Synthesis and Protein Kinase Inhibitory Activity of Balanol Analogues with Modified Benzophenone Subunits

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A series of analogues of the protein kinase C (PKC) inhibitory natural product balanol which bear modified benzophenone subunits are described. The analogues were designed with the goal of uncovering structure−activity features that could be used in the development of PKC inhibitors with a reduced polar character compared to balanol itself. The results of these studies suggest that most of the benzophenone features found in the natural product are important for obtaining potent PKC inhibitory compounds. However, several modifications were found to lead to selective inhibitors of the related enzyme protein kinase A (PKA), and several specific modifications to the polar structural elements of the benzophenone were found to provide potent PKC inhibitors. In particular, it was found that replacement of the benzophenone carboxylate with bioisosteric equivalents could lead to potent analogues. Further, a tolerance for lipophilic substituents on the terminal benzophenone ring was uncovered. These results are discussed in light of recently available structural information for PKA.

Introduction

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine-specific protein kinases which play an important role in the control of cell growth and differentiation.[1] Activation of PKC is a critical step in signal transduction pathways controlling processes such as cellular proliferation and gene expression,[2] and the enzyme has been implicated in the progression of numerous diseases, facts which have rendered PKC inhibitors attractive targets for therapeutic agents.[3] A selective inhibitor of the PKC-βII isozyme is currently undergoing clinical study for the treatment of diabetic retinopathy,[4] and the use of PKC inhibitors has been suggested for clinical applications ranging from the treatment of psoriasis to the treatment of cancer.[5]

The discovery of the PKC-inhibitory fungal metabolite balanol[6] provided a new structural motif to the PKC inhibitor area.[7] The novelty of the balanol structure coupled with the high level of interest in PKC inhibitors as therapeutic agents has resulted in a great deal of effort being devoted to the development of synthetic approaches to the natural material[8−14] and related structures.[15,16] However, most of the synthetic efforts and structure−activity studies presented to date have focused on the azepane subunit of balanol, and relatively little work has been directed toward modification of the benzophenone portion of the molecule. Nevertheless, we saw modification of the less well studied benzophenone as a critical step toward obtaining inhibitors which would be suitable for further consideration as potential development candidates. We expected that some attenuation of the highly polar nature of the benzophenone would be required to enable the inhibitors to reach their intracellular targets, and to provide compounds with ADME properties that would be appropriate for further development. We therefore undertook a systematic study of the structure−activity relationship (SAR) properties of the balanol benzophenone subunit, with an aim toward uncovering factors that would allow us to prepare potent inhibitors with decreased polarity. In this paper we present the full account of our investigations into the preparation of these balanol benzophenone analogues.

Results and Discussion

Synthesis. The target compounds in this study were prepared with one of three central core subunits, the azepane core which is found in balanol itself, a pyrrolidine core, as in **2**, or a cyclopentane core, as in **3**. All compounds were prepared in racemic form, with the exception of one case (compound **18**), which is noted below. The final target structures were obtained by coupling of a suitably protected, generally perbenzylated, benzophenone subunit to the protected core subunit **4**, **5**, or **6**, followed by deprotection.[8e] For example, as shown in Scheme 1, conversion of carboxylic acid **43** to the acid chloride followed by coupling to **5** gave after deprotection the fully elaborated balanol analogue **28**. All but a few of the analogues were prepared by couplings using the benzophenone acid chloride; analogues that proved sensitive to these conditions were prepared by acylation with the acyl imidazole or by carbodiimide-mediated esterification. The preparation of core units **4**−**6** and the effects they exert on the relative potency of balanol analogues into which they have been incorporated have been described in detail elsewhere,[15j] and will not be described here.

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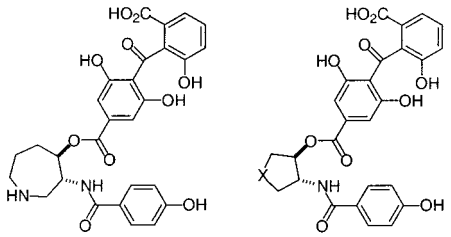
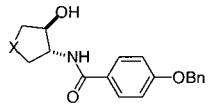


Balanol, **1**

2, X = NH
3, X = CH_2

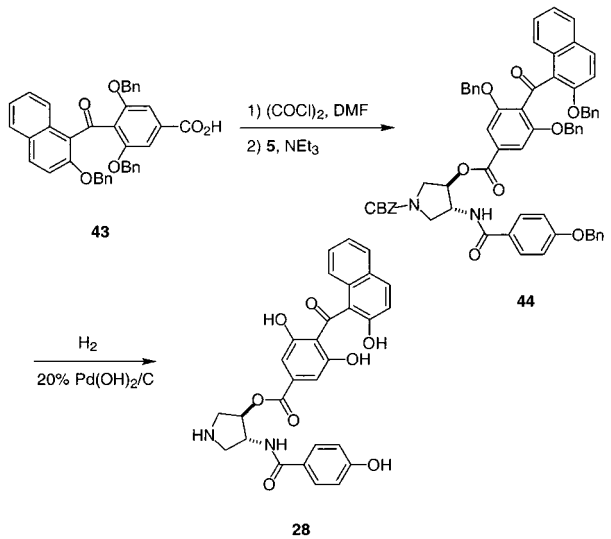


4, X = CH_2CH_2NBn
5, X = NCBZ
6, X = CH_2

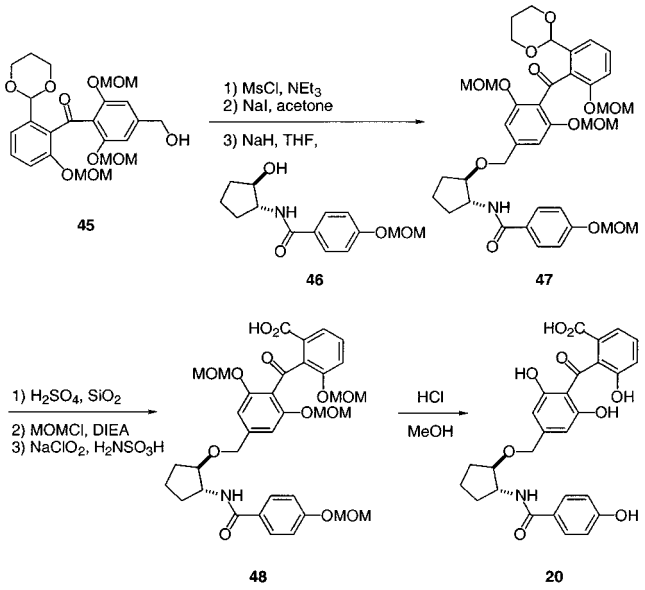
Scheme 2 provides an example of coupling in which the benzophenone is attached to the core unit by way of an ether linkage. Benzyl alcohol **45** was converted to the corresponding iodide by way of the mesylate, and the iodide was reacted with the sodium alcoholate derived from the MOM-protected analogue of core unit **6**. Hydrolysis of the acetal followed by oxidation served to unmask the carboxylic acid,[8c] after which acid hydrolysis provided the fully deprotected benzyl ether analogue **20**. The use of benzyl ethers as protecting groups in this case is obviously precluded by the presence of a benzyl ether in the target structure.

The synthesis of the majority of the compounds in this study required the development of syntheses for the benzophenone units themselves. General methods used for the preparation of these benzophenones are described below. Many of the simpler compounds could be directly prepared by metalation of an aryl halide followed by addition to an electrophilic form of the exterior ring. Aryl bromide **49**[8e] proved to be an extremely useful precursor to the interior benzophenone ring for reactions of this type. Acid chlorides and anhydrides were suitable exterior ring electrophiles when they were sterically unencumbered (method A). In the case of more crowded analogues, addition to an aldehyde followed by oxidation of the resulting alcohol gave access to the benzophenone (method B).[8c,e] Examples of these preparations are shown in Scheme 3. In some cases it proved advantageous to reverse the sense of the addition such that the electrophilic partner provided the interior ring; for these cases the 2-(1,3-dioxan-2-yl)aryllithium species described by Hollinshead and co-workers[8c] were particularly useful as nucleophiles. The benzophenone *tert*-butyl esters prepared using these and subsequently described routes were converted to the corresponding acids prior to coupling, typically by treatment with neat formic acid or, in the case of acid-sensitive substrates, by thermolysis in quinoline.[8e]

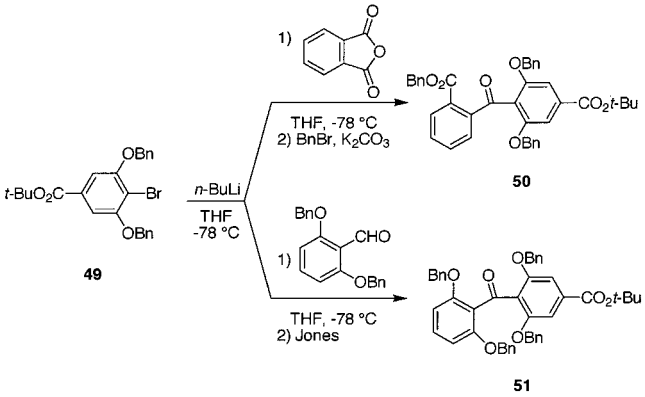
Scheme 1



Scheme 2



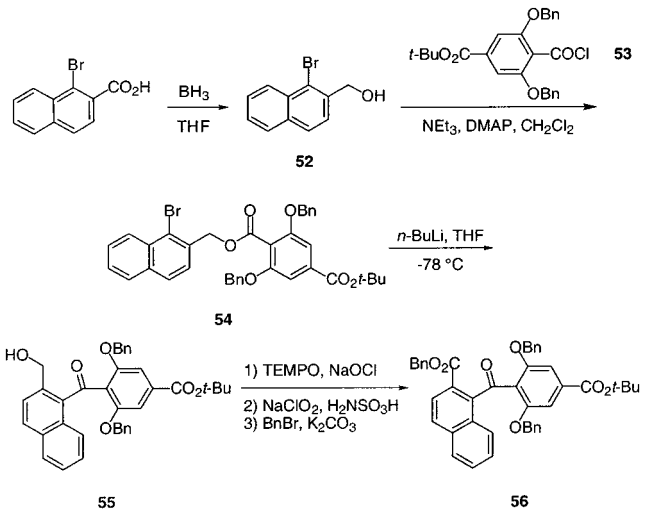
Scheme 3. Methods A and B



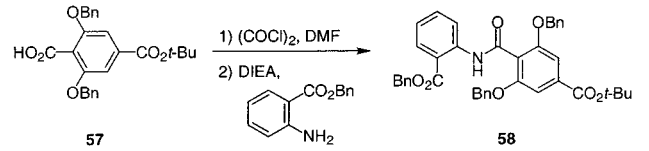
Sterically crowded benzophenones that had carboxylic acid substituents required alternative approaches because of the need to mask the carboxylic acid during the aryllithium addition. One analogue of this type was prepared using the anionic homo-Fries rearrangement[17] approach that we reported in the total synthesis of balanol[8e] (method C), as shown in Scheme 4. Acylation of 1-bromonaphthalene-2-methanol with the interior ring precursor **53** gave the rearrangement substrate **54**. Treatment of **54** with *n*-BuLi resulted in transmetalation followed by rearrangement to give product **55**, which after oxidation and protection as the benzyl ester gave the naphthalene-containing benzophenone analogue **56**.

Target compounds in which the benzophenone carbonyl had been replaced by an amide linkage were prepared in straightforward fashion as shown in Scheme

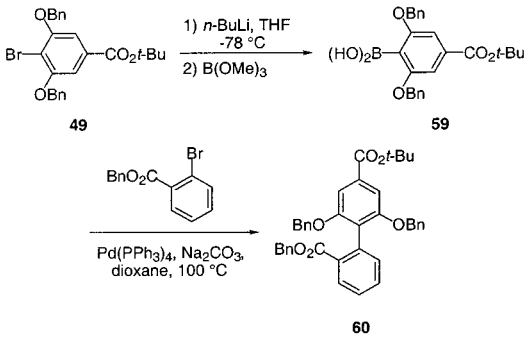
Scheme 4. Method C



Scheme 5. Method D



Scheme 6. Method E

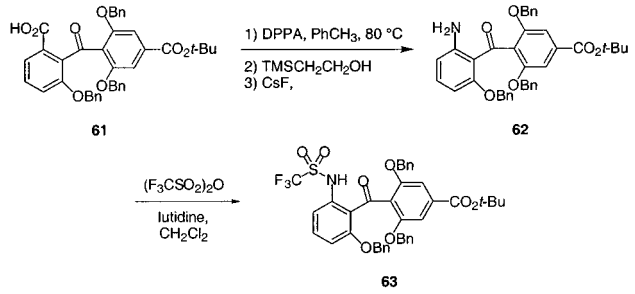


5 (method D). Conversion of carboxylic acid **57** to its acid chloride followed by reaction with benzyl anthranilate gave the amide analogue **58**.

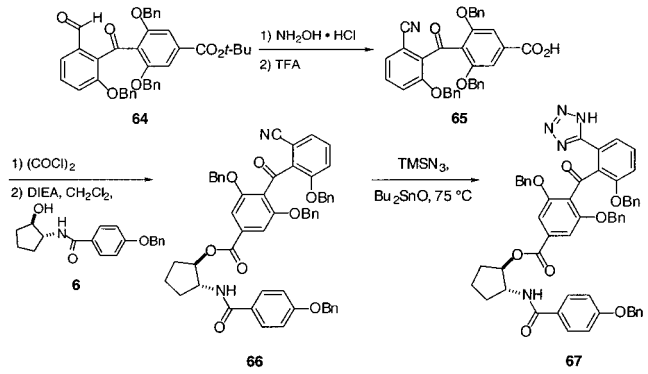
Analogues in which the benzophenone was replaced by related biphenyls were prepared by Suzuki coupling of the two aryl rings of the biphenyl.[18] An example is shown in Scheme 6 (method E). Metalation of aryl bromide **49** followed by reaction of the aryllithium with trimethyl borate provided the arylboronic acid **59**. Palladium-mediated coupling of the arylboronic acid with appropriately substituted aryl halides,[19] for example, benzyl 2-bromobenzoate, gave the biphenyl benzophenone analogue. In some cases it proved advantageous to reverse the sense of the coupling by making the external ring the boronic acid component, and to attach the aryl halide component to the balanol core prior to the Suzuki coupling step.

Several compounds were prepared in which the benzophenone carboxylic acid was replaced by an acylamine bioisostere.[15a] These compounds were prepared by acylation of the amine **62**, an example of which may be found in Scheme 7 (method F). Curtius rearrangement of carboxylic acid **61**[8c] followed by trapping of the isocyanate intermediate and subsequent deprotection[20]

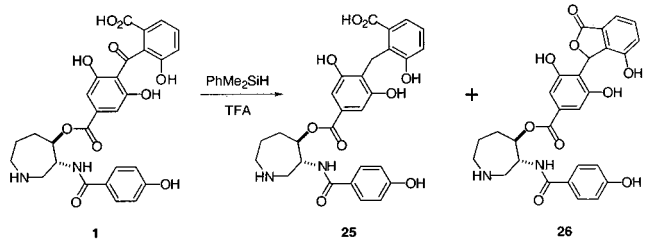
Scheme 7. Method F



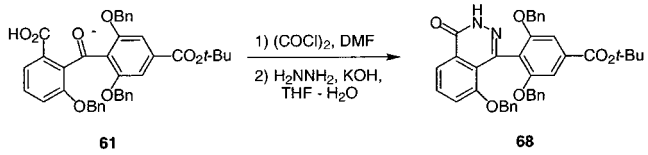
Scheme 8. Method G



Scheme 9. Method H



Scheme 10. Method I

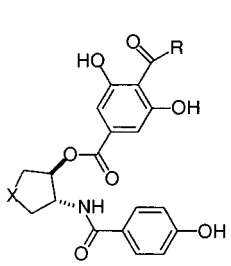


afforded amine **62**. Acylation with trifluoromethylsulfonic anhydride gave the desired triflamide **63**.

