Hypoglycemic Prodrugs of 4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid

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SAH 51-641 (**1**) is a potent hypoglycemic agent, which acts by inhibiting hepatic gluconeogenesis. It is a prodrug of 4-(2,2-dimethyl-1-oxopropyl)benzoic acid (**2**) and 4-(2,2-dimethyl-1-hydroxypropyl)benzoic acid (**3**), which sequester coenzyme A (CoA) in the mitochondria, and inhibits medium-chain acyltransferase. **1**−**3** and 4-*tert*-butylbenzoic acid all cause testicular degeneration in rats at pharmacologically active doses. **14b** (FOX 988) is a prodrug of **3**, which is metabolized in the liver at a rate sufficient enough to have hypoglycemic potency (an ED_{50} of 65 μmol/kg, 28 mg/kg/day, for glucose lowering), yet by avoiding significant escape of the metabolite **3** to the systemic circulation, it avoids the testicular toxicity at doses up to 1500 μmol/kg/day. **14b** was selected for clinical studies.

Introdction

Type 2 diabetes is a chronic, progressive metabolic disease, typically characterized by hyperglycemia, hyperlipidemia, and insulin resistance. Diabetes is most frequently diagnosed by the presentation of fasting hyperglycemia, severely impaired oral glucose tolerance, or the classical symptoms (polydipsia, polyphagia, and polyuria).[1] Type 2 diabetes, diagnosed and undiagnosed, occurs in >5% of the U.S. population (affecting 16 million people in 1996).[2] In addition, the prediabetic state of impaired glucose tolerance (IGT, normal basal glycemia with impaired glucose tolerance) is even more prevalent affecting approximately 35−40 million adults in the United States, and many of these subjects will progress into overt type 2 diabetes.

As type 2 diabetic patients are frequently overweight, and since weight loss and exercise lessen insulin resistance, diet and exercise are usually the first prescribed treatments for most type 2 diabetic patients.[3,4] The rapid reversal of the positive effects of exercise and weight loss after noncompliance leaves a large number of patients in need of medication to help restore euglycemia. The importance of such treatments was recently emphasized when the Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that tight control of blood glucose reduced the development of retinopathy, nephropathy and neuropathy, each by >50% in type 1 diabetes (insulin-dependent diabetes, IDDM).[5] The magnitude of these findings, together with the similarity of the pathologies seen in type 1 and type 2 diabetes, strongly suggests that a similar control of blood glucose levels in type 2 diabetic patients is equally important.[6] Indeed, virtually the same results as those seen in the DCCT were reported in a prospective 6-year study in Japan with type 2 diabetic patients.[7]

A major factor in the impaired ability to dispose of an oral glucose load (as occurs in type 2 diabetes and in IGT) is resistance to the peripheral biological effects of insulin. In patients with fasting blood glucose of under 200 mg/dL, such peripheral insulin resistance is primarily manifested as a defect in the uptake and storage of glucose in skeletal muscle.[8] The impaired ability of insulin to clear glucose from the blood leads to a compensatory hyperinsulinemia, which in turn characteristically leads to an increase in insulin resistance. Hyperglycemia, and eventually type 2 diabetes, results in those patients unable to secrete sufficient insulin to overcome this reflexive cycle. When fasting blood sugars rise to greater than 200 mg/dL, further changes in metabolism occur, driven by an elevation in the flux of free fatty acids (FFAs) from adipocytes. The increased oxidation of free fatty acids directly increases the rate of gluconeogenesis and significantly exacerbates the hyperglycemia. Clinical studies have demonstrated that decreasing free fatty acid levels or inhibiting their oxidation results in a reduction in this fatty-acid-driven gluconeogenesis and, importantly, in the prevailing hyperglycemic state.

SAH 51-641 (**1**) is a potent hypoglycemic agent, which acts by inhibiting gluconeogenesis via an inhibition of fatty acid oxidation.[9] **1** is metabolized via sequential oxidation/reduction to 4-(2,2-dimethyl-1-oxopropyl)benzoic acid (**2**) and 4-(2,2-dimethyl-1-hydroxypropyl)benzoic acid (**3**) which, as a substrate for the medium-chain fatty acyl CoA ligase, is transformed to the corresponding CoA ester (Figure 1). Such an esterification is common with many benzoic acids, which are then typically subjected to glycine conjugation to afford the corresponding hippurates, which are in turn excreted.[10] *To the extent that this second step is rate-limiting, the net effect is to lower intramitochondrial CoA levels.* Because of the integration of control of metabolic pathways, this diminution of CoA in turn would be expected to elicit several effects (Figure 2). Initially a decrease in carnitine palmitoyltransferase II (CPT II) activity and thus a lessening of fatty acid oxidation would be expected, while the resultant lower levels of acetyl CoA would result in increased pyruvate dehy-

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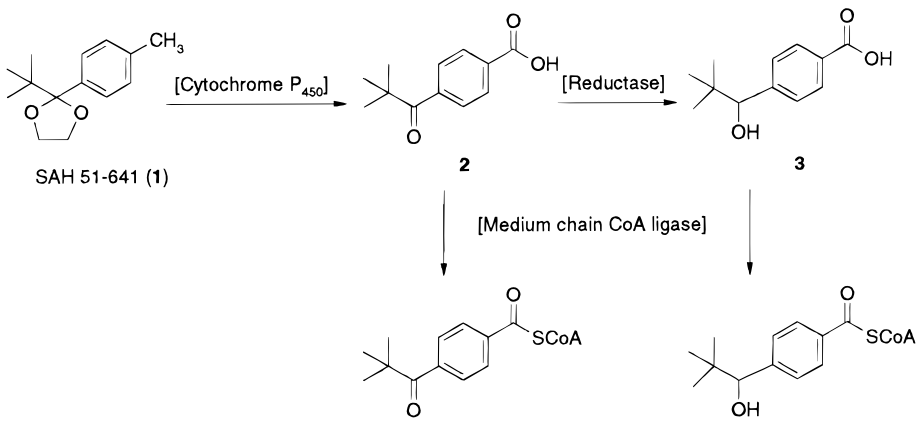
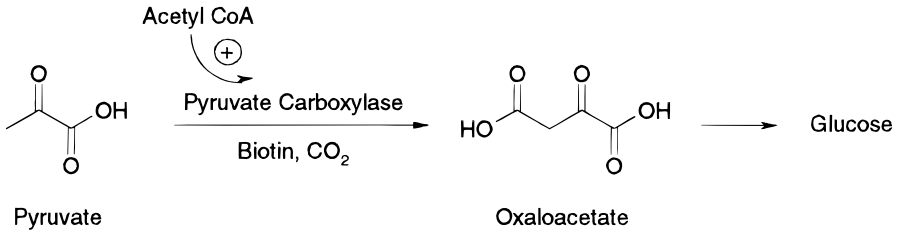


Figure 1. Metabolism of SAH 51-461 (**1**).

1) Lower Fatty Acid Oxidation from Palmitate.

Km for CoA are in this order:
Long chain fatty acid ligase > medium chain/butyryl acid ligase > octanoyl ligase ≥ other metabolic enzymes

2) Decreased Allosteric Activation of Pyruvate Carboxylase by Acetyl CoA, and consequently lower gluconeogenesis.



3) Decreased Allosteric Inactivation of Pyruvate Dehydrogenase by Acetyl CoA, and consequently increased oxidative disposal of gluconeogenic precursors.

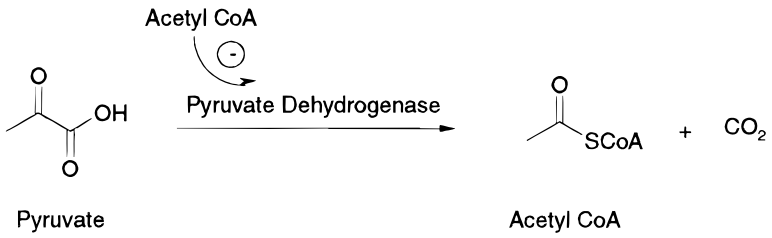


Figure 2. Metabolic consequences of lower CoA/AcCoA levels elicited by **3**.

drogenase activity, leading to lower gluconeogenic conversion of lactate, pyruvate, and alanine. Furthermore, lower levels of acetyl CoA would lead to a diminished acetyl CoA-mediated allosteric activation of the rate-limiting gluconeogenic enzyme pyruvate carboxylase. This mechanism of action is similar to that proposed for 4-*tert*-butylbenzoic acid.[11] Unfortunately, like 4-*tert*-butylbenzoic acid, **1**−**3** caused a marked reduction in testis weights.[12] This effect was observed at all doses where hypoglycemic activity was seen in a low-dose streptozotocin (STZ)-treated diabetic animal model. As such, these testicular effects were clearly development-limiting.

