2,7-Dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine as a New Template for the Design of CCK_2 Receptor Antagonists

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A novel series of nonpeptide CCK_2 receptor antagonists has been prepared, in which 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (**5**) was used as a chemical template. This uncommon ring system was obtained in a highly substituted form and in high yield by ozonolysis of the enamine bond of 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole derivatives (**4**), in which the configuration of the substituents was established stereoselectively via the Pictet−Spengler reaction. Further structural manipulation was guided by molecular modeling through comparison of fieldpoint-based structures of candidate compounds with a selected low-energy conformation of the representative CCK_2 receptor antagonist 5-[[[(1*S*)-[[(3,5-dicarboxyphenyl)-amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)amino]carbonyl]-indole (JB93182 (**3**)). By this approach compounds such as (3*R*,5*S*)-4-acetyl-3-(1-adamantyl)-methyl-1-(2-chlorobenzyl)-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (**32**) were prepared. Compound **32** behaved as a competitive CCK_2 receptor antagonist in vitro as judged by its inhibition of pentagastrin-stimulated acid secretion in an isolated, lumen-perfused, immature rat stomach assay ($pK_B = 6.74 \pm 0.27$) and by its displacement of [^{125}I]CCK-8S from CCK_2 sites in mouse cortical homogenates ($pK_i = 6.99 \pm 0.05$). Compound **32** was 100-fold selective for CCK_2 over CCK_1 receptors based on the affinity estimate obtained in a guinea pig pancreas radioligand binding assay ($pK_i = 5.0$).

Introduction

Blocking the action of the polypeptide hormones cholecystokinin and gastrin has attracted interest because of their roles in both the CNS and peripheral tissues.[1] In the periphery, cholecystokinin mediates gall bladder contraction and pancreatic secretion via CCK_1 receptors, stimulation of which, to full effect, requires at least the C-terminal octapeptide fragment of the hormone in its tyrosine-sulfated form (Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-PheNH_2 or CCK-8S).[2] CCK_1 receptors are also found in the CNS where they are associated with the regulation of food intake. In addition there also exist receptors which, depending on where they are located, can be stimulated by either or both gastrin and cholecystokinin and which require only the C-terminal tetrapeptide (Trp-Met-Asp-Phe-NH_2), which is common to both hormones, to elicit a full response.[3] In the CNS these receptors have been associated with panic, anxiety, and pain, whereas in peripheral tissues, where they are mainly activated by gastrin, they stimulate gastric acid secretion[4] and gastrointestinal cell growth.[5] Their similarity in responsiveness to the hormone fragments and their subsequent cloning has confirmed that, whether located in the periphery or in the CNS, these receptors are identical, and they are now designated CCK_2 receptors.[6] Our interest in the physiological effects of gastrin prompted our efforts to obtain CCK_2 receptor antagonists which are postulated to have benefit in antisecretory therapy as well as in CNS disorders.[7] Much effort has been devoted to obtaining such compounds; however, none of the CCK_2 receptor antagonists available so far have fulfilled their expected therapeutic role.[8]

CCK_2 receptor antagonists have been devised by one of two main approaches and span a diverse range of chemical structures.[9] Optimization of the natural product lead asperlicin has yielded compounds such as L-365,260 (**1**) (Chart 1) and other 1,4-benzodiazepines, and subsequently 1,5-benzodiazepine-2,4-diones, and ureido acetamides, in addition to quinazolinone-based compounds. Alternatively, the peptoid-based compound CI 988 (**2**) (Chart 1) was derived by rational design from the native hormone.[10] By adopting this latter approach we obtained competitive CCK_2 receptor antagonists based on bicyclic heteroaromatic skeletons.[11] These compounds exhibited comparable affinity estimates between species as judged by in vitro bioassays, selectivity with respect to CCK_1 receptors, and potent in vivo behavior. This strategy involved identification of novel chemical structures potentially capable of replacing or mimicking the tertiary structure of the native hormone. Molecular modeling, through the use of fieldpoint-based comparison rather than structure-based comparison,[12] was used to help choose the most suitable chemical structures. Having successfully derived novel CCK_2 receptor antagonists from the native hormone agonist using this approach, culminating in the discovery of the highly potent JB93182 (**3**), we now sought to devise new structures with similar in vitro behavior to **3** (Chart 1) but with improved in vivo properties.[13] We envisaged that comparison of fieldpoint distribution patterns of the new compounds with **3** would be a suitable means of