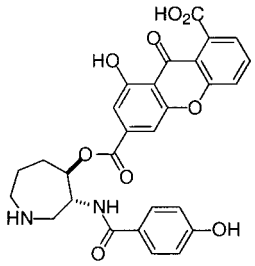
The preparation of compounds bearing tetrazole carboxylic acid isosteres[15a] is outlined in Scheme 8 (method G). Several attempts to couple fully elaborated tetrazole-bearing benzophenones to core subunits were unsuccessful; however, the coupling of benzophenone nitrile **65**, prepared by treatment of aldehyde **64**[8c] with hydroxylamine, proceeded without difficulty. Treatment of the resulting coupled nitrile product **66** with trimethylsilyl azide in the presence of dibutyltin oxide[21] gave after deprotection the desired tetrazole analogue **39**.

A small number of analogues were prepared by simple elaboration of balanol or the benzophenone subunit itself. For example, silane-mediated reduction[22] of balanol in TFA afforded a mixture of the methylene analogue **25** and the lactone **26**, albeit in low yield, as shown in Scheme 9 (method H).

Table 1. Modifications to the Terminal Benzophenone Ring[a]



7 - 13



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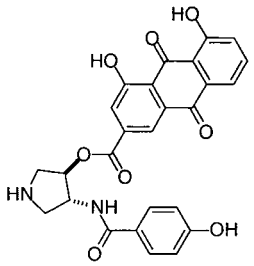
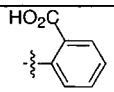
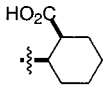
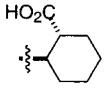
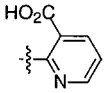
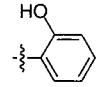
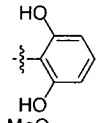
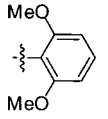
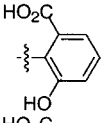
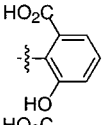
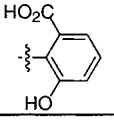


15

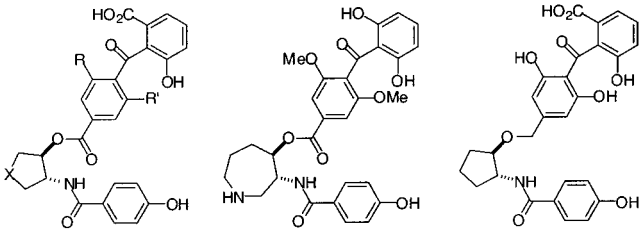
Compd	X	R	Method	PKC α	PKC βII	PKC ε	PKA
7	CH_2CH_2NH		A	10	3.7	3.5	1.0
8	CH_2CH_2NH		A	>150	124	97	7.9
9	CH_2CH_2NH		A	>150	>150	47	6.7
10	CH_2CH_2NH		A	37	13	8.1	NT
11	CH_2CH_2NH		B	97	38	8.0	0.44
12	CH_2CH_2NH		B	0.86	7.6	2.1	0.44
13	CH_2CH_2NH		B	31	26	6.7	0.36
14	--	--	A	>150	>150	10	>15
15	--	--	--	43	25	3.3	1.2
1, balanol	CH_2CH_2NH		--	0.067	0.030	0.038	NT
2	NH		--	0.022	0.033	0.01	0.06
3	CH_2		--	0.04	0.05	0.05	0.02

[a] IC_{50} values in μM. IC_{50} values were calculated from four-point curves of 10-fold dilutions; the assays were carried out using partially purified recombinant human PKC isozymes and PKA from commercial sources as described previously.[15h,23]

Activation of the benzophenone precursor **61** as the acid chloride followed by reaction with hydrazine provided the phthalazine analogue **42**, as shown in Scheme 10 (method I).

Biological Results. Target compounds were examined for their ability to inhibit partially purified recombinant human PKC isozymes as described previously.[23] The results of these assays are shown expressed as IC_{50} values in Tables 1−5. Eight isozymes were generally used in these studies; the results for two calcium-sensitive PKCs, PKC-α and PKC-βII, and one calcium-insensitive PKC, PKC-ϵ, are shown here as representative of the data as a whole. The activity of the compounds as inhibitors of cyclic-AMP-dependent pro-

Table 2. Modifications to the Internal Benzophenone Ring



				PKC			
Compd	X	R, R′	Method	α	βII	ε	PKA
16	CH_2	OH, H	A	2.6	2.7	4.3	0.35
17	CH_2	H, H	B	34	4.5	30	1.7
18[a]	CH_2	CH_3, CH_3	B	>50	>50	>50	NT
19	--	--	B	>150	>150	36	4.3
20	--	--		0.46	0.29	0.37	0.32

[a] Compound **18** was prepared in optically pure form with the (1*R*,2*R*) configuration, the same configuration found in naturally occurring balanol.

tein kinase (PKA) was also studied[24] as a measure of the selectivity of these compounds as kinase inhibitors, and is also shown in the tables.

The activities of (±)-balanol (**1**) and the pyrrolidine and cyclopentane core analogues **2** and **3** are shown in Table 1 for reference. We had found in earlier studies[15j] that changing among these three different cores generally resulted in comparable activities in compounds that were otherwise identical in structure, as can be seen from comparing **1**−**3**. As a result, it was possible to make qualitative assessments of the effect of modifications to the benzophenone nucleus even when the modifications appeared in compounds containing different central cores selected from this group of three. As the pyrrolidine and cyclopentane cores were much more easily accessible, we generally used them in preference to the azepane in our later synthetic work.

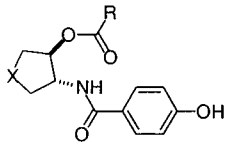
Our initial efforts at understanding the SAR of the benzophenone subunit were aimed at determining which if any of the substitutents could be modified or removed altogether without severely reducing the potency of the final compound. We thought it possible that some of the benzophenone substituents were not involved in direct binding interactions with the enzyme, but rather were responsible for enforcing on the benzophenone a conformation that was appropriate for binding.[25] Since our eventual goal was to reduce the overall polarity of the molecule, we sought to remove polar substituents or replace them with less polar types that might still provide the necessary conformational control and features for binding. Recent computational analysis of the PKA−balanol interaction[26] lends support to the notion that this might be a successful approach.

The results of these initial efforts are shown in Tables 1 and 2. Table 1 shows compounds in which the bulk of the modification occurred in the terminal benzophenone ring. Compound **7**, in which the single hydroxyl group on the terminal benzophenone ring has been removed, shows that even this small change has a substantial deleterious effect on activity.[16] Compounds **8** and **9**, two diastereomeric compounds related to **7** in which the terminal aromatic ring has additionally been saturated, were prepared to examine further the effect of adjusting the position of the carboxylic acid relative to the ring, and were found to be essentially devoid of PKC inhibitory activity. Substitution of a pyridine nitrogen for the hydroxyl group on the terminal phenyl ring gave compound **10**. This compound was comparable in activity to the simple deshydroxy compound **7**, showing that the potential hydrogen-bonding ability provided by the pyridine was not enough to make up for the loss of the hydroxyl group.

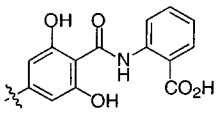
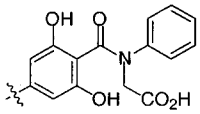
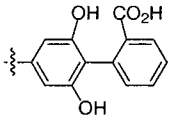
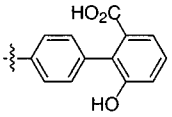
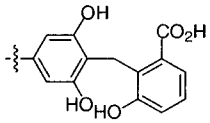
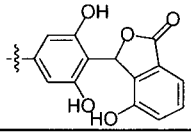
Similar investigations were made into the possibility for removal of the carboxylic acid functionality. As can be seen in the activity of compound **11**, simple removal of the acid functionality results in a compound with only trace activity against most PKC isozymes, although considerable activity against PKA is retained.[16] Intriguingly, however, replacement of the carboxylic acid with an additional phenol, as in **12**, gave a compound which, although it is notably less potent than compounds with the full benzophenone, still retains substantial activity compared to deletion compounds such as **11**. One compound with a symmetrical 2,6-disubstituted terminal benzophenone ring, **13**, was prepared to see if either simple hydrogen bond accepting or bulky lipophilic substituents could lead to active compounds by providing conformational rigidity to the benzophenone. These modifications resulted in almost complete loss of PKC inhibitory activity, and provided a compound that was a selective and potent inhibitor of PKA. This was particularly noteworthy in light of the drastic nature of the structural changes this compound incorporates. Finally, two compounds into which planar benzophenone analogues had been incorporated, **14** and **15**, both showed very poor activity, although interestingly **15**, the compound retaining the hydroxyl group but not the carboxylic acid, showed the greater activity of the two, especially against PKA. The poor activity of these two planar analogues is not surprising, in light of the probable staggered conformation adopted by the natural benzophenone.

We then turned our attention to modification of the internal benzophenone ring. Results of these studies are shown in Table 2. Deletion of one of the internal hydroxyl groups, as in compound **16**, resulted in significant reduction of activity, comparable to that observed on removal of the terminal ring hydroxyl group. Removal of the second hydroxyl, as in **17**, further reduced the potency of the compounds,[16] although not as significantly as the removal of the first hydroxyl group, particularly as measured against PKC-βII. Replacement of the substituents with simple lipophilic or hydrogen bond accepting substituents, as in **18** and **19**, completely abolished activity against PKC. It should be noted in considering these data that compound **18** was prepared in optically pure form, with the same (1*R*,2*R*) configuration as is found in naturally occurring balanol. Interestingly, **19** showed significant activity against PKA, not unlike the results seen with **13**. These results would appear to be partially consistent with the analysis of Wong and co-workers,[26] who predict that small nonpolar substituents in this position should give analogues with improved PKA inhibitory activity. Finally, compound **20**, in which the carboxylic ester linkage to the core was replaced with a benzyl ether, was prepared and was found to retain a substantial portion of the activity of the parent compound. This was

Table 3. Replacements of the Benzophenone Carbonyl



21 - 26

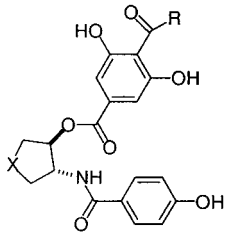
Compd	X	R	Method	PKC α	PKC βII	PKC ε	PKA
21	NH		D	>150	117	39	1.9
22	NH		D	>150	>150	>150	29
23	NH		E	>50	>50	NT	NT
24	NH		E	>50	40	>50	NT
25	CH_2CH_2NH		H	>5	>5	>5	0.47
26	CH_2CH_2NH		H	18	0.80	16	0.3

a gratifying discovery, since the ester linkage could prove to be a labile site in an in vivo setting.

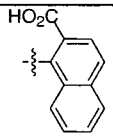
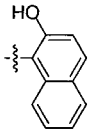
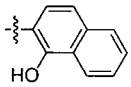
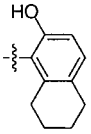
A limited series of compounds were prepared in which the benzophenone carbonyl was replaced by another linking functionality, and may be seen in Table 3. We hoped by doing this that we might improve the synthetic accessibility of the resulting benzophenone subunits, and at the same time might remove or reduce the acidifying effect of the carbonyl on the adjacent phenolic hydroxyl groups, and thus reduce the polarity of the molecules. Unfortunately, difficulties in the syntheses limited our ability to prepare compounds with the full substitution pattern of the parent benzophenone, although we were able to gain access to analogues that were close enough in structure to allow evaluation of the linker types. Two compounds with an amide linkage, **21** and **22**, were prepared and were found to be substantially less potent than the corresponding deshydroxy benzophenone compound **7**, although **21** did retain significant activity against PKA. Two biphenyl analogues, **23** and **24**, the first analogous to **7** and the second related to the bis(deshydroxy) analogue **17**, were found to be essentially devoid of activity. An analogue bearing a methylene in place of the carbonyl, **25**, was likewise inactive. We were unable to examine the activity of this compound above a dose of 5 μM due to compound quantity limitations; however, we observed no detectable inhibition of the PKC isozymes at the 5 μM concentration. Surprisingly, the lactone byproduct **26** did show inhibitory activity against some PKC isozymes, notably PKC-βII, and both it and **25** were found to inhibit PKA. Taken together, these results suggest that the combination of the geometric constraints and the acidifying effect provided by the carbonyl are critical to obtaining potent PKC inhibition in these balanol analogues.

The results of these initial studies suggested that each of the benzophenone substituents plays an important role in contributing to the potency of an inhibitor. We therefore turned our attention to analogues that were based on single changes to the substituents on the terminal benzophenone ring, and particularly to the carboxylic acid, so as to focus our efforts more closely on identifying tolerable replacements for the most polar substituents. A short series of compounds, shown in Table 4, were prepared in which a benzene ring fusion was used to replace these substituents. We reasoned on doing this that the greater bulk of the fusion might provide some necessary conformational control, and that the increased lipohilicity would enhance the distribution properties of the resulting compounds. Compounds **27** and **28**, in which a benzene fusion replaced the carboxylic acid and the phenol of the terminal ring, respectively, both displayed modest activity, and were essentially equipotent. Compound **29**, a regioisomer of **28** in which the ring fusion is adjacent to the phenol, showed no activity against any of the PKC isozymes or against PKA. Remarkably, compound **30**, an even more lipo-

Table 4. Fused Ring Modifications to the Terminal Benzophenone Ring



27 - 30

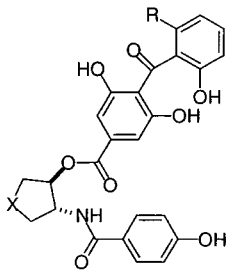
				PKC			
Compd	X	R	Method	α	βII	ε	PKA
27	NH		C	7.8	8.0	4.6	0.33
28	NH		B	5.6	5.6	2.2	0.29
29	CH_2CH_2NH		A	>150	>150	>150	>150
30	NH		B	0.43	0.26	0.30	0.05

philic analogue of **28** in which the ring fusion was saturated, proved more potent than either **27** or **28**, and showed activity approaching that of balanol itself. This is especially surprising in light of the substantial nature of the change in this analogue, and in particular in light of the absence of a carboxylic acid.

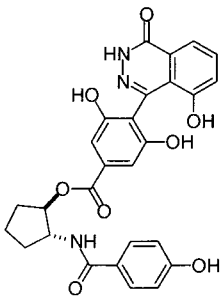
Table 5 shows those compounds that involved a single direct replacement of another substituent for the carboxylic acid. Compound **31**, which bears a methoxy substituent that could potentially serve as a hydrogen bond acceptor, displayed only modest activity. Compound **42**, which has an amide-like replacement for the carboxylic acid which possesses a modestly acidic proton, but which is fixed in a planar orientation, was inactive. Interestingly, nitrile-substituted compound **32** was found to be comparable in potency to deshydroxy compound **7**, and clearly more potent than compound **11**, the compound in which the carboxylic acid is deleted. This finding is consistent with the prediction of Wong and co-workers[26] that the balanol carboxylate might be successfully replaced with an electron-withdrawing substituent. The best activity in this series was found in compounds bearing bioisosteric replacements for carboxylic acids.[27] A series of acylamino isosteres, **35**–**38**, were prepared, and were found to display activity which roughly paralleled the expected acidity of the acylamino substituent. Compound **35** was notable in this series for having activity that was essentially equivalent to that of balanol itself. A tetrazole isostere compound, **39**, was also found to possess potent inhibitory activity. Unexpectedly, **40** and **41**, two regioisomeric methylated analogues of **39**, showed modest activity, even though they lack an acidic proton on the tetrazole. Taken as a whole, these results reinforce the notion that some ionizable carboxylate-like functionality is required to provide an acceptable substitute for the balanol carboxylic acid.