Our goal was to design a prodrug of **3** which would be targeted only to the liver and which would produce **3** at concentrations which would be sufficient to lower gluconeogenesis, yet not lead to undesirably high concentrations of **3** in the systemic circulation (i.e., in the blood supply to the testes—Figure 3). If the prodrug did not produce **3** at a sufficient rate to lower CoA levels, then it would be ineffective as a hypoglycemic agent. If **3** is formed at too great a rate, it would "spill" into the general circulation leading to unacceptable effects on the testes.

To pursue this goal, a large number of potential prodrugs of **3** were synthesized, the title compounds being illustrative examples. Four general conceptual approaches toward limiting the effect of **3** to the liver were attempted. One was to replace the ketal of **1** with a different chemical moiety which only slowly would

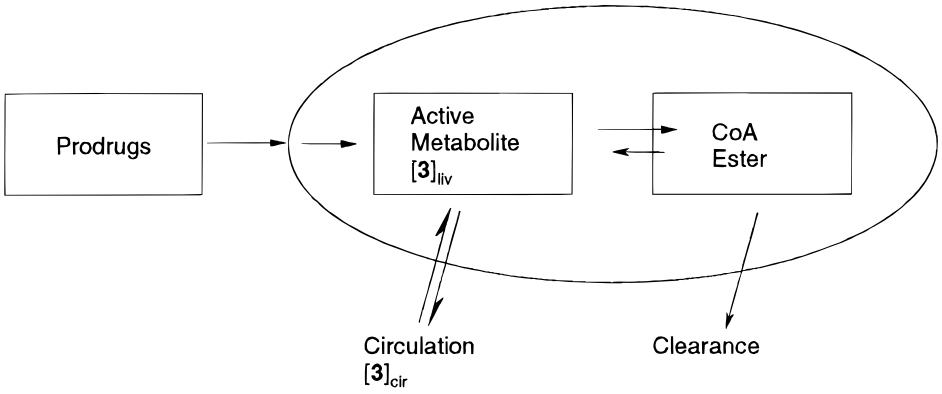
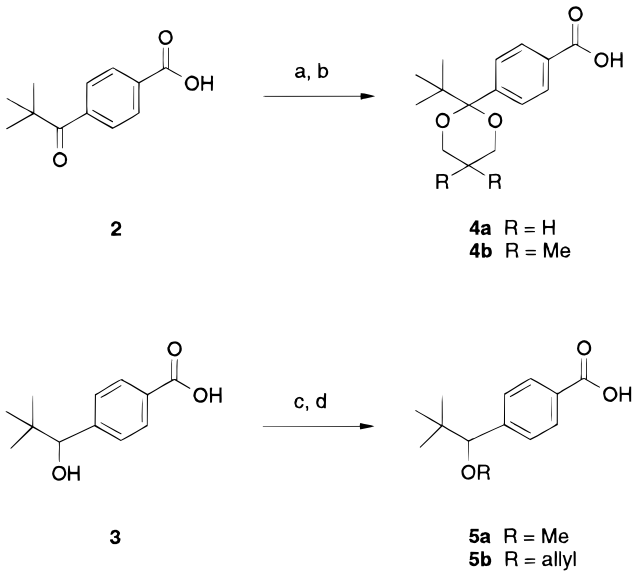


Figure 3. Design concept: make metabolic production of **3** rate-limiting.

Scheme 1. Synthesis of Ketal and Ether Prodrugs[a]



[a] Conditions: (a) *p*-TsOH, diol, toluene; (b) KOH, aq EtOH; (c) KH, alkyl halide, THF; (d) KOH, aq EtOH.

undergo a transformation to an eventual alcohol and which would thus produce **3** in a time-limited fashion. The second approach was to limit the rate of metabolism of a carboxylic acid prodrug. Clearly, a methyl group was too rapidly converted into the acid. Would a carboxylic acid prodrug, which was designed to be a poor substrate for metabolizing enzymes, be successful? Several amides, esters, ethers, and imides were synthesized as compounds which potentially would produce the carboxylic acid more slowly. A third approach was to produce the chiral enantiomers of **3** in the expectation that the pharmacodynamics of the enantiomers would be different. The fourth approach was to target **3** to the liver as an ester of glycerol.[13−15] Our initial criteria of success would be a compound which lowered the gluconeogenic capacity of freshly isolated hepatocytes, which lowered fatty acid oxidation and glucose production in vivo in the STZ diabetic animal model, and which produced minimal circulating levels of **3**.

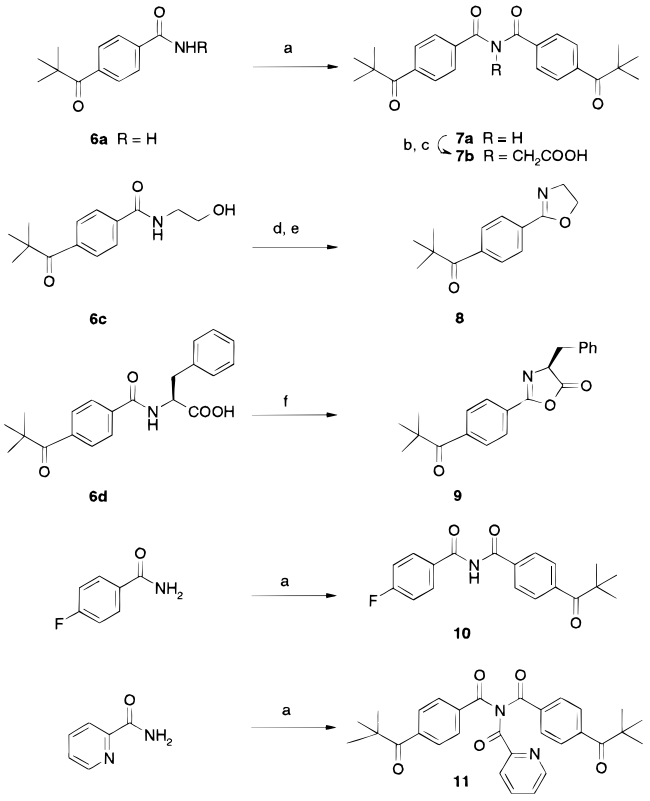
Chemistry

SAH 51-641 (**1**) was prepared via condensation of 2,2,4′-trimethylpropiophenone with ethylene glycol with a catalytic amount of acid. Oxidation of 2,2,4′-trimethylpropiophenone with aqueous $KMnO_4$ afforded **2**. Reduction of **2** with $NaBH_4$ in alcohol afforded **3**. Ketals **4a** and **4b** were prepared via treatment of **2** with the appropriate diol and a catalytic amount of acid. Alkylation of **3** with methyl iodide or allyl bromide yielded **5a** and **5b** (Scheme 1).

Treatment of **2** with thionyl chloride afforded 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride which when added to the appropriate amine, hydroxylamine, or alkoxylamine afforded **6a, 6c**, **6d**, **12**, **13a**, and **13g** (Schemes 2 and 3). **6a,** when treated with a 2-fold excess of KH and of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride, afforded **7a**. In a similar manner acylation of 4-fluorobenzamide afforded **10**. More extensive acylation of nicotinamide afforded **11**. Dehydration of **6c** via a modification of Desneuelle's procedure[16] afforded **8**, and cyclization of **6d** in analogy to Suda's procedure[17] yielded **9**.

Hydroxamates **13c−f** and **13h** were prepared via alkylation of the hydroxamic acid **12** with the appropriate halide. Acylation of **13a−g** with 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride to yield **14a−g** could be effected with either triethylamine or KH as the base. The stereochemistries of the resulting products were initially assigned via analogy to literature examples.[18] In the case of **14b**, this assignment was subsequently proven correct by X-ray analysis. Preparation of the chiral enantiomers of **3** was accomplished by utilizing the CBS chiral reducing agent developed in Corey's laboratory (Scheme 4).[19] Interestingly, while the reduction of **15** to afford **16a** and **16b** proceeded at 0 °C with high enantiomeric excess, the reduction of **14b** did not produce **17a** in high optical purity at 0 °C. However, when the reaction was done at room temperature, the percentage of **17a** in the crude product significantly increased. Isolation of pure **17a** and **17b** was then effected via crystallization of the major diastereomer from the crude product.

Scheme 2. Synthesis of Amide and Imide Prodrugs[a]



[a] Conditions: (a) KH, 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride, THF; (b) KH, *tert*-butyl bromoacetate, THF; (c) TFA; (d) $SOCl_2$; (e) NaOH, EtOH; (f) DCC, dioxane.

Results and Discussion

The compounds described were first evaluated for their ability to inhibit oleate-dependent gluconeogenesis in hepatocytes which had been freshly prepared from 18-h fasted rats according to the procedure of Berry and Friend,[20] with minor modifications as described by Young et al.[9] All compounds which significantly decreased glucose production at a concentration of less than or equal to 100 μM were evaluated in vivo. All compounds listed in Table 1 had IC_{50} values of less than 100 μM (data not shown).