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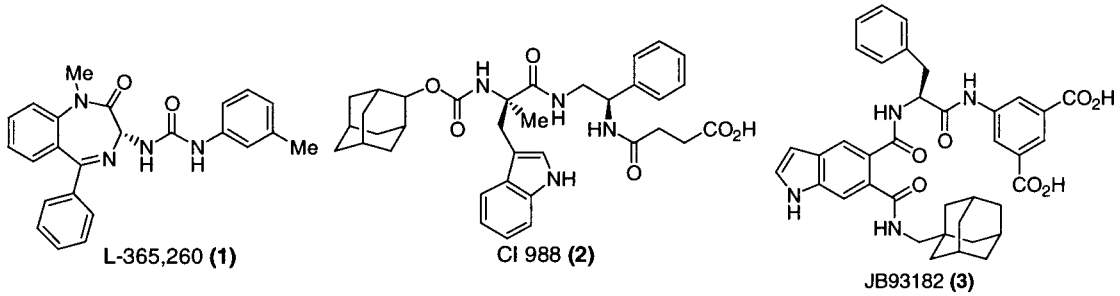
Chart 1. Structures of CCK_2 Receptor Antagonists

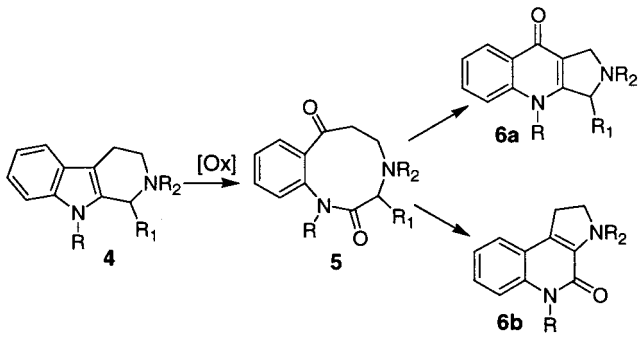


predicting their in vitro behavior. In this paper we describe the implementation of this strategy through the discovery of a novel series of nonpeptide CCK_2 receptor antagonists, in which a 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine ring (**5**) is used as a structural template.

Substitution of the conformationally flexible secondary structure of peptides by nonpeptide frameworks and replacement of individual amino acid residues or dipeptide fragments by constrained derivatives are adopted frequently as tactics in peptido-mimetic design.[14] These techniques have been employed principally with the aim of attaining a more favorable entropic component on receptor binding by limiting the accessible conformations, through substitution of intramolecular hydrogen bonding by covalent bonds or by restriction of available conformational space.[15] In addition these changes have at times conferred improved pharmacokinetic properties, such as increased metabolic stability and prolonged half-life, on the new ligands.[16] **3** and its analogues largely evolved from this strategy but with an additional aim being the abolition of the efficacy of the native hormone from which it evolved. It is evident by the biological behavior of **3** that this latter objective has clearly been met. However, the high potency of **3** was achieved at a cost of relatively high molecular weight, and the calculated low-energy conformations relied on intramolecular H-bonding for stabilization. Nonetheless, the combination of high affinity, lack of efficacy, and selectivity over CCK_1 receptors identified **3** as a suitable candidate for use in the design of new ligands. Compared to the bicyclic heteroaromatic-based series of CCK_2 receptor antagonists, of which **3** is an example, benzodiazepines are relatively conformationally constrained. Due to their varied syntheses and ease of substitution, they have been used widely as dipeptide mimics and as templates for mimetics of larger peptides,[17] as well as occupying a pivotal position in the area of CCK research.[18] We considered that higher homologues of benzodiazepines might fulfill a similar role in our aim to design novel CCK_2 receptor antagonists, using **3** as a guide.

While medium-sized rings have been utilized with some success in other areas of peptide mimetics, their application has been hampered by the difficulty in preparing them in highly functionalized form.[19] On the other hand, bicyclic ring fragmentation offers an efficient alternative means of accessing medium-sized rings. To satisfy our requirements it was necessary that the synthesis of the bicyclic precursor allowed a high degree of functionality and was stereoselective. To this end we considered that if the enamine bond of an

Scheme 1. Oxidative Fragmentation of 1,2,3,4-Tetrahydro-9*H*-pyrido[3,4-*b*]indole (**4**)