Several of the above compounds were studied in models designed to measure their capacity to block PKC-mediated signal transduction in a cellular setting. Inhibition of the phorbol-12-myristate-13-acetate (PMA) induced superoxide burst in human neutrophils[15h] was used as our primary cellular assay for this purpose. As can be seen in Table 6, many of the compounds which show potent PKC-inhibitory activity in the enzymatic assays, including balanol itself, fail to reach an IC_{50} at doses up to the 10 μM maximum concentration studied in this assay. A few of the compounds in which the carboxylic acid group has been replaced by less polar functionality, for example, the phenol **12** and the acid isostere analogue **36**, did reach the 50% inhibition level at or near the 10 μM concentration. Compound **36** was of special interest in that it showed greater activity in this assay than the more acidic analogue **35**, which was also more potent in the enzyme assay. This suggests that it may be possible to tune the acidity of the acid isostere so as to provide a balance between the neutral species for improved transport across the cell membrane and the ionized species for improved binding. Two compounds that were particularly noteworthy for their activity in this assay were **28** and **30**. These clearly more lipophilic compounds show that the cellular activity of balanol analogues can be enhanced by limiting the polarity of the substituents in the benzophenone region.

Table 5. Carboxylic Acid Replacements



31 - 41



42

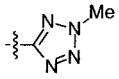
				PKC			
Compd	X	R	Method	α	βII	ε	PKA
31	CH_2CH_2NH	OCH_3	B	25	9.5	2.6	0.25
32	CH_2	CN	G	3.7	2.1	0.83	0.50
33	CH_2	$OCH_2CH_2NH_2$	B	>50	24	5.0	3.9
34	CH_2	OCH_2CO_2H	B	2.2	0.33	0.41	0.47
35	CH_2	$NHSO_2CF_3$	F	0.10	0.05	0.31	0.35
36	CH_2	$NHSO_2CH_3$	F	0.50	0.11	NT	NT
37	CH_2	$NHCOCF_3$	F	>50	>50	NT	NT
38	CH_2	$NHCOCH_3$	F	>50	4.8	NT	NT
39	CH_2		G	0.34	0.26	2.0	0.21
40	CH_2		G	3.6	1.3	3.8	1.8
41	CH_2		G	11	3.5	4.7	0.47
42	--	--	I	>50	>50	>50	NT

Table 6. Cellular Activity of Benzophenone Analogues[a]

Compd	Neutrophil Assay IC_{50}
7	>10
12	9.2
17	>10
27	>10
28	1.5
30	0.47
32	>10
35	>10
36	10
39	>10
41	10
1	>10

[a] IC_{50} values in μM. IC_{50} values were calculated from four-point curves of 10-fold dilutions; the assays were carried out as described previously.[15h]

Discussion

Our primary goal in undertaking the work described in this paper was to improve the advancement potential of balanol analogues by removing or replacing benzophenone functionality that increased the polar nature of the inhibitors and thus might prevent them from reaching their intracellular targets. Although recent work has provided direct evidence that balanol itself can function as a PKC inhibitor in cellular assays,[28] it was our expectation that some attenuation of the polarity of balanol would be required to obtain compounds with the overall physical properties suitable for continued pharmaceutical development. Our approach in the work described in this paper was based on the thinking that some of the substituents on the balanol benzophenone subunit might not be involved in critical binding interactions with the protein at the kinase active site. Rather, it seemed that at least some of the substituents were contributing by providing reduced conformational mobility in the inhibitor, or perhaps were not contributing significantly to the potency of the inhibitor at all. We reasoned that substituents that were providing conformational control through intramolecular hydrogen bonding might be replaced by less polar substituents which could provide the same control through simple steric effects. Such substituents might further contribute to potency by reducing the impact of the desolvation of the inhibitor prior to binding.[29]

At first glance, the results of this study suggest that most of the substituents on the benzophenone are required for potent PKC inhibitory activity. Even the least deleterious of the simple changes, such as deletion of an internal ring hydroxyl group, significantly decreased the potency of the analogue. These results were

consistent with similar findings reported earlier by Nicolaou and co-workers for the simplest compounds, **7**, **11**, and **17**.[16] Further, simple replacement of the substituents by small alkyl groups, which would provide conformational control through steric effects, was totally unsuccessful in the cases we studied, although these modifications did frequently lead to selective PKA inhibitors. Modifications that involved clearly bioisosteric substitutions, such as the tetrazole and trifluoromethyl sulfonanilide substitution for the carboxylate, were successful in yielding potent enzyme inhibitors, but these had only modest impact on the cellular availability of the analogues in our studies.

Nevertheless, several fascinating anomalous results were encountered in this study that suggest that some of the benzophenone substituents might be open to replacement. Foremost among these are the fused ring analogues **28** and **30**, which lack the benzophenone carboxylate and which have in its place a lipophilic ring fusion. Other compounds which retain some activity and in which the carboxylate has been replaced by nonacidic functionality include the methyl tetrazoles **40** and **41**, and the nitrile compound **32**. These compounds are similar in that they all retain an acidic phenol on the terminal benzophenone ring, and their activity might best be explained by postulating that they bind to the enzyme in a conformation that allows the phenol to occupy the site normally filled by the carboxylate. In some of these compounds, for example, the tetrazoles **40** and **41**, the other terminal ring substituent may be fulfilling the function formerly carried out by the phenol, perhaps providing a conformation-limiting intramolecular hydrogen bond. However, the fused ring analogues **28** and **30** cannot be functioning in this way. The increase in potency on saturating **28** to give **30** suggests that the potency of these analogues is related to the lipophilicity of the new ring, and it is attractive to speculate that these analogues may be binding in such a way as to take advantage of nonpolar interactions available at the ATP binding region of the enzyme.

Although we have no direct evidence to support this mode of binding for these analogues at this time, the recently published structure of a balanol−PKA complex[30] provides some additional information that is consistent with this view. This structure reveals a host of bonding interactions between balanol and the protein, nonpolar as well as hydrogen-bonding and ionic interactions, and in fact all of the benzophenone substituents are involved in significant interactions with the protein. In particular, the terminal benzophenone ring region interacts extensively with the kinase glycine-rich loop, forming nonpolar contacts with Phe54 and hydrogen bonds between the benzophenone carboxylate and Ser53. Interestingly, no ionic interactions are seen between the protein and the benzophenone carboxylate, which functions rather as an acceptor of multiple hydrogen bonds. This would seem at first glance to be at odds with the PKC inhibition SAR, which would suggest that ionizable functionality is highly desirable at the position occupied by the carboxylate. However, the finding can be understood in light of the improved capacity of the carboxylate to accept multiple hydrogen bonds. Further, the result is less out of line with the PKA SAR, which is less restrictive with respect to a requirement for carboxylate-like functionality. It has been suggested that, for balanol-like inhibitors of PKA, hydrogen-bonding substituents contribute minimally to the overall energetics of binding, due to the compensating effect of the required desolvation of the substituent prior to binding to the enzyme.[31] This effect is less clear in the case of the PKC inhibition SAR, where the effect of the removal of hydrogen-bonding substituents on potency is more pronounced. However, it is clearly the case that any hydrogen-bonding substituents must be positioned appropriately so as to participate in binding, or else the effect of desolvation will result in a net deleterious effect of the substituent.[31] In light of this, it would seem reasonable that substituents which could accept multiple hydrogen bonds in a fashion analogous to that of the carboxylate, such as the more acidic acid isosteres which were studied, **35** and **39**, would be preferred as benzophenone substituents. In compounds where a less optimally oriented substituent capable of accepting a single hydrogen bond was used, **30**, the quality of binding might be improved by positioning lipophilic substituents on the opposite side of the ring so as to take advantage of nonpolar interactions available with the protein, particularly with Phe54 and Leu74 in the case of PKA. These notions are qualitatively consistent with the observed PKA inhibition data.

The use of PKA structural data in interpreting the trends in the PKC inhibitory potencies of these compounds is speculative, since we have no direct structural information for PKC itself to help guide the interpretation. Nevertheless, the PKA structural observations appear consistent with the PKA inhibitory data. Further, the sequence homology between PKA and PKC in the ATP binding region,[32] and particularly around the glycine-rich loop, coupled with similar trends for the PKA and PKC inhibitory potencies for this series of compounds, lends credence to the suggestion that nonpolar binding interactions may play an important role in the binding of these compounds.

Conclusion

We have described a series of balanol analogues that bear modified benzophenone subunits. Many of these compounds showed sharply reduced PKC inhibitory potency, showing that an appropriately functionalized benzophenone is critical for potent activity in these compounds. However, in the course of these modifications we uncovered several selective PKA inhibitors, such as **13** and **21**. Further, we showed that the carboxylic acid of the benzophenone could be replaced with suitable bioisosteric groups, and that these substitutions could provide inhibitors such as **35**, **36**, and **39** with PKC inhibitory potencies similar to that of balanol and in some cases with modestly enhanced activity in cellular assays. Finally, we showed that analogues such as **28** and **30** in which a highly lipophilic group had replaced the carboxylic acid could display potent activity in both enzymatic and cellular models, and we provided a hypothesis that might be used to rationalize this unexpected activity. It has been suggested that balanol might serve as a "protean structure" [28,33] from which to develop selective kinase inhibitors. Our findings further support this notion, and provide valuable information that could be used as the

basis for the design of the next generation of balanol analogues with cellular activity.

Experimental Section[34]

General Synthesis Method A. 2-[2,6-Dibenzyloxy-4-(1,1-dimethylethoxycarbonyl)benzoyl]benzoic Acid (69). To a solution of 4.69 g (10.0 mmol) of 3,5-dibenzyloxy-4-bromobenzoic acid *tert*-butyl ester (**49**) in 65 mL of dry THF at −72 °C under nitrogen was added 4.6 mL (11.0 mmol) of a 2.4 M solution of butyllithium in hexanes over 10 min. The solution was stirred at −72 °C for 10 min, after which it was transferred by cannula into a solution of 1.48 g (10.0 mmol) of phthalic anhydride in 30 mL of dry THF at −72 °C. After 1.5 h the reaction mixture was poured onto 350 mL of ether and 150 mL of saturated aqueous NH_4Cl, and this mixture was stirred for 30 min. The layers were separated, and the organic phase was washed with 0.1 M HCl, water, and brine, dried over $MgSO_4$, and evaporated to give 5.46 g (100%) of the crude product, which was used directly in the next reaction.

1,1-Dimethylethyl 4-[2-(Benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoate (50). To a solution of 5.46 g (10.0 mmol) of **69** in 35 mL of dry DMF were added 4.21 g (30.4 mmol) of K_2CO_3 and 1.21 mL (1.74 g, 10.2 mmol) of benzyl bromide. The solution was stirred at room temperature under nitrogen for 16 h. The mixture was then poured onto 600 mL of ether, washed with three 150 mL portions of water and then with 150 mL of brine, and dried over $MgSO_4$. Evaporation of the solvent afforded 6.58 g of the crude product, which was chromatographed on silica gel, eluting with 85/15 hexanes−EtOAc to give 3.74 g (59%) of the title compound as a colorless oil. Anal. ($C_{40}H_{36}O_7$) C, H.

4-[2-(Benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoic Acid (70). A solution of 3.63 g (5.77 mmol) of **50** in 50 mL of formic acid was stirred at room temperature under nitrogen. After 3 h the mixture was poured onto 450 mL of water and stirred. The mixture was cooled, and the precipitate was collected by filtration, washed with water, and dried at 60 °C in a vacuum oven to constant weight, yielding 3.08 g (93%) of the title compound as a tan solid. An analytical sample was obtained by recrystallization from 2-propanol: mp 174−176 °C. Anal. ($C_{36}H_{28}O_7$) C, H.

General Method for Coupling and Deprotection. 4-*trans*-[4-(2-Carboxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (7). Compound **70** (325 mg, 567 μmol) was dissolved in 2 mL of CH_2Cl_2 and treated with DMF (3 drops) followed by oxalyl chloride (370 μL of a 2 M solution in CH_2Cl_2, 738 mmol). After being stirred for 1 h, the mixture was concentrated under vacuum to a glass. The residue was redissolved in 5 mL of CH_2Cl_2 and added slowly to a stirred solution of *N*-benzyl-4-hydroxy-3-(4-benzyloxybenzamido)azepane (**4**) (244 mg, 567 μmol), DMAP (7 mg), and triethylamine (172 mg, 1.7 mmol) in 2 mL of CH_2Cl_2. After 10 min, the reaction mixture was poured directly onto a silica gel column and eluted (4/1 (1 L) and then 3/2 (1 L) hexanes−EtOAc) to give 378 mg (68%) of the product as a glass: ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.65−1.95 (m, 2H), 1.95−2.05 (m, 2H), 2.53−2.65 (m, 1H), 2.83 (dd, *J* = 4, 14, 1H), 2.92−3.02 (m, 2H), 3.57 (d, *J* = 13, 1H), 3.8 (d, *J* = 13, 1H), 4.25−4.34 (m, 1H), 4.99 (s, 4H), 5.11 (s, 2H), 5.15−5.22 (m, 1H), 5.19 (s, 2H), 6.72 (d, *J* = 8.2, 1H), 6.94 (d, *J* = 8.8, 2H), 7.05−7.52 (m, 29H), 7.44 (d, *J* = 6.6, 1H).

The ester product was dissolved in methanol and treated with excess trifluoroacetic acid. The sample was concentrated under vacuum for 16 h and then dissolved in a 4/1 ethanol−methanol mixture and a portion removed (305 mg, 277 μmol) for hydrogenation. The portion was diluted (25 mL of the 4/1 solution), treated with 100 mg of $Pd(OH)_2$, and hydrogenated at 55 psi on a Parr hydrogenator. After 5 h the reaction mixture was filtered through Celite and concentrated to give the product (164 mg, 93%) as a glass. The glass was triturated with water to give a solid which was filtered off to give slightly impure product (40 mg, 22%). The mother liquor was chromatographed on a Dynamax-60 C_{18} column (21 mm i.d. × 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 min at 15 mL/min. The clean product, which eluted in 20 min, was freeze-dried to give a light yellow powder (70 mg, 40%): mp 190−200 °C dec; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.8−2.0 (m, 3H), 2.05−2.2 (m, 1H), 3.1−3.2 (m, 2H), 3.2−3.4 (m, 2H), 4.4−4.55 (m, 1H), 5.2−5.3 (m, 1H), 6.78 (d, *J* = 9, 2H), 6.82 (s, 2H), 7.3 (d, *J* = 7, 1H), 7.54 (pseudo-t, 1H), 7.56 (pseudo-t, 1H), 7.63 (d, *J* = 9, 2H), 7.78 (d, *J* = 7, 1H). Anal. ($C_{28}H_{26}N_2O_9 \cdot H_2O \cdot$TFA) C, H, N.

4-*trans*-[4-(*cis*-2-Carboxycyclohexanoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (8). The benzophenone acid analogue required for the title compound was prepared in 21% overall yield from *cis*-1,2-cyclohexanedicarboxylic acid anhydride using general method A followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound (37 mg, 10%): mp 122−127 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.20 (m, 4H), 1.40 (m, 1H), 1.62 (m, 2H), 1.68−2.10 (m, 7H), 2.63 (m, 1H), 3.10 (m, 2H), 3.80 (m, 1H), 4.30 (m, 1H), 5.21 (m, 1H), 6.56 (d, *J* = 9, 2H), 6.72 (s, 2H), 7.41 (d, *J* = 9, 2H). Anal. ($C_{28}H_{32}N_2O_9 \cdot 2H_2O \cdot$1.2TFA) C, H, N.

4-*trans*-[4-(*trans*-2-Carboxycyclohexanoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (9). The benzophenone acid analogue required for the title compound was prepared in 18% overall yield from *trans*-1,2-cyclohexanedicarboxylic acid anhydride using general method A followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound as a tan solid (17 mg, 5%): ^{1}H NMR (CD_3OD) (*J* in hertz) δ 0.75−1.00 (m, 2H), 1.20 (m, 4H), 1.63 (m, 2H), 1.75−2.15 (m, 6H), 2.60 (m, 1H), 3.10 (m, 2H), 3.72 (m, 1H), 4.30 (m, 1H), 5.22 (m, 1H), 6.55 (d, *J* = 9, 2H), 6.72 (s, 2H), 7.41 (d, *J* = 9, 2H). Anal. ($C_{28}H_{32}N_2O_9 \cdot H_2O \cdot$1.2TFA) C, H, N.

