) was added followed by bis(trimethylsilyl)peroxide (0.855 mL, 3.98 mmol). The mixture was stirred at 0 °C for 5 min, then (*S*)-4-(3-(2,5-dimethoxyphenyl)-2-hydroxy-3-oxopropyl)phenyl pivalate (0.770 g, 1.99 mmol) was added as a CH_2Cl_2 solution (16.0 mL + 4.0 mL round-bottom rinse). The reaction stirred at 0 °C for 75 min, at which time the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ (20 mL) followed by a saturated aqueous $Na_2S_2O_3$ solution (15 mL). The mixture was warmed to ambient temperature and filtered through a Celite pad. The product was rinsed off the Celite with CH_2Cl_2 (150 mL) and the layers were then separated. The organic layer was washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, concentrated and purified via flash column chromatography (50% Et_2O/hexanes) to provide 0.665 g (83%) of the title compound as a fluffy white solid. Then, 0.510 g of the white solid was dissolved in a minimal amount of warm Et_2O/hexanes (1:1) and the product was allowed to recrystalize overnight. Removal of the residual solvent and subsequent drying of the needlelike crystals provided 0.380 g (75%) of the title compound with 95.8% ee. $[\alpha]^{23}_D$ −7.3° (*c* 1.0, $CHCl_3$); mp = 94−96 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.37 (m, 2H), 7.05−7.02 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.59 (d, *J* = 3.0, 1H), 4.73−4.70 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.34 (dd, *J* = 3.5, 14.0 Hz, 1H), 3.15 (dd, *J* = 7.0, 14.0 Hz, 1H), 2.79−2.76 (m, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 172.4, 153.9, 150.3, 145.2, 139.8, 133.9, 130.9, 121.6, 113.6, 112.1, 109.3, 71.4, 56.6, 56.0, 40.0, 39.3, 27.3; HRMS (FAB^+) found 425.1583 $[M + Na]^+$, calcd 425.1571 for $C_{22}H_{26}O_7Na$. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% IPA/hexane, 1.9 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 14.4 min, *R* (minor) 11.4 min, 96% ee).

(*S*)-2,5-Dimethoxyphenyl 2-Ethoxy-3-(4-pivalatephenyl)propanoate. To a flame-dried 25-mL round-bottom flask was added (*S*)-2,5-dimethoxyphenyl 2-hydroxy-3-(4-phenylpivalate)propanoate **27** (0.200 g, 0.497 mmol) and $CHCl_3$ (10.0 mL). The solution was cooled to 0 °C and proton sponge (0.425 g, 1.99 mmol) was added followed by triethyloxonium tetrafluoroborate (0.380 g, 1.99 mmol). The mixture was stirred for 60 min at 0 °C then warmed to ambient temperature where it stirred for 24 h. The mixture was then quickly passed through a small silica gel plug, eluting with EtOAc (75 mL). The eluent was then concentrated and purified via column chromatography (30% Et_2O/hex) to afford 0.169 g (79%) of the title compound as a white solid with 94.8% ee. TLC R_f = 0.40 (30% EtOAc/hex); $[\alpha]^{23}_D$ −1.4° (*c* 1.9, $CHCl_3$); mp = 100−102 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.34 (m, 2H), 7.04−7.01 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.74 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 4.27 (dd, *J* = 4.0, 8.0 Hz, 1H), 3.85−3.76 (obs m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.50−3.44 (m, 1H), 3.23 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.15 (dd, *J* = 9.0, 14.0 Hz, 1H), 1.36 (s, 9H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 170.6, 154.0, 150.2, 145.4, 140.2, 134.8, 130.7, 121.5, 113.8, 112.0, 109.4, 80.1, 66.7, 56.7, 56.0, 39.3, 39.0, 27.4, 15.3; HRMS (FAB^+) found 453.1892 $[M + Na]^+$, calcd 453.1884 for $C_{24}H_{30}O_7Na$. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 10.1 min, *R* (minor) 8.3 min, 95% ee).

(*S*)-Methyl 2-Ethoxy-3-(4-hydroxyphenyl)propanoate (28). To a 25-mL round-bottom flask containing (*S*)-2,5-dimethoxyphenyl 2-ethoxy-3-(4-pivalatephenyl)propanoate (0.078 g, 0.181 mmol) was added THF (1.80 mL) and the solution was cooled to 0 °C. Then a freshly prepared NaOMe/MeOH (0.1 M, 5.45 mL) solution was added and the mixture was allowed to slowly warm to ambient temperature over 2h. The reaction was stirred at ambient temperature for 24 h at which time a saturated aqueous NH_4Cl solution (10 mL) was added followed by H_2O (10 mL). The solution was then extracted with EtOAc (3 × 15 mL), the combined organic layers were then dried over Na_2SO_4, filtered, and concentrated. The product was isolated via radial chromatography (1 mm plate, 20% EtOAc/hex) to provude 0.038 g (94%) of the title compound as a yellow oil with 95.0% ee. $[\alpha]^{23}_D$ −18.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10−7.08 (m, 2H), 6.75−6.73 (m, 2H), 5.12 (m, 1H), 4.01 (dd, *J* = 6.0, 7.5 Hz, 1H), 3.71 (s, 3H), 3.63 (m, 1H), 3.39−3.33 (m, 1H), 2.98−2.91 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 154.6, 130.7, 129.2, 115.4, 80.6, 66.5, 52.1, 38.7, 15.2; HRMS (EI^+) found 224.1043 M^+, calcd 224.1049 for $C_{12}H_{16}O_4$. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 14.8 min, *R* (minor) 14.1 min, 95% ee).