Compounds were first tested in an acute in vivo study for inhibition of gluconeogenesis in normal male Sprague−Dawley rats (for details, see Acute Screen in the Experimental Section). In this test, glycogen stores in normal rats were exhausted by fasting for 18 h, and consequently glucose levels were maintained via gluconeogenesis stimulated by free fatty acid oxidation, which in turn directly elevated β-hydroxybutyrate levels. Both β-hydroxybutyrate levels and glucose were measured as percent of control values 3 h after dosing (see Table 1). Compounds which decrease β-hydroxybutyrate and/or glucose levels in the acute in vivo assay were subsequently tested in the streptozotocin (STZ)-treated diabetic animal model according to the procedure of Young et al.[9] with the modification that the animals were fed a high-fat diet. The doses of streptozotocin dosed were sufficient to significantly impair insulin secretion but generally not high enough to induce a type 1 diabetic state. However, even at this relatively low dose of streptozotocin, some animals lost nearly all ability to secrete insulin and consequently were removed from the screening pool. The selection procedure resulted in a rat model of type 2 diabetes in which animals exhibited hyperglycemia in the fed (175−260 mg/dL) and fasted states (160−230 mg/dL) with normal insulin levels (for details, see Chronic Study in STZ-Treated Rats Fed a High-Fat Diet in the Experimental Section). The results presented in Table 1 are 6 h postdose on days 8 and 11 and are presented as percent efficacy (where 100% efficacy is equal to a normalization of blood glucose levels to 60 mg/dL).[21]

As stated in the Introduction, our goal was to design a prodrug of **3** which would produce **3** at concentrations in the liver sufficient to lower gluconeogenesis yet not lead to high concentrations of **3** in the systemic circulation. To pursue this aim, an assay to measure the concentration of **3** in the plasma was developed as a screening tool. Blood samples were centrifuged after collection at each time point. Plasma from each group was pooled to provide sufficient sample for analysis by HPLC. The AUC_{0-48h} of **3** in plasma was measured by HPLC at time points of 2, 4, 7, 8, 24, 36, and 48 h post-oral-dosing. The results are summarized (in μg·h/mL) in Table 1.

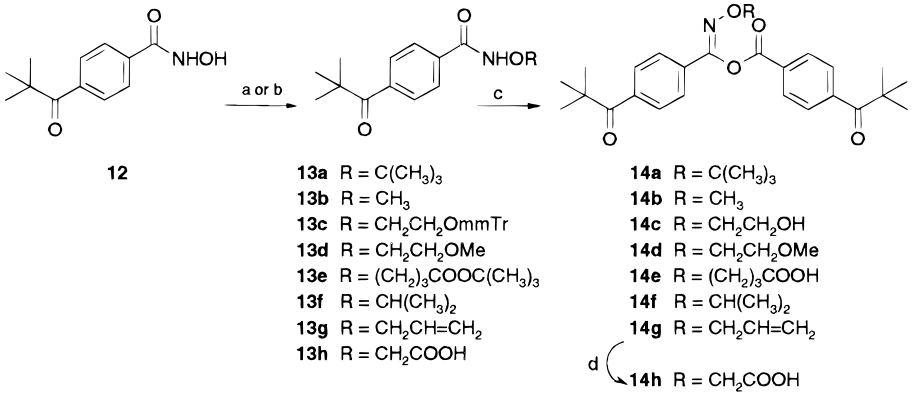
To preselect potential development compounds, those which had an AUC_{0-48h} of less than 500 μg·h/mL (this criterion was chosen as 4 times the AUC_{0-48h} of **7a**, which was the first compound which did not lower testes weights) and a hypoglycemic percent efficacy of greater than 60% in the STZ diabetic animal model were evaluated in a 28-day rat testicular toxicity assay. From the data produced by **1**, **7a**, **10**, **11**, **14a**, **14b**, and **14f** (discussed below), it became apparent that there existed a useful trend between the incidence and severity of testicular toxicity observed in a 28-day safety study and the AUC_{0-48h} of **3** in the blood observed following a single oral dose. The AUC_{0-48h} of **3**, however, did not correlate with the hypoglycemic efficacy of the compounds (i.e., **14a**, **14b**, and **14f** are all efficacious in the STZ-treated diabetic animal model yet afford a low AUC_{0-48h} of **3** in blood plasma). This useful trend was also utilized in the selection and evaluation of a different series of prodrugs of **3**.

Compounds which markedly decreased β-hydroxybutyrate without markedly decreasing glucose levels in the acute assay in some cases had an equivalent hypoglycemic effect as **1** in the chronically STZ-treated diabetic animal model (i.e., compare **7a**, **14b**, and **14f** to **1** and **10** in Table 1). Also compounds which inhibited fatty acid oxidation while not immediately lowering glucose levels tended to afford a lower area under the curve (AUC_{0-48h}) and to have lesser effects on the testes (i.e., compare **7a**, **14a**, **14b**, and **14f** to **1**, **2**, **3**, **6a**, and **10** in Table 1; data discussed further below).

The chiral acid **16a** has an approximately 4-fold lower IC_{50} (7 μM vs 32 μM) than exhibited by its enantiomer **16b** for the inhibition of oleate-derived gluconeogenesis in the hepatocyte assay. When these compounds were tested orally, it was demonstrated by chiral HPLC with a Chiracel column (see Experimental Section) that the two compounds did not interconvert. Therefore a chiral version of **14b** was prepared.

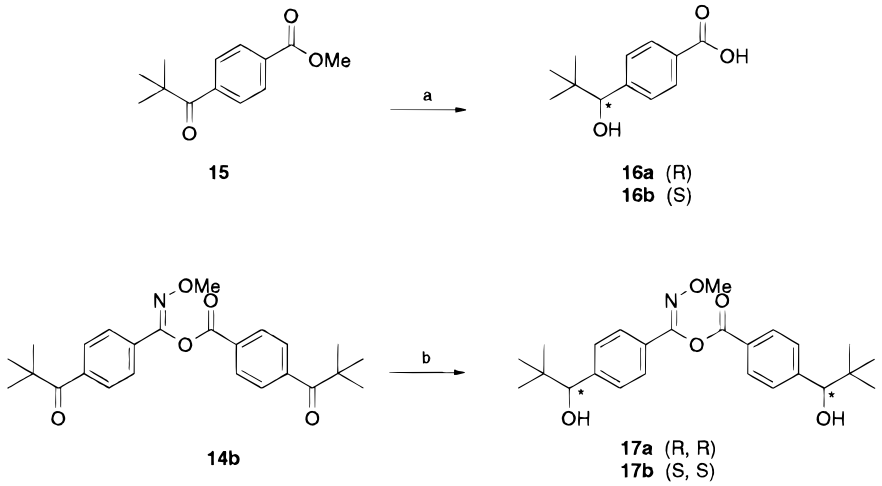
The testis was shown to be an organ adversely affected by **1**, **2**, **3**, **6a**, and **10**. These compounds caused severe testicular toxicity as measured by decreased

Scheme 3. Synthesis of Hydroxylamine-Derived Prodrugs[a]



[a] Conditions: (a) NaOH, RX, THF; (b) NH_2OR, 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride, aq THF; (c) KH, 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride, THF; (d) OsO_4, NMMO, aq acetone.

Scheme 4. Synthesis of the Chiral Enantiomers of **3** and Prodrugs of **3**[a]



[a] Conditions: (a) BH_3·TMS, CBS catalyst, 0 °C, THF; (b) BH_3·TMS, CBS catalyst, rt, THF.

testicular weights (greater than 25% decrease each) after chronic treatment for 28 days in normal rats. In addition, there was an absence of mature sperm cells similar to that reported for 4-*tert*-butylbenzoic acid.[12]

The first compounds which afforded hope that testicular toxicity could indeed be reduced while simultaneously maintaining the desired hypoglycemic effect were the imides **7a** and **11**. These compounds afforded a relatively low AUC_{0-48h} of **3** and had a less severe effect on the testis in chronic dosing. Our initial enthusiasm for these compounds, based upon the observation that weights of testes from rats treated with **7a** and **11** were not changed significantly upon chronic dosing, was dampened when it was observed that there still remained significant histological changes in testicular tissue upon dosing at 700 μmol/kg for 28 days (sloughing/degeneration of germinal epithelium with giant cell formation to a much lower extent, however, than with **1**).[22]

It was hypothesized that the imide **7a** was not as easily metabolized to **3** as were previously synthesized amide or ester prodrugs, presumably because there existed no lipase or amidase which would easily recognize the imide functionality for hydrolysis. Consequently, other imides and other constrained amide motifs were prepared for evaluation. Substitution of the imide of **7a** with polar moieties, such as **7b**, afforded a significantly higher systemic exposure (AUC_{0-48h}) to the metabolite **3**.