4-*trans*-[4-(3-Carboxy-2-pyridylcarbonyl)-3,5-dihydroxybenzoyloxy]-3-(4- hydroxybenzamido)azepane (10). The benzophenone acid analogue required for the title compound was prepared in 8% overall yield from 2,3-pyridinedicarboxylic acid anhydride using general method A (a 1/4 ratio of regioisomers is produced in the first step) followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acyl imidazole followed by deprotection afforded the title compound as a yellow solid (11 mg, 3%): mp 198−205 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.78−1.95 (m, 3H), 2.06 (m, 1H), 3.10 (m, 4H), 4.25 (m, 1H), 5.20 (m, 1H), 6.58 (d, *J* = 9, 2H), 6.71 (s, 2H), 7.42 (d, *J* = 9, 2H), 7.64 (dd, *J* = 6, 8, 1H), 7.92 (dd, *J* = 2, 8, 1H), 8.16 (dd, *J* = 2, 6, 1H). Anal. ($C_{27}H_{25}N_3O_9 \cdot 2H_2O \cdot$1.8TFA) C, H, N.

4-*trans*-[4-(2-Hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (11). The benzophenone acid analogue required for the title compound was prepared in 46% overall yield from 2-benzyloxybenzaldehyde using general method B followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (30 mg, 26%): mp 174−176 °C dec; ^{1}H NMR (DMSO-d_6) (*J* in hertz) δ 1.64 (m, 1H), 1.74 (m, 1H), 1.91 (m, 2H), 2.73−2.83 (m, 3H), 2.91 (dd, 1H), 4.19 (m, 1H), 5.18 (m, 1H), 6.77 (d, *J* = 8.7, 2H), 6.87 (td, 1H), 6.98 (s, 2H), 6.70 (d, *J* = 6.5, 1H), 7.26 (dd, *J* = 1.6, 7.9, 1H), 7.54 (td, 1H), 7.65 (d, *J* = 8.6, 2H). Anal. ($C_{27}H_{26}N_2O_8 \cdot 1.25H_2O$) C, H, N.

General Synthesis Method B. 2,6-Dibenzyloxybenzyl Alcohol (71). To a solution of 2,6-dihydroxybenzoic acid (5.0 g, 32.4 mmol) and K_2CO_3 (13.5 g, 97.2 mmol) in DMF (100 mL) was added benzyl bromide (12.7 mL, 107 mmol). The reaction was stirred for 2 h at 80 °C. The reaction was diluted with EtOAc (200 mL) and washed three times with water. The organic phase was then isolated, dried over Na_2SO_4, and concentrated to yield 17 g of yellow liquid. The yellow liquid (10 g, 19.1 mmol) was dissolved in THF (80 mL). Lithium aluminum hydride (47 mL, 1.0 N in THF) was then slowly added to the solution with stirring under nitrogen. The reaction was stirred at room temperature for 20 h, and then

quenched with water (10 mL), followed by 3.0 N NaOH (10 mL). The reaction was stirred for 1 h, and then filtered. The filtrate was diluted with EtOAc (100 mL), the aqueous phase was removed, and the remaining organic solution was washed with brine. The organic phase was then dried over Na_2SO_4 and concentrated to yield a clear liquid. The liquid was triturated in hexanes, whereupon a white solid precipitated. The solid was filtered and rinsed with hexanes to yield a white powder (5.72 g, 94%): ^{1}H NMR ($CDCl_3$) (J in hertz) δ 2.59 (t, J = 13, 1H), 4.91 (d, J = 8.1, 2H), 5.12 (s, 4H), 6.66 (d, J = 8.2, 2H), 7.21 (t, J = 9.5, 1H), 7.30−7.47 (m, 10H).

2,6-Dibenzyloxybenzaldehyde (72). To a solution of **71** (5.0 g, 15.6 mmol) in CH_2Cl_2 (70 mL) was added PDC (8.9 g, 23.7 mmol). The reaction was stirred for 3 days at room temperature, then poured over CH_2Cl_2 (300 mL), and washed three times with 0.5 N NaOH. The organic phase was isolated, dried with Na_2SO_4, filtered over silica gel, and concentrated. The residue was triturated in EtOAc−hexanes to yield a light yellow solid (1.67 g, 34%): ^{1}H NMR ($CDCl_3$) (J in hertz) δ 5.20 (s, 4H), 6.64 (d, J = 8.5, 2H), 7.31−7.49 (m, 11H), 10.67 (s, 1H). Anal. ($C_{21}H_{18}O_3$) C, H.

3,5-Dibenzyloxy-4-(2,6-dibenzyloxybenzylhydroxy)benzoic Acid 1,1-Dimethylethyl Ester (73). To a solution of **49** (757 mg, 1.61 mmol) in THF (15 mL) at −78 °C under nitrogen was added a 2.0 N solution of butyllithium in cyclohexane (0.88 mL) over a period of 20 min. Next, a solution of **72** (640 mg, 2.01 mmol) in THF (5 mL) was added. The reaction was stirred for an additional 30 min at −78 °C, then quenched with water (10 mL), and allowed to warm to room temperature. The resulting solution was extracted with EtOAc and washed with 0.5 N NH_4Cl and 1.0 N HCl. The organic phase was then isolated, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel eluting with 9/1 hexanes−EtOAc to yield a clear glue (510 mg, 45%): ^{1}H NMR ($CDCl_3$) (J in hertz) δ 1.59 (s, 9H), 4.80 (s, 8H), 4.81 (d, J = 6.0, 1H), 5.80 (d, J = 10.5, 1H), 6.50 (d, J = 10.4, 2H), 6.92 (d, J = 10.2, 1H), 7.06−7.14 (m, 10H), 7.19−7.25 (m, 12H).

3,5-Dibenzyloxy-4-(2,6-dibenzyloxybenzoyl)benzoic Acid 1,1-Dimethylethyl Ester (51). To a solution of **73** (450 mg, 0.635 mmol) in acetone (10 mL) at room temperature was added a previously prepared solution of Jones Reagent (H_2O−H_2SO_4−CrO_3, 25 mL/5.5 mL/5 g) (2.0 mL, dropwise). The reaction was stirred for 20 min, and then concentrated. The residue was dissolved in EtOAc (100 mL) and washed with 3.0 N aqueous NaOH and brine. The organic phase was dried over Na_2SO_4, filtered over silica gel, and concentrated to yield a light yellow foam (390 mg, 87%): ^{1}H NMR ($CDCl_3$) (J in hertz) δ 1.65 (s, 9H), 4.73 (s, 4H), 4.75 (s, 4H), 6.50 (d, J = 10.5, 2H), 7.02−7.50 (m, 23H).

***trans*-4-[3,5-Dihydroxy-4-(2,6-dihydroxybenzoyloxy)]-3-(4-hydroxybenzamido)azepane (12).** The benzophenone acid analogue required for the title compound was prepared in 29% yield from **51** by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound (7.5 mg, 9%): mp 168 °C; ^{1}H NMR (DMSO-d_6) (J in hertz) δ 1.87−2.00 (m, 2H), 2.05−2.30 (m, 2H), 2.70−3.00 (m, 2H), 3.10−3.21 (m, 2H), 4.42−4.60 (m, 1H), 5.24−5.37 (m, 1H), 6.25 (d, J = 7.9, 2H), 6.79 (d, J = 8.2, 2H), 6.86 (s, 2H), 7.19−7.30 (m, 2H), 7.68 (d, J = 8.4, 2H), 8.48 (d, J = 7.7, 1H), 9.00 (br s, 1H), 9.96 (s, 2H), 10.07 (s, 1H), 11.29 (s, 2H). Anal. ($C_{27}H_{26}N_2O_9$·1.5H_2O·1.2TFA·0.2DMF) C, H, N.

4-*trans*-[4-(2,6-Dimethoxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (13). The benzophenone acid analogue required for the title compound was prepared in 15% overall yield from 2,6-dimethoxybenzaldehyde using general method B followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (158 mg, 26%): mp 189−193 °C dec; ^{1}H NMR (CD_3OD) (J in hertz) δ 1.77−2.14 (m, 4H), 3.11 (m, 3H), 3.43 (m, 1H), 3.45 (s, 6H), 4.27 (m, 1H), 5.20 (m, 1H), 6.42 (d, J = 10, 2H), 6.57 (d, J = 10, 2H), 6.67 (s, 2H), 7.08 (t, J = 10, 1H), 7.41 (d, J = 10, 2H). Anal. ($C_{29}H_{30}N_2O_9$·2H_2O·1.3TFA) C, H, N.

4-*trans*-[(1-Carboxy-8-hydroxy-9-oxoxanthen-6-yl)carbonyloxy]-3-(4-hydroxybenzamido)azepane (14). 4-[2-(Benzyloxycarbonyl)-6-nitrobenzoyl]-3,5-dibenzyloxybenzoic acid was prepared in 15% overall yield from 3-nitrophthalic anhydride using general method A with benzylation of the intermediate carboxylic acid followed by TFA cleavage of the *tert*-butyl ester.

A mixture of this benzophenone acid (270 mg, 0.512 mmol) and carbonyldiimidazole (95.4 mg, 0.589 mmol) in DMF (2 mL) was stirred at room temperature for l.5 h. To this mixture was added **4** (253 mg, 0.589 mmol) followed by DBU (89.6 mg, 88 μL, 0.589 mmol). The resulting mixture was stirred at room temperature for 16 h, then poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and chromatographed on silica gel eluting with 3/2 hexanes−ethyl acetate to afford as a white solid (210 mg, 46%) the coupled product in which an intramolecular displacement of the nitro group to yield a xanthene had taken place: FAB-MS m/z 894 $(M + H)^+$.

Deprotection of this coupled product in the standard way afforded the title compound as a yellow solid (70 mg, 57%): mp 224−226 °C dec; FAB-MS m/z 533 $(M + H)^+$; ^{1}H NMR (CD_3OD) (J in hertz) δ 1.8−2.1 (m, 3H), 2.2 (m, 1H), 3.2 (m, 4H), 4.60 (m, 1H), 5.29 (m, 1H), 6.76 (d, J = 9, 2H), 7.24 (s, 1H), 7.45 (d, J = 7, 1H), 7.49 (s, 1H), 7.66 (d, J = 9, 2H), 7.76 (d, J = 8, 1H), 7.97 (t, J = 8, 1H), 8.6 (br d, 1H), 10.05 (br d, 1H). Anal. ($C_{28}H_{24}N_2O_9$·TFA) C, H, N.

4-*trans*-(4,5-dihydroxyanthraquinone-2-carbonyloxy)-3-(4-hydroxybenzamido)pyrrolidine (15). Standard coupling of rhein to *trans*-1-benzyloxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine (**5**) by way of the acyl imidazole followed by deprotection by hydrogenolysis at 53 psi afforded the title compound as an orange solid (11 mg, 3.5%): mp 168 °C dec; FAB-MS m/z 489 $(M + H)^+$; ^{1}H NMR (CD_3OD) (J in hertz) δ 3.30−3.55 (m, 2H), 3.71 (m, 1H), 3.83 (m, 1H), 4.50 (m, 1H), 5.54 (m, 1H), 6.63 (d, J = 10, 2H), 7.18 (m, 2H), 7.55 (d, J = 10, 2H), 7.61 (m, 1H), 7.75 (s, 1H), 8.18 (s, 1H). Anal. ($C_{26}H_{20}N_2O_8$·1.4TFA) C, H, N.

General Synthesis Method A: Alternative Bond-Forming Strategy. Benzyl 4-Bromo-3-benzyloxybenzoate (74). To a solution of 4-bromo-3-hydroxybenzoic acid (16.7 g, 76.7 mmol, prepared by bromination of 3-hydroxybenzoic acid as described by Buehler and co-workers[35]) in anhydrous DMF (260 mL) under nitrogen was added anhydrous K_2CO_3 (23.5 g, 169 mmol) followed by the dropwise addition of benzyl bromide (22.8 mL, 192 mmol). The reaction mixture was allowed to stir at room temperature for 72 h. The mixture was quenched by the dropwise addition of water and filtered to provide the title compound as a white solid (30.5 g, 100%): mp 79−8 °C; ^{1}H NMR ($CDCl_3$) δ 5.21 (s, 2H), 5.37 (s, 2H), 7.30−7.60 (m, 13H). Anal. ($C_{21}H_{17}O_3$) C, H.

4-Bromo-3-benzyloxybenzoic Acid (75). To a suspension of **74** (30.4 g, 76.7 mmol) in methanol (400 mL) was added 2 N NaOH (58 mL, 114 mmol), and the reaction mixture was heated at 60 °C for 4 h. After being stirred overnight at room temperature, the reaction mixture was acidified with 6 N HCl (20 mL), and the suspension was allowed to stir overnight. The solid was collected by filtration and washed with water. Drying overnight in a vacuum oven at 10 °C provided the title compound as a white solid (22.9 g, 97%): ^{1}H NMR (DMSO-d_6) (J in hertz) δ 5.30 (s, 2H), 7.30−7.55 (m, 6H), 7.65 (d, 1H, J = 2), 7.74 (d, 1H, J = 8).

4-Bromo-3-benzyloxybenzoic Acid 1,1-Dimethylethyl Ester (76). To a solution of **75** (22.9 g, 74.7 mmol) in anhydrous DMF (500 mL) under nitrogen was added CDI (18.2 g, 112 mmol), and the reaction mixture was heated at 40 °C for 3 h. After the addition of *tert*-butyl alcohol (14.1 mL, 149 mmol) and DBU (11.2 mL, 74.7 mmol), the reaction mixture was heated at 55 °C for 40 h. The reaction mixture was quenched by the dropwise addition of water (150 mL). The solid was collected by filtration and washed with water. Drying overnight in a vacuum oven at 55 °C provided the title

compound as a white solid (22.3 g, 82%): ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 9H), 5.21 (s, 2H), 7.31−7.52 (m, 5H), 7.57−7.59 (m, 2H), 7.61 (s, 1H).

4-*tert*-Butyloxycarbonyl-2-benzyloxybenzoic Acid (77). To a solution of **76** (19.0 g, 52.3 mmol) in anhydrous THF (500 mL) under nitrogen with an internal temperature of −74 °C was added butyllithium (39.2 mL, 62.8 mmol) dropwise over 20 min (the internal temperature was not allowed to rise above −72 °C). Carbon dioxide (23.0 g, 523 mmol) was bubbled into the reaction mixture over 20 min. The reaction mixture was quenched by the dropwise addition of saturated NH_4Cl (5 mL), and was allowed to stir while being warmed to room temperature overnight. The reaction mixture was diluted with distilled water and extracted three times with EtOAc. The combined EtOAc layers were washed with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography on silica gel eluting with a gradient from 2/98 to 5/95 methanol−chloroform provided the partially purified title compound as a white solid (7.12 g, 42%) which was used as is in the next step. An analytical sample was prepared by radial chromatography (silica gel, 100/1 chloroform−methanol): mp 114−117 °C; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.61 (s, 9H), 5.35 (s, 2H), 7.40−7.48 (m, 5H), 7.71 (d, 1H *J* = 8), 7.71 (d, 1H, *J* = 8), 7.77 (s, 1H), 8.23 (d, 1H, *J* = 8). Anal. ($C_{19}H_{20}O_5$) C, H.

1,1-Dimethylethyl 3-Benzyloxy-4-[6-benzyloxy-2-(1,3-dioxan-2-yl)benzoyl]benzoate (78). To a solution of **77** (2.03 g, 6.17 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen at 0 °C was added oxalyl chloride (6.13 mL, 10.4 mmol, 2 M in CH_2Cl_2) dropwise over 10 min followed by anhydrous DMF (5 drops). The reaction mixture was allowed to stir while being warmed to room temperature overnight. The volatiles were removed under reduced pressure, and the residual solid was dried under full vacuum at room temperature overnight.