2-(10*H*-Phenoxazin-10-yl)ethyl Methanesulfonate (29).[3] To a 100-mL round-bottom flask containing 2-(10*H*-phenoxazin-10-yl)ethanol (0.274 g, 1.20 mmol) were added CH_2Cl_2 (24 mL) and NEt_3 (0.835 mL, 6.0 mmol). Then methanesulfonyl chloride (0.390 mL, 5.04 mmol) was added dropwise and the reaction stirred at ambient temperature for 2 h. Then H_2O (25 mL) was added and the layers separated. The organic layer was washed with another 25 mL of H_2O, then dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by radial chromatography (2 mm plate, 3:1:6 CH_2Cl_2/Et_2O/hex mixture) to afford 0.318 g (86%) of the desired compound as a fluffy off-white solid. Mp = 90−92 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.85−6.81 (m, 2H), 6.73−6.70 (m, 2H), 6.67 (dd, *J* = 1.5, 7.5 Hz, 2H), 6.58 (d, *J* = 7.5 Hz, 2H), 4.42 (t, *J* = 7.0 Hz, 2H), 3.95 (t, *J* = 7.0 Hz, 2H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 132.7, 124.0, 122.0, 116.0, 111.7, 64.5, 43.6, 37.8; HRMS (EI^+) found 305.0721 M^+, calcd 305.0722 for $C_{15}H_{15}O_4NS$.

(*S*)-Methyl 3-(4-(2-(10*H*-Phenoxazin-10-yl)ethoxy)-phenyl)-2-ethoxypropanoate (30). To a 25-mL round-bottom flask containing (*S*)-methyl 2-ethoxy-3-(4-hydroxyphenyl) propanoate **28** (0.069 g, 0.308 mmol) were added toluene (4.0 mL) and K_2CO_3 (0.085 g, 0.620 mmol). Then 2-(10*H*-phenoxazin-10-yl)ethyl methanesulfonate **29** (0.125 g, 0.400 mmol) was added and the mixture warmed to 100−105 °C where it stirred for 45 h, with additional toluene being added at various intervals to maintain the reaction volume. The reaction was then cooled to ambient temperature where H_2O was added (10 mL) followed by a saturated aqueous NH_4Cl solution (10 mL). The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified via radial chromatography (1 mm plate, 10% EtOAc/hex) to afford 0.113 g (85%) of the desired product as an off-white solid in 94.6% ee. TLC R_f = 0.44 (50% Et_2O/hex); $[\alpha]^{23}_D$ −9.6° (*c* 1.9, $CHCl_3$); mp = 96−98 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.15 (m, 2H), 6.85−6.79 (m, 4H), 6.70−6.63 (m, 6H), 4.18 (t, *J* = 7.0 Hz, 2H), 4.00 (dd, *J* = 5.5, 7.5 Hz, 1H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.72 (s, 3H), 3.64−3.58 (m, 1H), 3.39−3.33 (m, 1H), 3.01−2.93 (m, 2H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 157.4, 145.0, 133.3, 130.6, 130.0, 123.8, 121.5, 115.7, 114.5, 111.8, 80.5, 66.5, 63.6, 52.0, 44.1, 38.6, 15.2; HRMS (FAB^+) found

456.1797 [M + Na]$^+$, calcd 456.1781 for $C_{26}H_{27}O_5NNa$. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 5% IPA/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times, *S* (major) 11.1 min, *R* (minor) 10.4 min, 95% ee).

(−)-Ragaglitazar. To a 25-mL round-bottom flask containing (*S*)-methyl 3-(4-(2-(10*H*-phenoxazin-10-yl)ethoxy)phenyl)-2-ethoxypropanoate **30** (0.10 g, 0.230 mmol) was added MeOH (2.30 mL) followed by 3 N NaOH (2.0 mL). The reaction mixture was stirred at ambient temperature for 6 h at which time H_2O (35 mL) was added and the mixture washed with Et_2O (15 mL). Then 1 M HCl was added dropwise until a pH of 2 was obtained. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O followed by a saturated aqueous NaCl solution, then dried over Na_2SO_4, filtered and concentrated to provide 0.089 g (92%) of the title compound as a foaming viscous oil that solidified into a white solid, which matched the following reported values. $[\alpha]^{23}_D$ −8.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (bs, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.85−6.79 (m, 4H), 6.70−6.63 (m, 6H), 4.17 (t, J = 7.0 Hz, 2H), 4.05 (dd, J = 4.5, 8.0 Hz, 1H), 3.97 (t, J = 7.0 Hz, 2H), 3.66−3.60 (m, 1H), 3.46−3.40 (m, 1H), 3.08 (dd, J = 4.5, 14.5 Hz, 1H), 2.97 (dd, J = 8.5, 14.0 Hz, 1H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 157.5, 145.0, 133.3, 130.8, 129.5, 123.8, 121.5, 115.7, 114.6, 111.8, 79.9, 67.0, 63.6, 44.1, 38.1, 15.2.

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Supporting Information Available: Experimental procedures and characterization for all compounds, and NMR spectral and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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