The *O*-acylation of the hydroxamates **13a**−**h** afforded the prodrugs **14a**−**h**. Such mixed esters are known in the literature to be resistant to hydrolysis by aqueous base.[18] **14a**−**h** inhibited fatty-acid-driven gluconeogenesis in hepatocytes, inhibited fatty acid oxidation in the acute in vivo model, and lowered glucose levels in the STZ-treated diabetic animal model. Based upon the AUC_{0-48h} of **3** produced by dosing of **14a**, **14b**, **14f**, and **14g**, it was predicted that the severity of testicular toxicity induced by these compounds would be lower than that of **1**. Indeed none of these compounds caused changes in testicular weights in rats upon chronic treatment. It was encouraging that the methyl imide **14b** at doses up to 1500 μmol/kg/day also failed to cause any significant histological changes in the testes of rats or dogs (in which it also lowered free fatty oxidation) after 4 weeks of dosing.[22,23]

Overall **14b** had an EC_{50} of 9.2 μM in lowering oleate-stimulated glucose production in hepatocytes from 18-h fasted normal rats, an ED_{50} of 47 μmol/kg for lowering β-hydroxybutyrate levels in 18-h fasted normal rats, and an ED_{50} of 65 μmol/kg (28 mg/kg/day) for glucose lowering in the STZ-treated diabetic animal model.[24] In addition to lowering glucose levels, **14b** also causes significant decreases in serum triglyceride (≥60% de-

Table 1. In Vivo Properties of Prodrugs of **3**

	AUC_{0-48h}[a] (μg·h/mL)			in vivo acute assay[b] (% of control)		in vivo chronic assay[c]		testes weight[d]
compd	150 μmol/kg	300 μmol/kg	700 μmol/kg	ketones	glucose	% efficacy (day 8.25)	% efficacy (day 11.25)	% of control (dose μmol/kg/day)
1		1513	3562	12***	58**	52***	64***	52 (700)***
1		1465						
2								47 (700)***
3					50***			74 (350)***
4a		1402		15***	111	41**	65***	
4b		263		18***	105	na	na	
5a		1015		17***	81*	23*	59**	
5a		775						
5b		941		29***	107	na	na	
6a								48 (700)***
6d		964	2928	4***				
7a		122	2669	21***	92			101 (700)
7b		1083		6***	56***	53**	47**	
8		886		20***	74**	na	na	
9		413		21***	90*	na	na	
10		588	2568	13***	65**	57**	54**	63 (700)***
11		64		46***	95	73***	74***	95 (350)
14a	0	55		50***	70**	80***	98***	102 (700)
14b		85	325	30***	98	64***	59***	96 (700)
14c	122	565		15***	98	92***	92***	
14d		1849		19***	49***	109***	108***	
14e		1629		15***	70**			
14f	94	155		41***	94	80***	98***	
14g		158		43***	105	53**	85***	
14h	1001	2033		19***	63***	90***	102***	
16a				23***	42***	64**	63**	59 (350)***
16b				80*	94	na	na	62 (350)***
17a		2370		17***	61***			
17b								

[a] Area under the curve of the active metabolite **3** in blood plasma, after dosing orally at the dose indicated. [b] In vivo acute screen (see Experimental Section). Data are reported as percent of control at 3 h postdosing (100 μmol/kg). [c] In vivo chronic study orally dosed at 70 μmol/kg in STZ-treated rats fed a high-fat diet (see Experimental Section). Data are reported as percent efficacy (where 100% efficacy is lowering of blood glucose levels to 60 mg/dL) (na, no statistical significance to activity). [d] [(Testes weight(treated)/body weight(treated)]/[testes weight(control)/body weight(control)] × 100%. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

crease at all doses > 70 μmol/kg/day, $p < 0.001$), serum insulin levels (≥40% decrease at all doses ≥ 35 μmol/kg/day, $p < 0.01$), serum free fatty acid levels (≥25% decrease at all doses ≥ 35 μmol/kg/day, $p < 0.05$), and cholesterol levels (≥30% decrease at all doses ≥ 35 μmol/kg/day, $p < 0.001$) following multiple dose in the STZ-treated diabetic animal model on day 11.[24] On the basis of these data, **14b** was selected for clinical trials since toxicity from systemic effects on the testes should no longer be a limiting factor for dosing patients.

The authors recognize that the hypothesis that **7a** and **14b** cause less testicular lesions due to greater difficulty in their metabolic activation may not be correct. Indeed it is troubling for this hypothesis that the more polar derivatives of **7a** and **14b** cause higher systemic exposure to **3**. Three possible explanations for this divergence have been considered. First, it is possible that the greater hydrolysis of **14c**, **14h**, and **7b** and other polar moieties could be due to intramolecular assistance in the hydrolysis. Indeed, transacetylation and decomposition of many of these compounds occur slowly in solution (however **17a** does not have this route of decomposition available to it). A second possibility is that **14b** and **7a**, although absorbed well, are not delivered to the liver at the same rate as the more polar analogues. A possible mechanism for such a pharmacokinetic effect is the incorporation of **7a** and **14b** into lipid vesicles. Such a route of delivery could be highly liver-selective.[14] A future paper will address a different compound series which was designed for such a route of delivery.

Experimental Section

Pharmacology. 1. Acute Screen. The acute screen is conducted in normal male Sprague−Dawley rats (200−300 g) which are fasted for 18 h prior to the experiment. Five animals per group are dosed orally (po) by gavage with vehicle (carboxymethylcellulose, CMC) or compound in vehicle. At 3 h postdose, animals are anesthetized briefly (approximately 30 s) with CO_2 and a blood sample is obtained via cardiac puncture. After the sample is obtained, animals are allowed to recover from the CO_2 and may potentially be used for up to three times in studies spaced at weekly intervals. Serum levels of β-hydroxybutyrate, glucose, and lactate are measured. Comparisons between metabolite levels of control and treated groups are made using Student's *t*-tests. During a 6-month period, mean ± SEM control values for po administration have been 11.7 ± 0.3 mg/dL for ketones, 115 ± 1 mg/dL for serum glucose, and 1.22 ± 0.05 mM for serum lactate.

2. Chronic Study in STZ-Treated Rats Fed a High-Fat Diet. The selection procedure of the rats for this model is similar to the previously described model, with the significant modification that rats (250−300 g) were fed a high-fat purified diet throughout the study (Purina 5814M-4).[9,25] In short, 3 days after initiation of the diet, the rats were rendered diabetic by injection of 40 mg/kg streptozotocin into the tail vein. Five days later, animals with blood glucose levels greater than 200 mg/dL were excluded. Those remaining were fasted for 18 h prior to an oral glucose load (1.35 g/kg dextrose). Three hours later, animals with blood glucose levels between 40 and 100 mg/dL were retained. The screen began 4 days later, using animals with blood glucose levels > 180 mg/dL. Animals were dosed once per day (1 mL/100 g of body weight) with vehicle (CMC) or compound in vehicle. Blood glucose levels were checked at 0 and 6 h postdose on days 1, 4, 8, and 11 of the 11-day screen. Food was removed at the 0-h sample and returned after the 6-h sample. The results are expressed as

percent efficacy, which is calculated with the assumption that normal fasting blood glucose is 60 mg/dL in the rat. Therefore, 100% efficacy would indicate complete normalization of blood glucose levels in STZ-treated rats. Total cholesterol and triglycerides were analyzed by standard enzymatic assays (Electro-Nucleonics, Fairfield, NJ).

3. Statistics. Responses of treated animals were compared to control responses using Student's *t*-test.

Chemistry. All melting points (mp) were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Bruker AC 300-MHz NMR or a JEOL 270-MHz NMR spectrometer. Chemical shifts were recorded in ppm (δ) and are reported relative to the solvent peak or TMS. Mass spectra were run on a Finnigan Mat 4600 spectrometer. Elemental analyses were performed with a CHNS-O EA 1108 elemental analyzer produced by Carlo Erba, and the data for C, H, and N are within 0.4% of theoretical values unless otherwise indicated. Thin-layer chromatography (TLC) was carried out on Macherey-Nagel Polygram Sil G/U_{254} plates. Column chromatography separations were carried out using Merck silica gel 60 (mesh 230−400). Reagents and solvents were purchased from common suppliers and were utilized as received. All reactions were conducted under a nitrogen atmosphere. Yields are of purified product and were not optimized. All starting materials are commercially available unless otherwise indicated.