To a solution of 2-[2-(bromo-3-(benzyloxy)phenyl)]-1,3-dioxane (**79**) (2.37 g, 6.79 mmol) in anhydrous THF (125 mL) under nitrogen with an internal temperature of −68 °C was added butyllithium (4.63 mL, 7.40 mmol) dropwise over 5 min (the internal temperature was not allowed to rise above − 68 °C). A solution of the above generated acid chloride in anhydrous THF (30 mL) was added dropwise over 15 min (the internal temperature was not allowed to rise above −68 °C), and the reaction mixture was allowed to stir for 3 h. The reaction mixture was quenched by the dropwise addition of saturated NH_4Cl (4 mL) at −68 °C and allowed to stir while being warmed to room temperature overnight. The reaction mixture was diluted with EtOAc and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography on silica gel eluting with 1/9 EtOAc−hexanes provided the title compound as a white solid (1.31 g, 37%): mp 42−45 °C; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.32 (d, 1H, *J* = 12), 1.61 (s, 9H), 2.02−2.18 (m, 1H), 3.78 (dt, 2H, *J* = 12, *J* = 2.5), 4.08 (dd, 2H, *J* = 5, *J* = 12), 4.80 (s, 2H), 4.88 (s, 2 H), 5.62 (s, 1 H), 6.82 (dd, 1H, *J* = 7, *J* = 3), 6.92 (d, 2H, *J* = 7), 7.10−7.35 (m, 10H), 7.52−7.57 (m, 2H), 7.69 (d, 1H, *J* = 8). Anal. ($C_{36}H_{36}O_7 \cdot 0.25H_2O$) C, H.

3-Benzyloxy-4-[6-benzyloxy-2-(1,3-dioxan-2-yl)benzoyl]-benzoic Acid (80). To a solution of **78** (1.30 g, 2.23 mmol) in methanol (45 mL) was added 1 N NaOH (4.43 mL, 4.43 mmol), and the reaction mixture was heated at 60 °C for 72 h. The reaction mixture was acidified with 1 N HCl (4.4 mL), and the suspension was allowed to stir overnight. The solid was collected by filtration to provide the title compound as a white solid (636 mg). The volatiles were removed from the filtrate. The residue was dissolved in EtOAc and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude product was purified by chromatography on silica gel eluting with 2/98 to 1/9 methanol−chloroform to provide an additional 323 mg of the title compound (959 mg, 89%): mp 146−148 °C; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.32 (d, 1H, *J* = 12), 2.02−2.19 (m, 1H), 3.79 (dt, 2H, *J* = 12, *J* = 2.5), 4.09 (dd, 2H, *J* = 5, *J* = 12), 4.71 (s, 2H), 4.88 (s, 2H), 5.66 (s, 1H), 6.82−6.87 (m, 1H), 6.90 (d, 2H, *J* = 8), 7.11−7.35 (m, 10 H), 7.62 (d, 1H, *J* = 1), 7.68 (dd, 1H, *J* = 1.5, *J* = 9), 7.72 (t, 1H, *J* = 8). Anal. ($C_{32}H_{28}O_7$) C, H.

***trans*-1-[4-(2-Carboxy-6-benzyloxybenzoyl)-3-benzyloxybenzoyloxy]-3-(4-benzyloxybenzamido)cyclopentane (81).** To a solution of **80** (903 mg, 1.72 mmol) in anhydrous DMF (13 mL) under nitrogen was added CDI (349 mg, 2.15 mmol), and the reaction mixture was allowed to stir for 3 h at room temperature. After the addition of *trans*-2-(4-benzyloxybenzamido)-1-hydroxycyclopentane (**6**) (589 mg, 1.89 mmol) and DBU (325 mL, 1.89 mmol), the reaction mixture was allowed to stir for 48 h at room temperature. The reaction mixture was diluted with EtOAc and washed five times with distilled water and once with brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography on silica gel eluting with 1/1 EtOAc−hexanes provided the ester as a partially purified white solid (1.06 g, 75%) which was used as is in the next step. An analytical sample was prepared by radial chromatography on silica gel eluting with 3/2 EtOAc−hexane: mp 80−83 °C. Anal. ($C_{51}H_{47}NO_9 \cdot 0.5H_2O$) C, H.

To a solution of the above acetal (1.01 g, 1.24 mmol) in 45 mL of HPLC grade acetone was added 2.5% HCl (30 drops), and the reaction mixture was allowed to stir for 96 h at room temperature. The reaction mixture was neutralized with 1 N NaOH (20 drops), and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed twice with water and with brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography on silica gel eluting with 80/1 to 60/1 CH_2Cl_2−acetone provided the aldehyde as a partially purified white solid (776 mg, 82%). This material was used as is in the next step.

To a solution of the above aldehyde (772 mg, 1.02 mmol) in acetonitrile (300 mL) was added rapidly dropwise a solution of $NaClO_2$ (154 mg, 1.36 mmol) in water (15.5 mL) followed by a solution of sulfamic acid (132 mg, 1.36 mmol) in water (15.5 mL). The reaction mixture was allowed to stir for 1 h at room temperature, after which the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography on silica gel eluting with 98/2 to 80/20 chloroform−methanol provided the title compound as a white solid (656 mg, 85%): mp 106−109 °C; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.64−1.96 (m, 4H), 2.17−2.34 (m, 2H), 4.53−4.64 (m, 1H), 4.76 (s, 2H), 4.92 (s 2H), 5.11 (s, 2H), 5.33 (ddd, 1H, *J* = 6), 6.81−7.45 (m, 19H), 7.59−7.67 (m, 2H), 7.79 (d, 2H, *J* = 9), 8.01 (d, 1H, *J* = 7), 8.41 (d, 1H, *J* = 8.5). Anal. ($C_{48}H_{41}NO_9$) C, H, N.

***trans*-1-[4-(2-Carboxy-6-hydroxybenzoyl)-3-hydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (16).** To a solution of **81** (220 mg, 0.283 mmol) in 2/1 ethanol−EtOAc (30 mL) under nitrogen was added trifluoroacetic acid (45 μL, 0.57 mmol) followed by $Pd(OH)_2$ (88 mg, 20% on carbon). The solution was placed under H_2 (1 atm) overnight. The reaction mixture was filtered, and the volatiles were removed from the filtrate under reduced pressure. The product was chromatographed on a Dynamax-60 C_{18} column (41 mm i.d. × 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 min at 25 mL/min. The product eluted in 57 min. Removal of the volatiles under reduced pressure provided the title compound as an off-white solid (120 mg, 82%): mp 160 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.66−1.96 (m, 4 H), 2.18−2.31 (m, 2H), 4.47−4.56 (m, 1 H), 5.29−5.38 (m, 1 H), 6.80 (d 2H, *J* = 9), 7.15 (d, 1H, *J* = 8), 7.27 (d, 1H, *J* = 8), 7.40 (dd, 1H, *J* = 8, *J* = 2), 7.45 (dd, 1H, *J* = 1, *J* = 8), 7.57 (d, 1H, *J* = 2), 7.61 (d, 1H, *J* = 8), 7.69 (d, 2H, *J* = 9); FAB-MS *m*/*z* 506 (M + H)$^+$. Anal. ($C_{27}H_{23}NO_9 \cdot H_2O$) C, H, N.

***trans*-1-[4-(2-Carboxy-6-hydroxybenzoyl)benzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (17).** The benzophenone acid analogue required for the title compound was prepared in 20% overall yield from 1,1-dimethylethyl 4-bro-

mobenzoate and 2-(3-benzyloxy-2-formylphenyl)-1,3-dioxane[8c] (**82**) using general method B with MnO_2 as the oxidant followed by formic acid cleavage of the *tert*-butyl ester. The dioxane in this example was converted to the carboxylic acid as described for compound **16**. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a white fluffy solid (90 mg, 34%): mp 158−172 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.75 (m, 1H), 1.88 (m, 3H), 2.25 (m, 1H), 4.54 (m, 1H), 5.37 (m, 1H), 6.80 (d, $J = 9$, 2H), 7.13 (d, $J = 8$, 1H), 7.43 (t, $J = 8$, 1H), 7.59 (d, $J = 8$, 1H), 7.69 (d, $J = 9$, 2H), 7.82 (d, $J = 8$, 2H), 8.08 (d, $J = 8$, 2H), 8.32 (d, $J = 8$, 1H); FAB-MS *m*/*z* 490 (M + H). Anal. ($C_{27}H_{23}NO_8 \cdot 1.5H_2O$) C, H, N. *trans*-1-[4-(4-Hydroxy-3- phthalido)benzoyloxy]-2-(4-hydroxybenzamido)cyclopentane was also isolated by HPLC as a side product from the above reaction as 47 mg (18%) of a white solid: mp 150−160 °C; FAB-MS *m*/*z* 474 (M + H). Anal. ($C_{27}H_{23}NO_7 \cdot 2H_2O \cdot 0.1$TFA) C, H, N.

(−)-(1*R*,2*R*)-1-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dimethylbenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (18). The benzophenone acid analogue 4-[6-benzyloxy-2-(1,3-dioxane-2-yl)benzoyl]-3,5-dimethylbenzoic acid required for the title compound was prepared in 33% overall yield from 4-bromo-3,5-dimethylbenzoic acid 1,1-dimethylethyl ester and **82** using general method B with MnO_2 as the oxidant followed by cleavage of the *tert*-butyl ester with NaOH. Standard coupling of the acid to (−)-(1*R*,2*R*)-1-hydroxy-2-(4-benzyloxybenzamido)cyclopentane ((−)-**6**) by way of the acyl imidazole followed by conversion of the dioxane to the carboxylic acid as described for compound **16** and deprotection afforded the title compound as an off-white solid (81 mg, 3%): mp 162−165 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.96−1.66 (m, 4H), 2.21 (s, 6H), 2.32−2.21 (m, 2H), 4.58−4.51 (m, 1H), 5.37−5.32 (m, 1H), 6.82 (d, 2H, $J = 9$ Hz), 7.05 (d, 1H, $J = 9$ Hz), 7.08 (d, 1H, $J = 7.5$ Hz), 7.50 (dd, 1H, $J = 9$ Hz, $J = 7.5$ Hz), 7.66 (s, 2H), 7.70 (d, 2H, $J = 9$ Hz); FAB-MS *m*/*z* 518 $(M + H)^+$; $[\alpha]^{25}_D$ −162° ($c = 0.10$, EtOH). Anal. ($C_{29}H_{27}NO_8 \cdot 1.25H_2O$) C, H, N.

trans-4-[4-(2,6-Dihydroxybenzoyl)-3,5-dimethoxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (19). The benzophenone acid analogue required for the title compound was prepared in 12% overall yield from 4-bromo-3,5-dimethoxybenzoic acid using general method B followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (37 mg, 41%): mp 168 °C; ^{1}H NMR (DMSO-d_6) (*J* in hertz) δ 1.20−1.64 (m, 2H), 1.66−1.96 (m, 2H), 2.49−2.97 (m, 4H), 3.67 (s, 6H), 4.33−4.37 (q, $J = 9.3$, 1H), 5.03−5.05 (m, 1H), 6.23 (d, $J = 8.2$, 2H), 6.75 (d, $J = 8.5$, 2H), 7.15 (s, 2H), 7.23−7.29 (t, $J = 8.2$, 1H), 7.65 (d, $J = 8.7$, 2H), 8.20 (d, $J = 8.7$, 1H), 9.95 (br s, 1H). Anal. ($C_{29}H_{30}N_2O_9 \cdot 1.5H_2O$) C, H, N.

4-Methoxymethyleneoxybenzoic Acid (83). To a solution of the 4-hydroxybenzoic acid (10.0 g, 0.072 mol) in CH_2Cl_2 (20 mL) under nitrogen at 0 °C was added *N*,*N*-diisopropylethylamine (69.11 mL, 0.394 mol) followed by the dropwise addition of chloromethyl methyl ether (30 mL, 0.394 mol) over 1 h. The reaction mixture was allowed to stir at room temperature for 48 h. The reaction mixture was quenched with saturated NH_4Cl (100 mL) and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$, and the volatiles were removed under reduced pressure to provide the intermediate ether ester.

To a solution of this crude ester in methanol (100 mL) was added 15% NaOH (80 mL), and the mixture was heated at 70 °C for 3 h. The reaction mixture was cooled to 0 °C, and the pH was adjusted to 5 with 6 N HCl. Filtration of the reaction mixture provided the title compound as a white solid (11.1 g). Extraction of the aqueous phase with EtOAc provided an additional 1.1 g of the title compound (12.2 g, 98%): ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 3.50 (s, 3 H), 5.26 (s, 2 H), 7.10 (d, 2 H, $J = 9$), 8.08 (d, 2 H, $J = 9$).

1-Hydroxy-2-(4-methoxymethyleneoxybenzamido)-cyclopentane (46). To a suspension of NaH (876 mg, 21.9 mmol, 60% by weight in mineral oil) in anhydrous THF (45 mL) under nitrogen at 0 °C was added a solution of **83** (3.63 g, 19.9 mmol) in anhydrous THF dropwise over 20 min. The ice bath was removed, and the reaction mixture was allowed to stir for 0.5 h at room temperature. The reaction mixture was recooled to 0 °C, and oxalyl chloride (11.0 mL, 21.9 mmol, 2 M in CH_2Cl_2) was added dropwise over 15 min. The reaction mixture was allowed to stir for 24 h, and the volatiles were removed under reduced pressure.

A suspension of cyclopentene oxide (1.89 mL, 21.6 mmol) in concentrated NH_4OH (9 mL) was heated at 65 °C for 3 h. The reaction mixture was cooled to room temperature, and 1 N NaOH (30 mL, 30 mmol) was added. The reaction mixture was allowed to stir at room temperature while nitrogen was bubbled into the solution (to remove ammonia) for 0.5 h. The reaction mixture was cooled to 0 °C, and a solution of the above generated acid chloride in CH_2Cl_2 (40 mL) was added. The reaction mixture was allowed to stir overnight at room temperature, after which it was cooled to 0 °C and neutralized with 1 N HCl. EtOAc (300 mL) was added, and the layers were separated. The EtOAc layer was washed with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography on silica gel eluting with 98/2 chloroform−methanol provided the title compound as a white solid (1.66 g, 31%): mp 91−92 °C.

***trans*-1-[4-[2-(1,3-Dioxan-2-yl)-6-methoxymethyleneoxybenzoyl]-3,5-bis(methoxymethyleneoxy)benzyloxy]-2-(4-methoxymethyleneoxybenzamido)cyclopentane (47).** To a solution of 2′-(1,3-dioxan-2-yl)-6′-methoxymethyleneoxy-2,6-bis(methoxymethyleneoxy)-4-(1,1-dimethylethylsilyloxymethyl)benzophenone (858 mg, 1.45 mmol, prepared according to ref 8c) in anhydrous THF (10 mL) under nitrogen was added tetrabutylammonium fluoride (2.89 mL, 2.89 mmol, 1 M in THF) dropwise over 5 min. The reaction mixture was allowed to stir for 2 h at room temperature, then diluted with EtOAc (150 mL), and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with 3/1 EtOAc−hexanes to provide the alcohol **45** as a viscous oil (625 mg, 90%). Anal. ($C_{24}H_{30}O_{10}$) C, H.

To a solution of the above alcohol (560 mg, 1.17 mmol) in anhydrous CH_2Cl_2 (15 mL) under nitrogen at 0 °C were added triethylamine (326 μL, 2.34 mmol) and methanesulfonyl chloride (100 μL, 1.29 mmol) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature while being stirred for 1 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. To a solution of this crude mesylate product in HPLC grade acetone (20 mL) was added sodium iodide (523 mg, 3.51 mmol) under nitrogen, and the reaction mixture was allowed to stir for 2.5 h at room temperature. The reaction mixture was diluted with EtOAc (150 mL) and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure.

To a suspension of sodium hydride (140 mg, 3.51 mmol, 60% in mineral oil) in freshly distilled anhydrous THF (5 mL) under nitrogen at 0 °C was added a solution of **46** (330 mg, 1.24 mmol) in freshly distilled anhydrous THF (20 mL) dropwise over 15 min. The reaction mixture was allowed to stir while being warmed to room temperature over 1.5 h, during which time the reaction became a nearly clear homogeneous solution. A solution of the above generated iodide in freshly distilled anhydrous THF (20 mL) was added dropwise over 20 min. The reaction mixture was allowed to stir for 3 h at room temperature. The reaction mixture was recooled to 0 °C and quenched with saturated NH_4Cl (10 mL). The reaction mixture was diluted with EtOAc (250 mL) and washed with distilled water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude product was purified by chromatography on silica gel eluting with 99/1 chloroform−methanol to provide the title compound

as a white solid (604 mg, 71%): mp 43−46 °C. Anal. ($C_{38}H_{47}NO_{13}$·0.5H_2O) C, H, N.

***trans*-1-[4-(2-Formyl-6-methoxymethyleneoxybenzoyl)-3,5-bis(methoxymethyleneoxy)benzyloxy]-2-(4-methoxymethyleneoxybenzamido)cyclopentane (84).** To a suspension of silica gel (1.03 g) in CH_2Cl_2 (1.40 mL) was added 2.5% H_2SO_4 (103 mg). The reaction mixture was allowed to stir until the lower layer disappeared. Compound **47** (345 mg, 0.477 mmol) in CH_2Cl_2 (10 mL) was added, and the reaction mixture was allowed to stir overnight. The mixture was quenched with 1 N NaOH (50 μL) and filtered. The volatiles were removed under reduced pressure to provide a crude mixture of the aldehydes with partial removal of the methoxymethyl protecting groups.

To a solution of the above crude aldehydes in acetonitrile (20 mL) under nitrogen at 0 °C was added *N*,*N*-diisopropylethylamine (166 μL, 0.954 mmol) followed by the dropwise addition of chloromethyl methyl ether (72 μL, 0.954 mmol) over 10 min. The reaction mixture was allowed to stir at room temperature for 48 h, during which time additional diisopropylethylamine (966 μL, 5.72 mmol) and chloromethyl methyl ether (432 μL, 5.72 mmol) were added in six portions. The reaction mixture was diluted with EtOAc (75 mL) and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography of the residue on silica gel eluting with 100/1 chloroform−methanol followed by radial chromatography on silica gel eluting with 200/1 chloroform−methanol afforded the title compound as a viscous oil (206 mg, 65%). Anal. ($C_{35}H_{41}NO_{12}$) C, H, N.

***trans*-1-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzyloxy]-2-(4-hydroxybenzamido)cyclopentane (20).** To a solution of **84** (142 mg, 0.213 mmol) in acetonitrile (50 mL) was added a solution of sulfamic acid (28 mg, 0.285 mmol) in water (3 mL) dropwise over 5 min followed by the dropwise addition of a solution of $NaClO_2$ (32 mg, 0.285 mmol) in water (3 mL) over 5 min. After the reaction mixture was allowed to stir for 0.5 h at room temperature, the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (175 mL) and washed with water and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure.

To a solution of the crude carboxylic acid (90 mg, 0.132 mmol) in methanol (12 mL) was added concentrated HCl (30 drops) at room temperature, and the reaction mixture was allowed to stir for 5 h. The volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax-60 C_{18} column (21 mm i.d. × 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 min at 15 mL/min. The product eluted in 23 min. Removal of the volatiles under reduced pressure provided the title compound as a white solid (60 mg, 88%): mp 161−164 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.63−1.51 (m, 1H), 1.84−1.68 (m, 3H), 2.02−1.92 (m, 1H), 2.21−2.08 (m, 1H), 3.96−3.90 (m, 1H), 4.38−4.30 (m, 1H), 4.49 (ABq, 2H, $\Delta\gamma_{AB}$ = 18 Hz, *J* = 13.5 Hz), 6.28 (s, 2H), 6.80 (d, 2H, *J* = 9 Hz), 7.00 (d, 1H, *J* = 8 Hz), 7.24 (dd, 1H, *J* = 8 Hz, *J* = 8 Hz), 7.48 (d, 1H, *J* = 8 Hz), 7.68 (d, 2H, *J* = 9 Hz); FAB-MS *m*/*z* 508 $(M + H)^+$. Anal. ($C_{27}H_{25}NO_9$·0.5H_2O) C, H, N.

General Synthesis Method D. 1,1-Dimethylethyl 4-[*N*-(2-Benzyloxycarbonylphenyl)aminocarbonyl]-3,5-dibenzyloxybenzoate (58). A solution of 1.00 g (2.30 mmol) of 2,6-dibenzyloxy-4-(1,1-dimethylethoxycarbonyl)benzoic acid (**57**) in 25 mL of CH_2Cl_2 containing 6.4 μL of DMF was cooled to 0 °C. A 2.0 M solution of oxalyl chloride (1.73 mL, 3.46 mmol) was added, and the mixture was stirred under nitrogen at room temperature for 3 h. The reaction mixture was evaporated, and the residue was evaporated twice from 15 mL of CH_2Cl_2. The residue was dissolved in 20 mL of CH_2Cl_2, and 523 mg (2.30 mmol) of benzyl anthranilate, 481 μL (2.76 mmol) of diisopropylethylamine, and 14 mg of DMAP were added at 0 °C. The mixture was stirred at room temperature under nitrogen for 4 days, after which it was diluted with 200 mL of ether, washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give 1.47 g of the crude product. Chromatography on silica gel eluting with 4/1 hexanes−EtOAc gave 830 mg (56%) of the title compound as a yellow oil, which was taken directly to the next step.

***trans*-4-[4-[*N*-(2-Carboxyphenyl)aminocarbonyl]-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)pyrrolidine (21).** The benzophenone acid analogue required for the title compound was prepared in 89% yield from **58** by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **5** by way of the acid chloride followed by deprotection afforded the title compound as a white fluffy solid (120 mg, 34%): mp 210 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 3.63 (m, 2H), 3.88 (dd, *J* = 7, 12, 1H), 4.01 (dd, *J* = 6, 13, 1H), 4.65 (m, 1H), 5.66 (m, 1H), 6.87 (d, *J* = 9, 2H), 7.11 (s, 2H), 7.25 (t, *J* = 8, 1H), 7.61 (t, *J* = 7, 1H), 7.78 (d, *J* = 9, 2H), 8.10 (d, *J* = 6, 1H), 8.59 (d, *J* = 8, 1H); FAB-MS *m*/*z* 522 (M + H). Anal. ($C_{26}H_{23}N_3O_9$·3.5H_2O·TFA) C, H, N.

***trans*-4-[4-[*N*-(Carboxymethyl)-*N*-phenylaminocarbonyl]-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-pyrrolidine (22).** The benzophenone acid analogue required for the title compound was prepared in 50% overall yield from benzyl *N*-phenylglycinate toluenesulfonic acid salt using general method D followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **5** by way of the acid chloride followed by deprotection afforded the title compound as a white fluffy solid (140 mg, 41%): mp 180 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 3.53 (m, 2H), 3.78 (dd, *J* = 7, 12, 1H), 3.89 (dd, *J* = 6, 13, 1H), 4.57 (m, 3H), 5.50 (m, 1H), 6.80−6.85 (m, 4H), 7.16 (m, 3H), 7.40 (m, 2H), 7.73 (d, *J* = 9, 2H); FAB-MS *m*/*z* 536 (M + H). Anal. ($C_{27}H_{25}N_3O_9$·2.5H_2O·TFA) C, H, N.

General Synthesis Method E. 2,6-Dibenzyloxy-4-(1,1-dimethylethoxycarbonyl)phenylboronic Acid (59). To a solution of 10 g (21.3 mmol) of **49** in 60 mL of dry THF at −78 °C under nitrogen was added dropwise 8.5 mL (21.3 mmol) of a 2 M solution of butyllithium in hexanes. The purple solution was stirred for 15 min, after which a solution of trimethylborate (9.5 mL, 83.6 mmol) in 30 mL of THF was added as a steady stream. The now yellow solution was allowed to warm slowly to room temperature and stir for 16 h. A 5% HCl solution was added via pipet until a precipitate was formed and dissolved. The solution was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Chromatography on silica gel eluting with 7/1 hexanes−EtOAc afforded 3.5 g (38%) of the title compound.

1,1-Dimethylethyl 4-[2-(Benzyloxycarbonyl)phenyl]-3,5-dibenzyloxybenzoate (60). To a solution of benzyl 2-bromobenzoate (0.3 g, 1.1 mmol), tetrakis(triphenylphosphine)-palladium (39 mg, 0.03 mmol), and Na_2CO_3 (0.6 mL, 1.1 mmol, 2 M solution) in 5 mL of dioxane was added a solution of **59** (1.0 g, 2.3 mmol) in 10 mL of dioxane. The yellow solution was refluxed for 60 h. Water was added (25 mL), and the product was extracted into EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Chromatography on silica gel eluting with 16/1 hexanes−EtOAc gave 0.73 g (57%) of the title compound.

***trans*-4-[4-(2-Carboxyphenyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)pyrrolidine (23).** The benzophenone acid analogue required for the title compound was prepared in 80% yield from **60** by formic acid cleavage of the *tert*-butyl ester. The crude product was used in a standard coupling of the acid to **5** by way of the acid chloride followed by deprotection to afford the title compound as a white solid (58 mg, 12%): mp 197−198 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 3.45 (m, 2H), 3.70 (dd, *J* = 7, 12, 1H), 3.80 (dd, *J* = 6, 13, 1H), 4.49 (m, 1H), 5.51 (m, 1H), 6.64 (d, *J* = 9, 2H), 7.30 (s, 1H), 7.36 (s, 1H), 7.48 (t, *J* = 7, 1H), 7.57 (d, *J* = 9, 2H), 7.68 (t, *J* = 8, 1H), 8.18 (d, *J* = 8, 1H), 9.06 (d, *J* = 7, 1H). Anal. ($C_{25}H_{22}N_2O_8$·1.5H_2O·TFA) C, H, N.

***trans*-1-Benzyloxycarbonyl-4-(4-iodobenzoyloxy)-3-(4-benzyloxybenzamido)pyrrolidine (85).** To a suspension of **5** (1 g, 2.24 mmol) and diisopropylethylamine (0.89 g, 6.72

mmol) in 20 mL of CH_2Cl_2 were added 4-iodobenzoyl chloride (0.6 g, 2.24 mmol) and dimethylaminopyrridine (0.4 g, 3.36 mmol), and the suspension was stirred at room temperature under nitrogen for 16 h. The clear solution was washed with water, 5% HCl, and brine, dried ($MgSO_4$), and concentrated to a white semisolid. Chromatography on silica gel eluting with 2/1 hexanes−EtOAc afforded the title compound (1.23 g, 87%).

2-(Hydroxymethyl)-6-benzyloxyphenylboronic Acid Cyclic Monoester (86). To a solution of 3-benzyloxybenzyl alcohol (10 g, 46.9 mmol) in 70 mL of THF under nitrogen at −78 °C was added dropwise butyllithium (37.5 mL of a 2 M solution in hexanes, 94 mmol). The solution was stirred for 7 h at −20 °C, after which it was cooled to −78 °C, and a solution of trimethylborate (21 mL, 188 mmol) in 30 mL of THF was added to the mixture as a steady stream. The solution was allowed to warm slowly to room temperature and was stirred for 18 h. A 5% HCl solution was added via pipet until a precipitate formed and redissolved. The solution was extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Chromatography on silica gel eluting with 7/1 hexanes−EtOAc gave the title compound (7.2 g, 64%).

***trans*-1-Benzyloxycarbonyl-4-[4-[2-benzyloxy-6-(hydroxymethyl)phenyl]benzoyloxy]-3-(4-benzyloxybenzamido)pyrrolidine (87).** To a solution of **85** (0.35 g, 0.6 mmol), tetrakis(triphenylphosphine)palladium (6 mg, 0.02 mmol), and Na_2CO_3 (0.3 mL, 0.6 mmol, 2 M solution) in 5 mL of dioxane was added a solution of **86** (0.15 g, 0.6 mmol) in 10 mL of dioxane. The yellow solution was heated at reflux for 24 h. Water was added (25 mL), and the product was extracted into EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to a yellow oil. The crude product was purified by chromatography on silica gel eluting with 2/1 hexanes−EtOAc to give 0.45 g (93%) of the title compound.

***trans*-1-Benzyloxycarbonyl-4-[4-(2-benzyloxy-6-formylphenyl)benzoyloxy]-3-(4-benzyloxybenzamido)pyrrolidine (88).** To a cooled solution of **87** (61 mg, 0.080 mmol) in 5 mL of CH_2Cl_2 and 1 mL of THF were added sodium bromide (5 mg, 0.05 mmol), TEMPO (5 mg, 0.03 mmol), and a solution of $NaHCO_3$ (5 mg, 0.06 mmol) in Clorox (2 mL). The biphasic solution was stirred for 15 min under nitrogen, at which time additional CH_2Cl_2 and water were added. The organic layer was collected, washed with water and brine, dried ($MgSO_4$), and concentrated to afford the title compound in quantitative yield.

***trans*-1-Benzyloxycarbonyl-4-[4-(2-benzyloxy-6-carboxyphenyl)benzoyloxy]-3-(4-benzyloxybenzamido)pyrrolidine (89).** To a solution of **88** (61 mg, 0.080 mmol) in 4 mL of acetonitrile was added dropwise a solution of sulfamic acid (15 mg, 0.15 mmol) in water (0.92 mL), followed by the addition of a solution of $NaClO_2$ (15 mg, 0.13 mmol) in water (2 mL). The solution was stirred at room temperature under a nitrogen atmosphere for 30 min. Additional EtOAc and water were added, and the organic was collected, washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the title compound in quantitative yield.

***trans*-4-[4-(6-carboxy-2-hydroxyphenyl)benzoyloxy]-3-(4-hydroxybenzamido)pyrrolidine (24).** To a suspension of **89** (0.4 g, 0.49 mmol) in 10 mL of 1/1 methanol−THF was added $Pd(OH)_2$ (0.3 g, 0.4 mmol). The apparatus was deoxygenated and flooded with hydrogen under balloon pressure. The suspension was stirred at room temperature for 16 h. The catalyst was filtered and washed with methanol. The solution was concentrated and dissolved in CH_2Cl_2 (5 mL), and trifluoroacetic acid (0.5 mL) was added. The solution was stirred for 3 min, concentrated, and then evaporated twice from CH_2Cl_2. The title product was obtained as a white solid (79 mg, 37%) after purification by HPLC (41 × 300 mm C_{18} column, gradient 5% acetonitrile and 0.1% trifluoroacetic acid to 100% acetonitrile, 0−100% over 60 min, 25 mL/min): mp 137−138 °C dec; ^{1}H NMR (CD_3OD) δ 3.45 (m, 2H), 3.75 (br m, 2H), 5.50 (m, 1H), 6.65 (m, 2H), 6.87 (m, 1H), 7.01−7.25 (m, 4H), 7.60 (m, 2H), 7.90 (m, 2H). Anal. ($C_{25}H_{22}N_2O_7 \cdot 2H_2O \cdot$TFA) C, H, N.

General Synthesis Method H. *trans*-4-[4-(2-carboxy-6-hydroxybenzyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepine (25) and *trans*-4-[3,5-Dihydroxy-4-(4-hydroxy-3-phthlido)benzoyloxy]-3-(4-hydroxybenzamido)azepine (26). A solution of 70 mg (0.097 mmol) of balanol (**1**) in 5 mL of trifluoroacetic acid was treated with a total of 428 μL (2.79 mmol) of phenyldimethylsilane in four portions over a period of 26 days, during which time the reaction mixture was stirred at room temperature. The mixture was evaporated to a residue which was chromatographed on a 21 × 250 mm C_{18} column (solvent A 95/5 water−acetonitrile plus 0.1% TFA, solvent B 100% acetonitrile, gradient 0−50% B over 60 min, flow 15 mL/min). The fractions which contained the desired product were pooled and lyophilized to give 6.0 mg of partially purified material, which was rechromatographed as stated above, using this time a 0−25% B over 60 min gradient. The pure fractions were pooled, evaporated, and then lyophilized from water to give 1.0 mg of the title methylene compound as a tan fluffy solid: ^{1}H NMR (CD_3OD) (J in hertz) δ 2.04−2.30 (m, 4H), 3.46 (m, 2H), 4.31 (s, 2H), 4.43 (m, 1H), 5.38 (m, 1H), 6.77 (d, J = 9, 2H), 6.88 (d, J = 8, 1H), 6.95 (s, 2H), 7.10 (t, J = 8, 1H), 7.24 (d, J = 7, 1H), 7.60 (d, J = 9, 2H); FAB-MS m/z 537 (M + H); HRMS m/z calcd for $C_{28}H_{29}N_2O_9$ 537.1873, found 537.1866.