2-(1,1-Dimethylethyl)-2-(4-methylphenyl)-1,3-dioxolane (1). A solution of 2,2,4′-trimethylpropiophenone (105 g, 595 mmol), ethylene glycol (43.4 g, 700 mmol), benzene (1400 mL), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (500 mg, 1.5 mmol) was refluxed overnight using a Dean−Stark water separator. The mixture was cooled, washed with water (3 × 600 mL) and brine (600 mL), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from ether to afford 66.2 g (50%) of **1** as white crystals: mp 65−67 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H), 2.33 (s, 3H), 3.63−3.70 (m, 2H), 3.86−3.95 (m, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H); MS (DCI, isobutane) *m*/*z* (rel intensity) 222 (8), 221 (100). Anal. ($C_{14}H_{20}O_2$) C, H.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid (2). 2,2,4′-Trimethylpropiophenone (90 g, 510 mmol) was added to a solution of $KMnO_4$ (162 g, 1.03 mmol) in water (1.2 L). The mixture was refluxed for 2 h; additional $KMnO_4$ (154 g, 0.97 mmol) was added. The mixture was refluxed for an additional 2 h and filtered while hot, and the MnO_2 was washed with water. The combined filtrate was cooled in an ice bath and acidified to pH 2 with concentrated HCl. The white solid was filtered and washed several times with water. CH_2Cl_2 (190 mL) and MeOH (10 mL) were added, and the mixture was filtered. The filtrate was concentrated and recrystallized from ether to obtain 59 g (56%) of **2** as white crystals: mp 161−162 °C; ^{1}H NMR (CD_3OD) δ 1.31 (s, 9H), 7.67 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 8.6 Hz, 2H); MS (DCI, isobutane) *m*/*z* (rel intensity) 208 (8), 207 (100), 189 (31). Anal. ($C_{12}H_{14}O_3$) C, H.

4-(1-Hydroxy-2,2-dimethylpropyl)benzoic Acid (3). Sodium borohydride (8.0 g, 210 mmol) was added to a solution of **2** (15 g, 73 mmol) in absolute EtOH (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then stirred an additional 5 h at room temperature. The mixture was diluted with water (300 mL) and concentrated in vacuo to 200 mL. The mixture was washed with hexane. The aqueous layer was acidified to pH 2 with 2 N HCl and filtered. The white solid was recrystallized from aqueous ethanol to afford 14.1 g (93%) of the monohydrate of the acid **3** as fine white crystals: mp 162−163 °C; ^{1}H NMR (CD_3OD) δ 0.89 (s, 9H), 4.49 (s, 1H), 7.41 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H); MS (DCI, isobutane) *m*/*z* (rel intensity) 210 (8), 209 (100), 191 (35). Anal. ($C_{12}H_{16}O_3 \cdot H_2O$) C, H.

4-[2-(1,1-Dimethylethyl)-1,3-dioxan-2-yl]benzoic Acid (4a). A mixture of **2** (6.00 g, 29.1 mmol), 1,3-propanediol (12.6 mL, 175 mmol), toluene (100 mL), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (250 mg, 0.76 mmol) was refluxed overnight using a Dean−Stark water separator, cooled, and concentrated in vacuo. A solution of KOH (4.00 g, 71 mmol) in water (30 mL) and EtOH (50 mL) was added to the crude residue, and the mixture was refluxed for 1 h. Concentration in vacuo to 20 mL, dilution with water to 50 mL, and at 0 °C a careful acidification to pH 3 (with 2 N HCl) afforded a mixture which was filtered. The solids were washed several times with water and then hexanes and dried in vacuo to yield 3.38 g of **4a** (44%) as a white solid: mp 235−236 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.19 (m, 1H), 2.09 (m, 1H), 3.65 (m, 2H), 3.89 (m, 2H), 7.49 (d, J = 8.6 Hz, 2H), 8.13 (d, J = 8.6 Hz, 2H); MS (DCI, isobutane) *m*/*z* (rel intensity) 266 (16), 265 (100). Anal. ($C_{15}H_{20}O_4$) C, H.

4-[2-(1,1-Dimethylethyl)-5,5-dimethyl-1,3-dioxan-2-yl]-benzoic Acid (4b). Prepared in a similar manner, substituting 2,2-dimethyl-1,3-propanediol for 1,3-propanediol, was **4b**. From the acid **2** (5.00 g, 24.3 mmol) was obtained 6.28 g (89%) of **4b** as a white solid: mp 239 °C; ^{1}H NMR ($CDCl_3$) δ 0.53 (s, 3H), 0.93 (s, 9H), 1.25 (s, 3H), 3.30 (d, J = 11.1 Hz, 2H), 3.40 (d, J = 11.1 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H); MS (DCI, isobutane) *m*/*z* (rel intensity) 294 (21), 293 (100). Anal. ($C_{17}H_{24}O_4$) C, H.

4-(1-Methoxy-2,2-dimethylpropyl)benzoic Acid (5a). A slurry of potassium hydride (3.1 g, 77 mmol) in hexane (8 mL) was added to a solution of **3** (4.80 g, 23 mmol) in DMF (10 mL) and THF (10 mL) at 0 °C. After the mixture stirred for 15 min, an excess of methyl iodide (4.3 mL, 69 mmol) was added. This mixture was stirred overnight at room temperature and then quenched by the addition of MeOH (4 mL). The mixture was concentrated in vacuo to a paste, which was partitioned between CH_2Cl_2 and water. The organic layer was dried and concentrated. A solution of potassium hydroxide (4.00 g, 71 mmol) in water (20 mL), was added to the residue dissolved in EtOH (20 mL) and the resulting mixture was refluxed for 1 h, cooled, and concentrated to 20 mL. The concentrate was acidified with 2 N HCl to pH 3 and filtered. The solid was washed several times with water and dried in vacuo to yield 2.54 g (50%) of **5a** as a white solid: mp 171 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H), 3.18 (s, 3H), 3.82 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 224 (14), 223 (100). Anal. ($C_{13}H_{18}O_3$) C, H.

4-[2,2-Dimethyl-1-(2-propenyloxy)propyl]benzoic Acid (5b). Prepared in a similar fashion was **5b**. The above alkylation of **3** (4.00 g, 19.2 mmol) was repeated, using allyl bromide rather than methyl iodide, and after recrystallization of the crude product from CH_2Cl_2/hexane, there was obtained 3.32 g (70%) of **5b** as white crystals: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9H), 3.71 (m, 1H), 3.92 (m, 1H), 4.04 (s, 1H), 5.13 (m, 1H), 5.26 (m, 1H), 5.90 (m, 1H), 7.40 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 267 (16), 266 (100), 191 (50). Anal. ($C_{15}H_{20}O_3$) C, H.

4-(2,2-Dimethyl-1-oxopropyl)benzamide (6a). A mixture of **2** (135 g, 655 mmol) and $SOCl_2$ (135 mL, 1.85 mole) was refluxed for 90 min. The excess $SOCl_2$ was removed in vacuo, and the residual oil was dissolved in hexane (1.2 L). The solution was concentrated in vacuo to 300 mL, and the resulting crystallization from the mixture yielded 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (146.6 g, 99%) as white crystals: mp 39−40 °C.

4-(2,2-Dimethyl-1-oxopropyl)benzoyl chloride (5.62 g, 25 mmol) in ether (10 mL) was added dropwise to concentrated aqueous ammonia (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and stored overnight in the refrigerator. The mixture was filtered and washed with water and then with cold ether (2 × 50 mL) to afford 4.60 g (90%) as a white solid: mp 137−139 °C.

***N*-[4-(2,2-Dimethyl-1-oxopropyl)benzoyl]-L-phenylalanine (6d).** A solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (1.68 g, 7.5 mmol) in acetone (5 mL) was added to a solution of L-phenylalanine (3.30 g, 20 mmol) in 2 N NaOH (10 mL, 20 mmol) and acetone (10 mL) at 0 °C, while maintaining the pH at ∼11 by the dropwise addition of 2 N NaOH. After 1 h, the mixture was allowed to warm to room temperature. The mixture was acidified with 2 N HCl, diluted

with water (30 mL), and concentrated to 40 mL. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from ether/hexane to yield 2.33 g (88%) of **6d** as white crystals: mp 120−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.00 (m, 1H), 3.25 (m, 1H), 4.69 (m, 1H), 7.00−7.10 (m, 5H), 7.34 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 355 (20), 354 (100). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)-*N*-(4-fluorobenzoyl)benzamide (10). A slurry of potassium hydride (1.32 g, 33 mmol) in hexane (5 mL) was slowly added to 4-fluorobenzamide (1.53 g, 11.0 mmol) in THF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature over 1 h. A solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (1.35 g, 6.0 mmol), cooled to 0 °C, was added, and the mixture was stirred for 1 h at room temperature and poured onto ice. This mixture was extracted twice with CH_2Cl_2, and the combined organic layers were washed with brine, dried, and concentrated in vacuo. The product was isolated by column chromatography (CH_2Cl_2/MeOH, 99:1, as the elutant), followed by recrystallization with ether/hexane to yield 1.73 g (48%) of **10** as white crystals: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 7.13 (m, 2H), 7.59−7.94 (m, 6H), 9.05 (bs, 1H); MS (DCI, NH_3) m/z (rel intensity) 329 (17), 328 (100), 221 (38), 140 (18). Anal. ($C_{19}H_{18}FNO_3$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)-*N*-[4-(2,2-dimethyl-1-oxopropyl)benzoyl]benzamide (7a). Prepared in a similar fashion from 4-pivaloylbenzamide was **7a**. mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 18H), 7.68 (d, J = 7.2 Hz, 4H), 7.81 (d, J = 7.2 Hz, 4H), 9.08 (s, 1H); MS (DCI, isobutane) m/z (rel intensity) 395 (20), 394 (100). Anal. ($C_{24}H_{27}NO_4$) C, H, N.

2-[4-(2,2-Dimethyl-1-oxopropyl)phenyl]-4-(phenylmethyl)-5(4*H*)-oxazolone (9). A mixture of l-phenylalanine-4-pivaloylbenzamide (5.00 g, 14.2 mmol), DCC (2.92 g, 14.2 g), and dioxane (20 mL) was stirred for 2 days at room temperature and filtered, and the filtrate was concentrated in vacuo. The residue was recrystallized from CH_2Cl_2/hexane to yield 3.91 g (82%) of **9** as white crystals: mp 61 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H), 3.25 (dd, J = 14.0, 5.9 Hz, 1H), 3.37 (dd, J = 14.0, 5.8 Hz, 1H), 5.10 (m, 1H), 6.57 (d, J = 7.7 Hz, 1H), 7.15−7.38 (m, 4H), 7.63−7.75 (m, 4H); MS (DCI, NH_3) m/z (rel intensity) 337 (21), 336 (100). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)-*N*-[4-(2,2-dimethyl-1-oxopropyl)benzoyl]benzamide *N*-2-Acetic Acid (7b). A mixture of potassium hydride (0.35 g, 8.75 mmol) in THF (2 mL) was added to a stirred solution of **7a** (3.14 g, 8.0 mmol) in THF (15 mL). After 15 min, a solution of *tert*-butyl bromoacetate (1.42 mL, 8.8 mmol) was added, and the mixture was refluxed for 24 h. Ether (50 mL) was added, and the mixture was filtered. The filtrate was concentrated and subjected to column chromatography using CH_2Cl_2 as the elutant. The major product was crystallized from ether/hexane to yield 4.50 g of the *tert*-butyl ester as white crystals: mp 61 °C.

A solution of the *tert*-butyl ester in trifluoroacetic acid (10 mL) was stirred at 0 °C for 2 h. The mixture was concentrated and crystallized from ether/hexane to afford 3.75 g (98%) of **7b** as white crystals: mp 159−160 °C; ^{1}H NMR ($CDCl_3$) 1.17 (s, 18H), 4.84 (s, 2H), 7.35 (d, J = 8.4 Hz, 4H), 7.49 (d, J = 8.4 Hz, 4H), 8.74 (bs, 1H); MS (DCI, NH_3) m/z (rel intensity) 470 (29), 469 (100), 246 (73), 223 (22). Anal. ($C_{26}H_{29}NO_6$) C, H, N.

1-[4-(4,5-Dihydro-2-oxazolyl)phenyl]-2,2-dimethyl-1-propanone (8). A solution of 4-(2,2-dimethyl-1-oxopropyl)-benzoyl chloride (5.58 g, 24.8 mmol) in acetone (5 mL) was added to a solution of ethanolamine (1.5 mL, 24.8 mmol) in 2 N NaOH (12.4 mL, 24.8 mmol) at 0 °C. The mixture was stirred at room temperature and concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and 2 N HCl. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue, *N*-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(2,2-dimethyl-1-oxopropyl)benzamide (**6b**), was dissolved in thionyl chloride (20 mL), heated to 60 °C for 1 h, cooled, and poured onto saturated $NaHCO_3$ solution. The mixture was extracted with ether, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from ether/hexane to yield 4.45 g (67%) of 4-(2,2-dimethyl-1-oxopropyl)-*N*-(2-chloroethyl)benzamide.

A solution of NaOH (662 mg, 60.4 mmol) in water (2 mL) was added to a solution of this product (4.42 g, 16.5 mmol) in EtOH (20 mL), and the mixture was heated to 65 °C for 15 min, diluted in cold water, and extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from ether/hexane to yield 2.56 g (67%) of **8** as white crystals: mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H), 4.12 (t, J = 9.6 Hz, 2H), 4.47 (t, J = 9.6 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 233 (14), 232 (100). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

***N*,*N*-Bis[4-(2,2-dimethyl-1-oxopropyl)benzoyl]-3-pyridinecarboxamide (11).** A slurry of potassium hydride (1.06 g, 26 mmol) in THF (5 mL) was added to a solution of nicotinamide (1.46 g, 12 mmol) in THF (30 mL). After 20 min, the mixture was cooled to 0 °C, and a solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (5.39 g, 24 mmol) in THF (15 mL) was added. The reaction mixture was stirred for 1 h, ether (100 mL) was added, and the mixture was filtered. The filtrate was concentrated; the major product was isolated via chromatography using MeOH/CH_2Cl_2 (1:99) as the elutant and recrystallized from ether/hexane to afford 2.80 g (47%) of **11** as white crystals: mp 151−152 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 18H), 7.44 (dd, J = 8.1, 4.7 Hz, 1H), 7.64 (d, J = 8.4 Hz, 4H), 7.88 (d,, J = 8.4 Hz, 4H), 8.15 (ddd, J = 8.1, 4.7, 2.3 Hz, 1H), 8.80 (dd, J = 4.7, 1.5 Hz, 1H), 9.01 (d, J = 2.3 Hz, 1H); MS (DCI, NH_3) m/z (rel intensity) 517 (32), 516 (100), 499 (30). Anal. ($C_{30}H_{30}N_2O_5$) C, H, N.

4-[[[(2,2-Dimethyl-1-oxopropyl)benzoyl]amino]oxy]acetic Acid (13h). A solution of hydroxylamine hydrochloride (4.90 g, 71 mmol) dissolved in 2 N NaOH (35.5 mL, 71 mmol) was slowly added to a stirred solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (8.00 g, 35.6 mmol) in ether (50 mL) at 0 °C. The mixture was poured into 2 N HCl (30 mL) and extracted twice with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized (hexane/ether, 4:1) to yield 6.5 g (82%) of 4-(2,2-dimethyl-1-oxopropyl)-*N*-hydroxybenzamide (**12**) as white crystals: mp 125−126 °C.

To a solution of NaOH (1.70 g, 42.5 mmol) in EtOH (80 mL) was added bromoacetic acid (3.06 g, 22 mmol) followed by the hydroxamic acid **12** (4.42 g, 20 mmol). The mixture was refluxed for 2 h and concentrated in vacuo, and the residue was washed with ether. The solids were dissolved in water, and the solution was acidified with 2 N HCl. The precipitated solids were filtered off and recrystallized from CH_2Cl_2/Et_2O to yield 2.93 g (72%) of **13h** as white crystals: mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 4.67 (s, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 297 (37), 280 (11), 224 (13), 223 (100), 206 (23). Anal. ($C_{14}H_{17}NO_5$) C, H, N.

Prepared in a similar manner, using the appropriate halide and with the following reactions times, were **13c**−**g**:

4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-hydroxyethoxy)benzamide (13c). Hydroxamic acid **12** (12.6 g, 56.9 mmol) and 2-bromoethanol (5.26 mL, 74.2 mmol) were refluxed as above for 1 day. Crystallization of the product from CH_2Cl_2/hexane gave 9.50 g (63%) of **13c** as a white solid: ^{1}H NMR (CD_3OD) δ 1.33 (s, 9H), 3.78 (t, J = 7.1 Hz, 2H), 4.07 (t, J = 7.1 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 283 (37), 266 (13), 224 (13), 223 (100).

4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-methoxyethoxy)benzamide (13d). Hydroxamic acid **12** (8.00 g, 36.2 mmol) and 2-bromoethyl methyl ether (4.40 mL, 46.8 mmol) were refluxed as above for 1 day. Crystallization of the product from CH_2Cl_2/MeOH yielded 6.41 g (63%) of **13d** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 3.41 (s, 3H), 3.63 (t, J = 5.0

Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 7.65−7.84 (m, 4H), 9.41 (bs, 1H); MS (DCI, NH_3) *m/z* (rel intensity) 297 (34), 280 (55), 223 (100).