In the initial chromatography, fractions that contained the lactone product were pooled and lyophilized to give 30 mg of partially purified material. This material was also rechromatographed using a 0−25% B over 60 min gradient, and the pure fractions were pooled, evaporated, and then lyophilized from water to give 15.1 mg of the title lactone as a white fluffy solid: ^{1}H NMR (CD_3OD) (J in hertz) δ 2.02−2.20 (m, 3H), 2.26 (m, 1H), 3.47 (m, 2H), 4.48 (m, 1H), 5.39 (m, 1H), 6.78 (d, J = 9, 2H), 6.90 (br s, 2H), 6.97 (dd, J = 2, 7, 1H), 7.01 (s, 1H), 7.29−7.38 (m, 2H), 7.62 (dd, J = 4, 9, 2H); FAB-MS m/z 535 (M + H). Anal. ($C_{28}H_{26}N_2O_9 \cdot 2H_2O \cdot$TFA) C, H, N.

General Synthesis Method C. 2-(1-Bromonaphthyl)-methanol (52). To a solution of 1-bromo-2-naphthoic acid (8.00 g, 31.9 mmol) in anhydrous THF (40 mL) under nitrogen at 0 °C was added BH_3 (74 mL, 0.74 mol, 1 M in THF) dropwise over 0.5 h. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was quenched with methanol, and the volatiles were removed under reduced pressure. The reaction mixture was diluted with EtOAc (750 mL) and washed with 2.5% $NaHCO_3$. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography on silica gel eluting with chloroform provided the title compound as a white solid (7.59 g, 89%). Anal. ($C_{11}H_9BrO$) C, H.

2,6-Dibenzyloxy-4-(1,1-dimethylethoxycarbonyl)benzoic Acid 2-(1-Bromonaphthyl)methyl Ester (54). To a solution of **57**[8e] (6.38 g, 14.68 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen at 0 °C was added oxalyl chloride (11 mL, 22.0 mmol) dropwise over 15 min followed by anhydrous DMF (5 drops). The reaction mixture was allowed to stir while being warmed to room temperature over 3 h. The volatiles were removed under reduced pressure, and the resulting residue was dried under full vacuum at room temperature overnight.

To a solution of **52** (3.83 g, 16.2 mmol) and DMAP (179 mg, 1.47 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen at 0 °C was added triethylamine (6.14 mL, 44 mmol) followed by a solution of the above generated acid chloride in anhydrous CH_2Cl_2 (30 mL) over 0.5 h. The reaction mixture was allowed to stir while being warmed to room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (350 mL) and washed with water and brine. The organic layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography on silica gel eluting with 20/1 hexanes−EtOAc afforded the title compound as a white solid (4.85 g, 51%). Anal. ($C_{37}H_{33}O_6$) C, H.

3,5-Dibenzyloxy-4-[2-(hydroxymethyl)-1-naphthylcarbonyl]benzoic Acid 1,1-Dimethylethyl Ester (55). To a solution of **54** (4.65 g, 7.11 mmol) in anhydrous THF (70 mL) under nitrogen at −78 °C was added butyllithium (7.14 mL, 11.42 mmol, 1.6 M in hexanes) dropwise over 0.5 h, and the reaction mixture was allowed to stir for 2.5 h at −78 °C. The reaction mixture was quenched by the dropwise addition of

saturated NH_4Cl (2 mL) at −78 °C and was allowed to stir while being warmed to room temperature overnight. The mixture was diluted with EtOAc (500 mL) and washed with water. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure (no heat). Chromatography on silica gel eluting with 20/1 to 5/1 hexanes−EtOAc provided the title compound as a viscous oil (2.14 g, 52%).

3,5-Dibenzyloxy-4-(2-formyl-1-naphthylcarbonyl)benzoic Acid 1,1-Dimethylethyl Ester (90). To a solution of **55** (2.14 g, 3.72 mmol) in anhydrous CH_2Cl_2 (10 mL) were added water (10 mL), KBr (66 mg, 0.558 mmol), $NaHCO_3$ (625 mg, 7.44 mmol), and TEMPO (6 mg, 0.0372 mmol). The reaction mixture was cooled to 0 °C, and NaOCl (6 mL, 4.09 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir for 2 h at 0 °C. The mixture was diluted with ether and washed with water and brine, and the ether layer was dried over $MgSO_4$. The volatiles were removed under reduced pressure, and the residue was purified by chromatography on silica gel eluting with 10/1to 3/1 hexanes−EtOAc to afford the title compound as a white solid (740 mg, 35%).

3,5-Dibenzyloxy-4-(2-benzyloxycarbonyl-1-naphthylcarbonyl)benzoic Acid 1,1-Dimethylethyl Ester (56). To a solution of **90** (720 mg, 1.26 mmol) in acetonitrile (300 mL) was added a solution of sulfamic acid (171 mg, 1.76 mmol) in water (6 mL) dropwise over 5 min at room temperature followed by the dropwise addition of a solution of $NaClO_2$ (207 mg, 1.83 mmol) in distilled water (6 mL) over 10 min. The reaction mixture was allowed to stir for 1 h at room temperature, quenched with water (30 mL), and allowed to stir for 10 min before the volatiles were removed under reduced pressure. The residue was diluted with EtOAc (400 mL) and washed twice with water. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure, which provided the carboxylic acid as a white solid (730 mg, 99%).

To a solution of the above carboxylic acid (500 mg, 0.849 mmol) in anhydrous DMF under nitrogen at room temperature was added anhydrous K_2CO_3 (236 mg, 1.70 mmol) followed by the dropwise addition of benzyl bromide (121 μL, 1.02 mmol) over 3 min. The reaction mixture was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc (125 mL) and washed with water, 1 N HCl, and brine. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Chromatography of the crude product on silica gel eluting with 20/1 to 10/1 hexanes−EtOAc provided the title compound as a white solid (422 mg, 73%). Anal. ($C_{44}H_{38}O_7$) C, H.

3,5-Dibenzyloxy-4-(2-benzyloxycarbonyl-1-naphthylcarbonyl)benzoic Acid (91). A solution of **56** (345 mg, 0.508 mmol) in quinoline (3.5 mL) under nitrogen was heated at 205 °C for 3 h. The reaction mixture was diluted with EtOAc (125 mL) and washed with 1 N HCl. The EtOAc layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax-60 C_{18} column (41 mm i.d. × 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 min at 25 mL/min. The product eluted in 61 min (in pure acetonitrile). Trituration of the chromatographed product with methanol afforded the title compound as a white solid (170 mg, 54%): mp 157−159 °C. Anal. ($C_{40}H_{30}O_7 \cdot 0.25H_2O$) C, H.

***trans*-3-(4-Hydroxybenzamido)-4-[3,5-dihydroxy-4-(2-carboxy-1-naphthylcarbonyl)benzoyloxy]pyrrolidine (27).** Standard coupling of **91** to **5** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (60 mg, 32%): mp 192−195 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 3.56−3.64 (m, 2H), 3.83 (dd, *J* = 7, 12, 1H), 3.96 (dd, *J* = 5.5, 13, 1H), 4.62 (m, 1H), 5.62 (m, 1H), 6.83 (d, *J* = 9, 2H), 6.98 (s, 1H), 7.46 (t, *J* = 8.5, 1H), 7.60 (m, 2H), 7.74 (d, *J* = 9, 2H), 7.96−8.07 (m, 3H); FAB-MS *m*/*z* 557 $(M + H)^+$. Anal. ($C_{30}H_{24}N_2O_9 \cdot 1.5TFA \cdot 0.5H_2O$) C, H, N.

***trans*-4-[4-(2-Hydroxy-1-naphthoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)pyrrolidine (28).** The benzophenone acid analogue required for the title compound was prepared in 28% overall yield from 2-benzyloxy-1-naphthaldehyde using general method B followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **5** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (85 mg, 58%): mp 169−172 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 3.61−3.65 (m, 2H), 3.85 (dd, *J* = 12, 7, 1H), 3.98 (dd, *J* = 13, 5, 1H), 4.70 (m, 1H), 5.63 (m, 1H), 6.84 (d, *J* = 8, 2H), 7.04 (s, 2H), 7.12 (d, *J* = 9, 1H), 7.25−7.28 (m, 2H), 7.58 (m, 1H), 7.75 (m, 1H), 7.77 (d, *J* = 8, 2H), 7.84 (d, *J* = 9, 1H). Anal. ($C_{29}H_{24}N_2O_8 \cdot 1.2TFA$) C, H, N.

***trans*-4-[4-(2-Hydroxy-5,6,7,8-tetrahydro-1-naphthoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)pyrrolidine (30).** Standard coupling of the required benzophenone acid analogue to *trans*-1-(1,1-dimethylethoxycarbonyl)-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine (**92**) in a fashion similar to that described for compound **28** gave the coupled fully protected product in 68% yield. Deprotection by hydrogenolysis at 52 psi for 24 h followed by treatment with HCl in dioxane afforded a mixture of the title compound and compound **28** as a yellow solid (1.05 g, 59%). Reversed-phase chromatography of 50 mg of the mixture on a Dynamax-60 C_{18} column (41 mm i.d. × 25 cm length) using a linear gradient from 90% to 70% A (solvent A 0.1% TFA and 5% acetonitrile in water, solvent B pure acetonitrile) over 90 min at 25 mL/min afforded 38 mg of **28** and 27 mg of the title compound: mp 180−181 °C; FAB-MS *m*/*z* 533 $(M + H)^+$; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.3−1.7 (m, 4H), 2.54 (t, *J* = 6, 2H), 2.70 (t, *J* = 5.5, 2H), 3.55−3.65 (m, 2H), 3.83 (dd, *J* = 7.5, 9, 1H), 3.96 (dd, *J* = 7.5, 9, 1H), 4.64 (m, 1H), 5.64 (m, 1H), 6.59 (d, *J* = 8.5, 1H), 6.86 (d, *J* = 8.5, 2H), 6.92 (d, *J* = 8.5, 1H), 7.02 (s, 2H), 7.78 (d, *J* = 8.5, 2H). Anal. ($C_{29}H_{28}N_2O_8 \cdot 1.5TFA \cdot H_2O$) C, H, N.

4-*trans*-[4-(1-Hydroxy-2-naphthoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)azepane (29). The benzophenone acid analogue required for the title compound was prepared in 17% overall yield from 1-benzyloxy-2-naphthoyl chloride (prepared from the commercially available hydroxy acid by standard methods) using general method A followed by sodium hydroxide cleavage of the *tert*-butyl ester. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound (34 mg, 13%): mp 134−137 °C dec; ^{1}H NMR (DMSO-d_6) (*J* in hertz) δ 1.80−2.30 (m, 4H), 3.10−3.40 (m, 4H), 4.52 (m, 1H), 5.31 (m, 1H), 6.80 (d, *J* = 9, 2H), 7.01 (s, 2H), 7.16 (d, *J* = 9, 1H), 7.32 (d, *J* = 9, 1H), 7.61−7.68 (m, 3H), 7.74 (t, *J* = 7, 1H), 7.88 (d, *J* = 8, 1H), 8.38 (d, *J* = 8, 1H), 8.49 (d, *J* = 7.5, 1H), 8.98 (br s, 2H), 10.07 (s, 1H), 10.22 (s, 2H). Anal. ($C_{31}H_{28}N_2O_8 \cdot 0.25H_2O \cdot 2TFA$) C, H, N.

4-*trans*-[4-(2-Hydroxy-6-methoxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4- hydroxybenzamido)azepane (31). The benzophenone acid analogue required for the title compound was prepared in 8% overall yield from 2-benzyloxy-6-methoxybenzaldehyde using general method B followed by cleavage of the *tert*-butyl ester with KOH in methanol. Standard coupling of the acid to **4** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (11 mg, 7%): mp 159−161 °C dec; FAB-MS *m*/*z* 537 $(M + H)^+$; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 2.08 (m, 3H), 2.30 (m, 1H), 3.37 (s, 3H), 3.45 (br d, 2H), 4.50 (m, 1H), 5.40 (m, 1H), 6.39 (d, *J* = 8.7, 1H), 6.50 (d, *J* = 7.9, 1H), 6.78 (d, *J* = 8.8, 2H), 6.92 (s, 2H), 7.31 (dd, *J* = 7.9, 8.7, 1H), 7.63 (d, *J* = 8.7, 2H). Anal. ($C_{28}H_{28}N_2O_9 \cdot 2TFA \cdot CH_4OH$) C, H, N.

1-*trans*-[4-(2-Carboxymethoxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (34). The benzophenone acid analogue required for the title compound was prepared from 2-benzyloxy-6-methoxymethoxybenzaldehyde by first using general method B to give an intermediate MOM-protected benzophenone in 86% overall yield. Acid removal of the MOM protecting group followed by alkylation of the resulting phenol with benzyl 2-bromoacetate and standard thermolysis of the *tert*-butyl ester in quinoline afforded the fully elaborated benzophenone acid

in 56% yield. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a yellow solid (180 mg, 74%): mp 162−168 °C dec; FAB-MS *m*/*z* 551.9 $(M + H)^+$; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.42−1.71 (m, 4H), 2.06 (m, 2H), 4.15 (s, 2H), 4.31 (m, 1H), 5.08 (m, 1H), 6.15 (d, *J* = 8.2, 1H), 6.35 (d, *J* = 9.0, 1H), 6.59 (d, *J* = 8.7, 2H), 6.76 (s, 2H), 7.07 (t, *J* = 8.4, 1H), 7.49 (d, *J* = 8.7, 2H). Anal. ($C_{28}H_{25}NO_{11}\cdot1.5H_2O$) C, H, N.

1-*trans*-[4-[2-(2-Aminoethoxy)-6-hydroxybenzoyl]-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (33). The benzophenone acid analogue required for the title compound was prepared in 34% overall yield in a fashion similar to that described for **34**, using 2-bromoacetamide as the alkylating agent. The benzophenone acid in this case was converted to its methyl ester before the alkylation, and alkaline hydrolysis was used to yield the acid prior to coupling. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound, in which the acetamide had been fully reduced to the corresponding amine, as a yellow solid (21 mg, 31%): mp 140−145 °C dec; FAB-MS *m*/*z* 536.9 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) (*J* in hertz) δ 1.60−1.90 (m, 4H), 2.00−2.25 (m, 2H), 3.90−4.00 (m, 2H), 4.30−4.45 (m, 1H), 5.20−5.30 (m, 1H), 6.50−6.60 (m, 2H), 6.79 (d, *J* = 9, 2H), 6.91 (s, 2H), 7.33 (t, *J* = 8, 1H), 7.65−7.80 (m, 4H), 8.31 (d, *J* = 8, 1H), 10.02 (s, 1H), 10.63 (s, 2H), 11.21 (s, 1H). Anal. ($C_{28}H_{28}N_2O_9\cdot0.25H_2O\cdot1.5$TFA) C, H, N.

General Synthesis Method G. [4-(2-Benzyloxy-6-nitrilobenzoyl)-3,5-dibenzyloxy]benzoic Acid 1,1-Dimethylethyl Ester (65). To a solution of [4-(2-benzyloxy-6-formylbenzoyl)-3,5-dibenzyloxy]benzoic acid 1,1-dimethylethyl ester[8e] (**64**) (2.00 g, 3.15 mmol) in DMF (15.8 mL) was added hydroxylamine hydrochloride (438 mg, 6.30 mmol). The mixture was heated with stirring at 50−55 °C for 16 h, and then allowed to cool. The yellow solution was poured onto ice, and stirred while the ice was allowed to melt. The resulting white solid was collected by filtration, washed with ether, and dried under vacuum to provide the product (1.29 g, 65%) as a white solid: mp 139−140 °C; ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 1.63 (s, 9H), 4.71 (s, 2H), 4.85 (s, 4H), 6.84 (d, *J* = 9.0, 2H), 7.0−7.2 (m, 9H), 7.2−7.4 (m, 9H).

***trans*-2-[4-(6-Hydroxy-2-nitrilobenzoyl)-3,5-dhydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (32).** The benzophenone acid analogue required for the title compound was prepared in 60% yield from **65** by TFA cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acid chloride gave coupled product **66**, which after deprotection afforded the title compound as a yellow powder (48 mg, 36%): mp 125−130 °C dec; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.4−1.65 (m, 2H), 1.65−1.75 (m, 2H), 2.0−2.1 (m, 2H), 4.30 (dt, *J* = 13.6, 8.1, 1H), 5.08 (dt, *J* = 5.3, 5.2, 1H), 6.60 (d, *J* = 8.8, 2H), 6.77 (s, 2H), 6.93 (d, *J* = 8.2, 1H), 7.04 (d, *J* = 6.6, 1H), 7.22 (dd, *J* = 8.1, 7.9, 1H), 7.48 (d, *J* = 8.7, 2H); MS *m*/*z* calcd for $C_{27}H_{23}N_2O_8$ $(M^+ + 1)$ 503.1454, found 503.1380. Anal.($C_{27}H_{22}N_2O_8\cdot H_2O$) C, H, N.

General Synthesis Method F. 4-[6-Benzyloxy-2-[[(2-trimethylsilylethoxy)carbonyl]amino]benzoyl]-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester (93). A suspension of 8.30 g (12.9 mmol) of 4-(6-benzyloxy-2-carboxybenzoyl)-3,5-dibenzyloxybenzoic acid 1,1-dimethylethyl ester (**61**) in 40 mL of toluene was treated with 1.97 mL (1.43 g, 14.1 mmol) of triethylamine and 2.77 mL (3.54 g, 12.9 mmol) of diphenylphosphoryl azide, and the mixture was heated at 95 °C under nitrogen for 3.5 h. To this mixture was added 3.7 mL (3.1 g, 25.8 mmol) of 2-trimethylsilylethanol, and the mixture was stirred at 95 °C under nitrogen for 18 h. The mixture was cooled, diluted with 500 mL of ether, washed with 2 N HCl and twice with half-saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give 14.10 g of the crude product. Chromatography on silica gel eluting with 4/1 hexanes−EtOAc gave 7.57 g (77%) of the title compound as a yellow solid: mp 118−120 °C. Anal. ($C_{45}H_{49}NO_8Si\cdot0.25H_2O$) C, H, N.

4-(2-Amino-6-benzyloxybenzoyl)-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester (62). A solution of 7.50 g (9.87 mmol) of **93** in 50 mL of DMF was treated with 2.11 g (13.9 mmol) of cesium fluoride and stirred at 75 °C under nitrogen for 48 h. The mixture was diluted with 700 mL of ether, washed twice with water and brine, dried over $MgSO_4$, and evaporated to give 6.11 g of the crude product. Crystallization from EtOAc−hexanes afforded 3.72 g (61%) of the title compound as a yellow solid: mp 124−126 °C. Chromatography of the mother liquors afforded an additional 1.60 g (26%, total yield 87%) of pure material. Anal. ($C_{39}H_{37}NO_6$) C, H, N.

4-[2-Benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl]-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester (63). A solution of 1.30 g (1.8 mmol) of **62** in 30 mL of CH_2Cl_2 was treated at 0 °C with 0.56 mL (0.52 g, 4.8 mmol) of 2,6-lutidine and 0.639 mL (1.07 g, 3.8 mmol) of triflic anhydride, and the mixture was stirred at 0−10 °C under nitrogen for 3.5 h. An additional 0.18 mL of 2,6-lutidine and 0.21 mL of triflic anhydride were then added, and the mixture was stirred for an additional 2 h. The mixture was diluted with 300 mL of ether, washed twice with 5% citric acid and once with brine, dried over $MgSO_4$, and evaporated to give 1.77 g of the crude product. Chromatography on silica gel eluting with 4/1 hexanes−EtOAc gave 0.38 g (32%) of the title compound as a yellow oil, which was used directly in the next step.

***trans*-2-[3,5-Dihydroxy-4-[2-hydroxy-6-(trifluoromethanesulfonylamino)benzoyl]benzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (35).** The benzophenone acid analogue required for the title compound was prepared in 51% yield from **63** by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a yellow fluffy solid (11.8 mg, 7%): ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.70 (m, 1H), 1.89 (m, 2H), 2.22 (m, 1H), 4.52 (m, 1H), 5.30 (m, 1H), 6.78−6.84 (m, 3H), 6.88 (d, *J* = 8, 1H), 6.93 (s, 2H), 7.24 (t, *J* = 8, 1H), 7.70 (d, *J* = 9, 2H); FAB-MS *m*/*z* 625 (M + H). Anal. ($C_{27}H_{23}F_3N_2O_{10}S\cdot0.5H_2O$) C, H, N, S.

***trans*-2-[3,5-Dihydroxy-4-[2-hydroxy-6-(methanesulfonyl-amino)benzoyl]benzoyloxy]-1-(4-hydroxybenzamido)-cyclopentane (36).** The benzophenone acid analogue required for the title compound was prepared in 77% overall yield from **62** and methanesulfonyl chloride using general method F followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a yellow fluffy solid (42.5 mg, 24%): mp 139−154 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.70 (m, 1H), 1.89 (m, 2H), 2.27 (m, 1H), 2.89 (s, 3H), 4.52 (m, 1H), 5.29 (m, 1H), 6.65 (d, *J* = 8, 1H), 6.81 (d, *J* = 9, 2H), 6.94 (s, 2H), 7.06 (d, *J* = 7, 1H), 7.25 (t, *J* = 8, 1H), 7.69 (d, *J* = 9, 2H); FAB-MS *m*/*z* 571 (M + H). Anal. ($C_{27}H_{26}N_2O_{10}S\cdot2H_2O\cdot0.25CH_3CN$) C, H, N, S.

trans-2-[3,5-Dihydroxy-4-[2-hydroxy-6-(trifluoroacetyl-amino)benzoyl]benzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (37). The benzophenone acid analogue required for the title compound was prepared in 74% overall yield from **62** and trifluoroacetic anhydride using general method F followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a yellow fluffy solid (68 mg, 37%): mp 136−149 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.69 (m, 1H), 1.89 (m, 2H), 2.25 (m, 1H), 4.51 (m, 1H), 5.29 (m, 1H), 6.76−6.84 (m, 3H), 6.95 (s, 2H), 7.19 (d, *J* = 8, 1H), 7.34 (t, *J* = 8, 1H), 7.69 (d, *J* = 9, 2H); FAB-MS *m*/*z* 589 (M + H). Anal. ($C_{28}H_{23}F_3N_2O_9\cdot1.77H_2O$) C, H, N.

trans-2-[3,5-Dihydroxy-4-[2-hydroxy-6-(acetylamino)-benzoyl]benzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (38). The benzophenone acid analogue required for the title compound was prepared in 78% overall yield from **62** and acetyl chloride using general method F followed by formic acid cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acyl imidazole followed by deprotection afforded the title compound as a yellow fluffy solid (64 mg, 66%): mp 155−168 °C; ^{1}H NMR (CD_3OD) (*J* in hertz) δ 1.70 (m, 1H), 1.88 (m, 5H), 2.23 (m, 1H), 4.54 (m, 1H), 5.31 (m, 1H), 6.70 (d, *J* = 8, 1H), 6.81 (d, *J* = 9, 2H), 6.89 (d, *J* = 8, 1H), 6.97 (s, 2H), 7.27 (t, *J* = 8, 1H), 7.70 (d, *J* = 9, 2H), 8.32

(d, $J = 8$, 1H); FAB-MS m/z 535 (M + H). Anal. ($C_{28}H_{26}N_2O_9 \cdot 1.25H_2O$) C, H, N.

***trans*-2-[4-(6-Benzyloxy-2-tetrazolylbenzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(2-benzyloxybenzamido)cyclopentane (67).** To a solution of **66** (617 mg, 0.716 mmol) in 3.6 mL of toluene were added *n*-Bu_2SnO (178 mg, 0.716 mmol) and $TMSN_3$ (950 μL, 7.16 mmol). The mixture was heated at 70−80 °C under nitrogen for 20.5 h, at which time more toluene (1.0 mL) and $TMSN_3$ (950 μL) were added. After 48 h total the solution was allowed to cool, poured into 5% HCl, and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated. Flash column chromatography on silica gel eluting with 9/1 CH_2Cl_2−MeOH provided the title product (253 mg, 39%) as a tan foam: ^{1}H NMR ($CDCl_3$) (J in hertz) δ 1.5−1.75 (m, 2H), 1.8−1.95 (m, 2H), 2.2−2.3 (m, 1H), 2.3−2.45 (m, 1H), 4.5−4.6 (m, 1H), 4.68 (s, 2H), 4.70 (s, 3H), 5.06 (s, 2H), 5.07 (s, 1H), 5.25−5.35 (m, 1H), 6.76 (d, $J = 7.0$, 2H), 6.83 (d, $J = 6.9$, 1H), 6.9−7.0 (m, 7H), 7.0−7.1 (m, 4H), 7.1−7.2 (m, 5H), 7.3−7.4 (m, 6H), 7.45−7.5 (m, 1H), 7.7−7.8 (m, 3H).

***trans*-2-[4-(6-Hydroxy-2-tetrazolylbenzoyl]-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (39).** To a round-bottom flask containing **67** (132 mg, 0.146 mmol) and $Pd(OH)_2$ (33 mg of 20% on carbon) was added 13 mL of 1/1 THF−ethanol. The flask was evacuated and filled with H_2 three times, and then the mixture was stirred under H_2 (1 atm) for 15 h. The slurry was filtered through Celite, evaporated, and purified by reversed-phase HPLC (C18 column). The title product was obtained (53.0 mg, 67%) after lyophilization as a yellow powder: mp 154−164 °C dec; ^{1}H NMR (CD_3OD) (J in hertz) δ 1.4−1.6 (m, 2H), 1.6−1.7 (m, 2H), 1.95−2.1 (m, 2H), 4.2−4.3 (m, 1H), 5.05. dt (10.4, $J = 5.1$, 1H), 6.59 (d, 8.7H), 6.65 (s, 2H), 6.82 (d, $J = 8.2$, 1H), 7.07 (d, 8.8H), 7.19 (dd, $J = 7.9$, 8.0, 1H), 7.47 (d, $J = 8.7$, 2H); MS m/z calcd for $C_{27}H_{24}O_8N_5$ $(M + 2)^+$ 546.1624, found 546.1623. Anal.-($C_{27}H_{23}N_5O_8 \cdot 0.5TFA$) C, H, N.

***trans*-2-[4-[6-Hydroxy-2-(3-methyltetrazolyl)benzoyl]-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (40) and *trans*-2-[4-[6-Hydroxy-2-(2-methyltetrazolyl)benzoyl]-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (41).** To a solution of **39** (121 mg, 0.134 mmol) in 7 mL of 1/1 acetone−DMF were added Na_2CO_3 (21 mg, 0.20 mmol) and then iodomethane (83 μL, 1.34 mmol). The mixture was stirred at room temperature for 1 h, diluted with EtOAc, and washed with 5% HCl followed by H_2O. The organic layer was dried ($MgSO_4$), filtered, and evaporated. ^{1}H NMR of the crude reaction mixture showed signals consistent with a 1:1 mixture of two monomethylated products, and the mixture was used for the deprotection step without an attempt to separate the regioisomers.

To a round-bottom flask containing the above regioisomer mixture (0.134 mmol) were added $Pd(OH)_2$ (31 mg of 20% on carbon) and 12 mL of 1/1 THF−ethanol. The flask was evacuated and filled with H_2 three times, and then the mixture was stirred under H_2 (1 atm) for 15.5 h. The slurry was filtered through Celite, washed with methanol, and evaporated. Purification by reversed-phase HPLC (C_{18} column) provided the title products **40** (26.4 mg, 35%) and **41** (29.2 mg, 39%) and a fraction containing a mixture of regioisomers (9.0 mg, 12%), each as a yellow powder after lyophilization.

Data for **40**: mp 150−158 °C dec; ^{1}H NMR (CD_3OD) (J in hertz) δ 1.4−1.7 (m, 4H), 1.95−2.1 (m, 2H), 3.74 (s, 3H), 4.29 (dt, $J = 13.7$, 5.8, 1H), 5.04 (dt, $J = 10.8$, 5.3, 1H), 6.60 (d, $J = 8.8$, 2H), 6.64 (s, 2H), 6.77 (d, $J = 7.8$, 1H), 6.91 (d, $J = 8.9$, 1H), 7.28 (dd, $J = 8.2$, 7.8, 1H), 7.48 (d, $J = 8.7$, 2H); MS m/z calcd for $C_{28}H_{26}O_8N_5$ $(M^+ + 1)$ 560.1782, found 560.1778. Anal. ($C_{28}H_{25}O_8N_5 \cdot 0.4TFA$): C, H, N.

Data for **41**: mp 130−148 °C dec; ^{1}H NMR (CD_3OD) (J in hertz) δ 1.4−1.7 (m, 4H), 1.95−2.1 (m, 2H), 3.98 (s, 3H), 4.28 (dt, $J = 13.6$, 5.7, 1H), 5.06 (dt, $J = 10.6$, 5.3, 1H), 6.59 (d, $J = 8.7$, 2H), 6.65 (s, 2H), 6.75 (d, $J = 8.2$, 1H), 7.13 (dd, $J = 8.1$, 7.8, 1H), 7.31 (d, $J = 7.7$, 1H), 7.47 (d, $J = 8.7$, 2H); MS m/z calcd for $C_{28}H_{26}O_8N_5$ $(M^+ + 1)$ 560.1781, found 560.1772. Anal. ($C_{28}H_{25}O_8N_5 \cdot 0.6TFA$): C, H, N.

4-(3,4-Dihydro-8-benzyloxy-4-oxo-1-phthalazinyl)-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester (68). To a 0 °C solution of **61** (0.55 g, 0.85 mmol) in 15 mL of CH_2Cl_2 were added DMF (2 drops) and then oxalyl chloride (0.85 mL of a 2.0 M solution in CH_2Cl_2, 1.7 mmol). The mixture was stirred under nitrogen for 1.5 h, evaporated, then evaporated twice from CH_2Cl_2, and dried under vacuum 1 h before use.

To the acid chloride in THF (13 mL) were added 3 N KOH (0.51 mL) and then hydrazine hydrate (0.96 mL of a 55% solution in H_2O, 17 mmol). After being stirred under nitrogen for 24 h, the mixture was poured into 5% HCl and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel eluting with 1/1 hexanes−EtOAc provided the title compound (0.51 g, 95%) as a white powder: ^{1}H NMR ($CDCl_3$) (J in hertz) δ 1.63 (s, 9H), 4.65 (s, 2H), 4.92 (ABq, $J = 25$, 12.5, 4H), 6.64 (d, $J = 7.1$, 2H), 7.0−7.1 (m, 8H), 7.1−7.3 (m, 8H), 7.72 (dd, $J = 8.2$, 7.9, 1H), 8.14 (d, 7.7H), 10.26 (s, 1H).

***trans*-1-[4-(3,4-Dihydro-8-hydroxy-4-oxo-1-phthalazinyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (42).** The benzophenone acid analogue required for the title compound was prepared in quantitative yield from **68** by TFA cleavage of the *tert*-butyl ester. Standard coupling of the acid to **6** by way of the acid chloride followed by deprotection afforded the title compound as a yellow powder (44 mg, 22%): mp 187−196 °C dec; ^{1}H NMR (CD_3OD) δ 1.4−1.8 (m, 4H), 2.0−2.2 (m, 2H), 4.3−4.4 (m, 1H), 5.0−5.1 (m, 1H), 6.60 (d, $J = 8.7$, 2H), 6.83 (s, 2H), 6.93 (d, $J = 7.0$, 1H), 7.41 (dd, $J = 8.1$, 7.8, 1H), 7.50 (d, $J = 8.7$, 2H), 7.65 (d, $J = 8.0$, 1H); MS m/z calcd for $C_{27}H_{24}N_3O_8$ $(M^+ + 1)$ 518.1563, found 518.1558. Anal. ($C_{27}H_{23}N_3O_8 \cdot 0.5TFA \cdot 0.5H_2O$) C, H, N.

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