1,1-Dimethylethyl 4-[[[4-(2,2-Dimethyl-1-oxopropyl)-benzoyl]amino]oxy]butanoate (13e). Hydroxamic acid **12** and *tert*-butyl 4-bromobutanoate were refluxed for 5 h. Crystallization of the product from CH_2Cl_2/MeOH yielded **13e** as white crystals (62%): mp 67−71 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.48 (s, 9H), 2.11 (m, 2H), 2.47 (t, J = 7.2 Hz, 2H), 4.08 (t, J = 6.3 Hz, 2H), 7.67−7.84 (m, 4H), 9.49 (bs, 1H); MS (DCI, isobutane) *m/z* (rel intensity) 364 (21), 309 (17), 308 (100).

4-(2,2-Dimethyl-1-oxopropyl)-*N*-(1-methylethoxy)benzamide (13f). Hydroxamic acid **12** and isopropyl bromide were refluxed for 21 h. Recrystallization of the product from CH_2Cl_2/MeOH afforded **13f** as white crystals (46%): mp 80−83 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.3 Hz, 6H), 1.35 (s, 9H), 4.29 (heptet, J = 6.3 Hz, 1H), 7.63−7.81 (m, 4H), 8.75 (bs, 1H); MS (DCI, NH_3) *m/z* (rel intensity) 280 (15), 279 (100), 221 (25).

4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-propenyloxy)-benzamide (13g). To a mixture of THF (50 mL) and aqueous 2 N NaOH (39 mL, 78 mmol) was added *O*-allylhydroxylamine hydrochloride (5.0 g, 54.6 mmol), followed by a solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (6.90 g, 30.7 mmol) in THF (10 mL). The mixture was stirred for an additional 30 min and was then partitioned between *t*-BuOMe and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from hexane/CH_2Cl_2 to afford 7.82 g (97%) of **13g** as white crystals: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 4.50 (m, 2H), 5.25−5.48 (m, 2H), 6.01 (m, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H); MS (DCI, NH_3) *m/z* (rel intensity) 280 (18), 279 (81), 263 (21), 262 (100), 223 (61).

***N*-(1,1-Dimethylethoxy)-4-(2,2-dimethyl-1-oxopropyl)-benzamide (13a).** In a similar manner was prepared **13a**. From *O*-*tert*-butylhydroxylamine hydrochloride (5.00 g, 39.8 mmol) and 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (5.96 g, 26.6 mmol) was obtained 7.05 g (96%) of **13a** as white crystals: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.34 (s, 9H), 7.66 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 8.52 (bs, 1H); MS (DCI, NH_3) *m/z* (rel intensity) 279 (18), 278 (100).

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with *N*-(1,1-Dimethylethoxy)-4-(2,2-dimethyl-1-oxopropyl)benzenecarboximidic Acid (14a). A cooled solution of *O*-*tert*-butylhydroxylamine hydrochloride (10.06 g, 80 mmol) in aqueous 0.5 N NaOH (160 mL, 80 mmol), while being vigorously stirred, was slowly added to a solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (36.80 g, 164 mmol) and Et_3N (26 mL, 187 mmol) in toluene (400 mL) at 0 °C. After the addition was complete (20 min), the mixture was allowed to warm to room temperature overnight, diluted with EtOAc (300 mL) and hexane (300 mL), and washed with water (400 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified via column chromatography (CH_2Cl_2/hexane as elutant). The major component was recrystallized from hexane to yield 33.45 g of **14a** (89.8%) as white crystals: mp 104.5−105.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.33 (s, 9H), 1.36 (s, 9H), 7.65−7.85 (m, 6H), 8.23 (d, J = 8.4 Hz, 2H); MS (DCI, isobutane) *m/z* (rel intensity) 467 (28), 466 (100), 260 (19). Anal. ($C_{28}H_{35}NO_5$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with 4-(2,2-Dimethyl-1-oxopropyl)-*N*-methoxybenzenecarboximidic Acid (14b). Prepared in a similar manner was **14b**. From *O*-methylhydroxylamine hydrochloride was obtained **14b** in 91% yield as white crystals: mp 104−104.8 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.33 (s, 9H), 4.00 (s, 3H), 7.62−7.82 (m, 6H), 8.23 (d, J = 8.4 Hz, 2H); MS (DCI, isobutane) *m/z* (rel intensity) 425 (27), 424 (100). Anal. ($C_{25}H_{29}NO_5$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with 4-(2,2-Dimethyl-1-oxopropyl)-*N*-(1-methylethoxy)-benzenecarboximidic Acid (14f). A solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (4.11 g, 18.3 mmol) in THF (15 mL) was added to a solution of the hydroxamate **13f** (4.16 g, 15.8 mmol) and Et_3N (2.88 mL, 20.7 mmol) in THF (20 mL). After the mixture stirred for 2 h at room temperature, Et_2O (100 mL) was added and the mixture was filtered. The filtrate was concentrated in vacuo, and the residue was purified via column chromatography. The major product was recrystallized from hexane to yield 5.00 g (70%) of **14f** as white crystals: mp 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.3 Hz, 6H), 1.31 (s, 9H), 1.35 (s, 9H), 4.49 (heptet, J = 6.3 Hz, 1H), 7.70−7.88 (m, 6H), 8.23 (d, J = 8.4 Hz, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 21.3, 27.6, 27.9, 44.2, 44.4, 125.4, 127.5, 128.0, 129.7, 129.9, 130.1, 132,1, 139.9, 144.0, 146.2, 161.3, 208.4, 209.2; MS (DCI, NH_3) *m/z* (rel intensity) 470 (13), 469 (47), 453 (27), 452 (100). Anal. ($C_{27}H_{33}NO_5$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with 4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-hydroxyethoxy)-benzenecarboximidic Acid (14c). *p*-Anisylchlorodiphenylmethane (13.0 g, 42.2 mmol) was added to a stirred solution of the hydroxamate ester **13c** (9.41 g, 35.5 mmol) in CH_2Cl_2 (20 mL) and pyridine at 0 °C, and the temperature was allowed to rise to room temperature over 2 h. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The major product was purified via column chromatography using hexane/EtOAc (5:1) as the elutant to afford 18.6 g of the trityl ether.

A slurry of potassium hydride (4.70 g, 120 mmol) in hexane (15 mL) was added to a stirred solution of this ether (18.6 g) in THF (100 mL) at 0 °C. After 30 min, a solution of 4-(2,2-dimethyl-1-oxopropyl)benzoyl chloride (9.56 g, 42.6 mmol) in THF (15 mL) was added. After stirring at room temperature for 1 h, the mixture was poured onto a mixture of ice and saturated aqueous NH_4Cl. The mixture was extracted twice with *t*-BuOMe (100 mL), and the combined organic layers were washed with brine, dried, and concentrated. The crude product was dissolved in THF (50 mL), and at 0 °C, 2 N HCl (2 mL) was added. The mixture was stored at 0 °C for 2 days and then poured onto saturated aqueous $NaHCO_3$. The mixture was extracted twice with *t*-BuOMe, and the combined organic layers were washed with brine, dried, and concentrated. The major product was first isolated via column chromatography eluting with hexane/EtOAc (1:1) and then triturated from hexane/CH_2Cl_2 (6:1) to afford 8.99 g (56%) of **14c** as an amorphous solid: mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.31 (s, 9H), 2.46 (bs, 1H), 3.88 (t, J = 4.5 Hz, 2H), 4.30 (t, J = 4.5 Hz, 2H), 7.68−7.77 (m, 6H), 8.26 (d, J = 8.5 Hz, 2H); MS (DCI, NH_3) *m/z* (rel intensity) 471 (26), 455 (25), 454 (100), 206 (18). Anal. ($C_{26}H_{31}NO_6$) C, H, N.

Prepared in a similar manner were **14d**, **14e**, and **14g**:

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with 4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-methoxyethoxy)-benzenecarboximidic Acid (14d). From hydroxamate ester **13d** (6.40 g, 22.9 mmol) 4.32 g (40%) of **14d** was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.34 (s, 9H), 3.34 (s, 3H), 3.66 (t, J = 5.0 Hz, 2H), 4.33 (t, J = 5.0 Hz, 2H), 7.67−7.83 (m, 6H), 8.23 (d, J = 8.4 Hz, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 27.6, 27.8, 44.2, 44.4, 59.0, 70.5, 125.5, 127.5, 128.0, 129.4, 130.2, 131.6, 140.3, 144.2, 147.2, 161.1, 208.4, 209.2; MS (DCI, NH_3) *m/z* (rel intensity) 485 (17), 469 (27), 468 (100). Anal. ($C_{27}H_{33}NO_6$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid [(3-Carboxypropoxy)imino][4-(2,2-dimethyl-1-oxopropyl)phenyl]-methyl Ester (14e). From hydroxamate ester **13e** (4.42 g, 20 mmol) was obtained 4.50 g (62%) of the *tert*-butyl ester as white crystals: mp 65−67 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.36 (s, 9H), 1.43 (s, 9H), 2.01 (m, 2H), 2.31 (t, J = 7.3 Hz, 2H), 4.22 (t, J = 6.1 Hz, 2H), 7.67−7.84 (m, 6H), 8.25 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) *m/z* (rel intensity) 553 (28), 552 (87), 496 (30), 308 (32), 307 (86), 290 (78), 223 (58), 176 (50), 122 (100).

A solution of the *tert*-butyl ester (4.20 g, 7.61 mmol) in trifluoroacetic acid (85 mL) was stirred for 20 h, concentrated in vacuo, added to heptane (50 mL), and CH_2Cl_2 (50 mL) and again concentrated in vacuo. The residue was purified via column chromatography (CH_2Cl_2/MeOH, 98:2, as the elutant). The major product was crystallized from ether/hexane to yield

2.10 g (56%) of **14e** as white crystals: mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.36 (s, 9H), 2.03 (m, 2H), 2.41 (t, J = 7.3 Hz, 2H), 4.24 (t, J = 6.1 Hz, 2H), 7.64−7.82 (m, 6H), 8.22 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 496 (8), 308 (59), 307 (100), 290 (47), 223 (62), 206 (27), 205 (32), 122 (16). Anal. ($C_{28}H_{33}NO_7$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with 4-(2,2-Dimethyl-1-oxopropyl)-*N*-(2-propenyloxy)-benzenecarboximidic Acid (14g). From the hydroxamate ester **13g** (6.64 g, 25.4 mmol) was obtained, after crystallization with hexane/2-propanol, 7.52 g (66%) of **14g** as white crystals: mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.36 (s, 9H), 4.72 (m, 1H), 5.31 (m, 1H), 6.02 (m, 1H), 7.70−7.89 (m, 6H), 8.28 (d, J = 8.4 Hz, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 27.6, 27.8, 44.2, 44.4, 76.2, 118.0, 125.5, 127.5, 128.0, 129.4, 130.2, 131.6, 133.3, 140.2, 144.2, 146.9, 161.1, 208.4, 209.2; MS (DCI, NH_3) m/z (rel intensity) 451 (29), 450 (100), 205 (32). Anal. ($C_{27}H_{31}NO_5$) C, H, N.

4-(2,2-Dimethyl-1-oxopropyl)benzoic Acid Anhydride with *N*-(2,3-Dihydroxypropoxy)-4-(2,2-dimethyl-1-oxopropyl)benzenecarboximidic Acid (14h). A 1 N solution of OsO_4 in *tert*-butyl alcohol (1 mL) was added to a solution of **14g** (4.00 g, 8.90 mmol) and *N*-methylmorpholine oxide (2.10 g, 17.9 mmol) in water (3 mL) and acetone (27 mL), and the mixture was stirred for 1 day. Excess sodium *m*-bisulfite was added, and the mixture was stirred for 30 min and concentrated in vacuo. The residue was purified via column chromatography (hexane/EtOAc, 1:1, as the elutant). The major product was crystallized from CH_2Cl_2:hexane to yield 2.74 g (64%) of **14h** as white crystals: mp 64 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.36 (s, 9H), 2.17 (bs, 1H), 2.99 (bs, 1H), 3.60 (dd, J = 11.4, 5.3 Hz, 1H), 3.74 (dd, J = 11.4, 3.7 Hz, 1H), 4.08 (m, 1H), 4.20 (dd, J = 11.8, 7.3 Hz, 1H), 4.30 (dd, J = 11.8, 7.6 Hz, 1H), 7.65−7.82 (m, 6H), 8.27 (d, J = 8.8 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 485 (23), 484 (80), 244 (37), 206 (60), 205 (77), 188 (100). Anal. ($C_{27}H_{33}NO_7$) C, H, N.

Methyl 4-(2,2-Dimethyl-1-oxopropyl)benzoate (15). HCl gas was added to a solution of the acid **2** (41.0 g, 200 mmol) in MeOH (300 mL) until saturated. The mixture was refluxed for 3 h, stirred overnight, and concentrated to an oil. The concentrate was diluted in ether (300 mL), washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The crude product was crystallized from hexane/CH_2Cl_2 to afford 39.6 g (90%) of **15**.

(+)-(*R*)-4-(1-Hydroxy-2,2-dimethylpropyl)benzoic Acid (16a). A solution of the ketone **15** (10.0 g, 45.5 mmol) and (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (630 mg, 2.3 mmol) was added to a solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (630 mg, 2.3 mmol) in THF (20 mL) and a 2 M solution of BH_3−dimethyl sulfide complex in THF (15 mL, 30 mmol) at −30 °C. After 5 min, the mixture was quenched with MeOH (10 mL) and concentrated to a paste. The crude product was crystallized from aqueous ethanol (80:20 EtOH/H_2O, 100 mL) to afford 9.6 g (95%) of the methyl ester as white crystals. The optical purity of the product was determined to be 98% by chiral HPLC analysis using a Chiracel OD column with hexane/EtOH as elutant. An identical run of the reaction afforded an additional 9.1 g of the methyl ester.

A solution of the methyl ester (19.2 g, 86.5 mmol) in EtOH (60 mL) was added to a solution of potassium hydroxide (5.23 g, 130 mmol) in water (10 mL) and EtOH (75 mL). The mixture was heated to 80 °C for 5 h, cooled, and concentrated to 30 mL. The mixture was dissolved in water (100 mL) and washed with Et_2O (2 × 60 mL). The aqueous layer was acidified to pH 2 with 2 N HCl. The mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried and concentrated. The residue was recrystallized from aqueous ethanol to afford 16.9 g (94%) of the acid **16a** as fine white crystals: mp 188 °C; $[\alpha]_D$ = 18.8 ± 1.5 (c = 1.00, EtOH).

Prepared in a similar manner substituting (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine for (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine was **16b**: mp 188 °C; $[\alpha]_D$ = −20.8 ± 1.5 (c = 1.00, EtOH).

4-(1-Hydroxy-2,2-dimethylpropyl)benzoic Acid Anhydride with [*R*-(*R,*R**)]-4-(1-Hydroxy-2,2-dimethylpropyl)-*N*-methoxybenzenecarboximidic acid (17a).** A solution of the ketone **14b** (5.00 g, 11.8 mmol) and (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (500 mg, 1.8 mmol) in THF (20 mL) was added over 10 min to a solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (500 mg, 1.8 mmol) in THF (20 mL) and a 2 M solution of BH_3−dimethyl sulfide complex in THF (8 mL, 16 mmol) at 0 °C. After stirring 20 min, the mixture was poured onto MeOH (30 mL) and then concentrated to a paste. The residue was purified via a column chromatography using 4:1 hexane/EtOAc as the elutant. The crude product had a purity of 91% as determined by chiral HPLC with a Chiracel OD column with hexanes/EtOH as the elutant. The crude product was recrystallized from hexane/Et_2O (20:1, 100 mL) to afford 4.00 g (80%) of **17a** as white crystals: mp 93−95 °C; $[\alpha]_D$ = 18.5 ± 1.0 (c = 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9H), 0.97 (s, 9H), 1.92 (bs, 1H), 1.99 (bs, 1H), 3.98 (s, 3H), 4.42 (s, 1H), 4.50 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 429 (24), 428 (100). Anal. ($C_{25}H_{33}NO_5$) C, H, N.

Prepared in a similar manner substituting (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine for (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine was **17b**: mp 93−95 °C; $[\alpha]_D$ = −19.1 ± 1.5 (c = 1.00, MeOH).

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(21) Normal rats fasted for 6 h were assumed to have a blood glucose of 60 mg/dL, and the percent efficacy was calculated based upon the percent normalization of glucose levels of treated vs control groups. The percent efficacy so calculated was utilized as a tool to be able to qualitatively compare two different experiments in which the diabetic nontreated control groups had blood values of 220 or 170 mg/dL after a 6-h fast. In a representative experiment with FOX 988, the glucose of the untreated diabetic animals was 200 ± 10 mg/dL. The treated animals (140 mmol/kg) displayed a glucose level of 100 ± 20 mg/dL ($p < 0.001$). This may actually represent a normalization of glucose. In our table, we represent these data as displaying a 70% efficacy.

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(24) The STZ-treated diabetic animal model, as described in the Experimental Section, on day 11 following a 6-h fast. The doses in the study were 35, 70, 100, and 140 μmol/kg/day with 9 rats/group.

(25) With our normal chow-fed model (see ref 9), blood glucose was often variable and the model was not stable for more than a few days. The addition of a high-fat diet has significantly improved each of these parameters, allowing testing of compounds for up to 15 days.

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