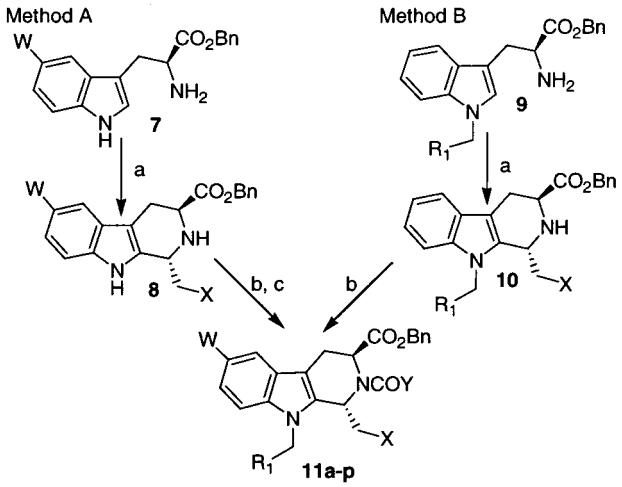


appropriately substituted 1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole **4** were oxidized, the resultant keto-lactam product **5** could serve as a framework suitable for further elaboration (Scheme 1). Rare examples of the desired 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*]-[1,4]diazonine ring system **5** are known. For instance, a ring system of this type was the principal product obtained on singlet oxygenation of the alkaloid vincamine,[20] as an unexpected byproduct from the attempted *m*-chloroperoxybenzoic acid-promoted Meisenheimer rearrangement of 1,2,4,5,10,10b-hexahydroazeto[1′,2′:1,2]-pyrido[3,4-*b*]indoles,[21] and prepared as an intermediate in the biomimetic synthesis of the alkaloid camptothecin.[22] However, the conditions employed in the oxidation of 1,2,3,4-tetrahydro-*β*-carbolines **4** has more often led to the formation of the tricyclic 1,2,3,4-pyrrolo[3,4-*b*]quinolin-9-ones **6a** via **5** by transannular ketone enolate addition to the amide, followed by dehydration.[23] The presence of an ester group at C-1 of **4** was found to influence this reaction in favor of the isomeric 1,2,3,4-pyrrolo[2,3-*c*]quinolin-4-ones **6b**.[24] We sought to obtain a practical and general route to the uncommon 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine ring system **5**.[25]

Chemistry

The compounds listed in Table 1 were prepared by the general routes outlined in Schemes 2−5. L-Tryptophan benzyl esters **7**, unsubstituted on the indole nitrogen, were condensed with the appropriate acetaldehyde in a Pictet−Spengler reaction to form the 1,2,3,4-tetrahydropyrido[3,4-*b*]indole ring system **8** (Scheme 2, method A).[26] This product was generally obtained as a mixture of *cis*-(1*S*,3*S*) and *trans*-(1*R*,3*S*) diastereoisomers, from which the predominant *trans* isomer was isolated by column chromatography. This product was first acylated on the pyrido nitrogen then alkylated on the indole nitrogen to afford the protected *trans*-(1*R*,3*S*)-

Scheme 2. Synthesis of 1,2,3,4-Tetrahydro-9*H*-pyrido[3,4-*b*]indoles **11a**−**p**[a,b]

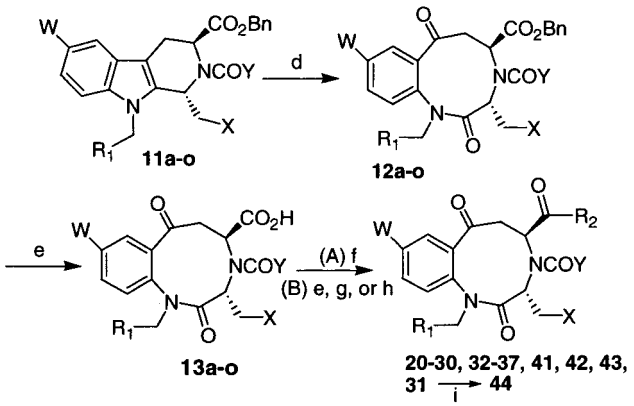


11	W	R_1	X	Y	Method
a	H	Ph	1-Ad	Me	A
b	H	Ph	1-Ad	Me	A
c	H	Ph	*t*-Bu	Me	A
d	H	Ph	*c*-C_6H_{11}	Me	A
e	H	Ph	*c*-C_7H_{13}	Me	A
f	H	H	1-Ad	Me	A
g	H	4-F-C_6H_4	1-Ad	Me	A
h	H	3-F-C_6H_4	1-Ad	Me	A
i	H	2-F-C_6H_4	1-Ad	Me	B
j	H	2-Cl-C_6H_4	1-Ad	Me	B
k	OMe	Ph	1-Ad	Me	A
l	Me	Ph	1-Ad	Me	A
m	F	Ph	1-Ad	Me	A
n	H	2-Cl-C_6H_4	1-Ad	OMe	B
o	H	2-Cl-C_6H_4	1-Ad	Et	B
p	H	Ph	1-Ad	O-*t*Bu	A

[a] (a) XCH_2CHO, CF_3CO_2H, 3A molecular sieves, CH_2Cl_2; (b) YCOCl, NEt_3, CH_2Cl_2; (c) NaH, R_1CH_2Br, DMF. [b] Only the preparation of the (3*R*,5*S*) diastereoisomers is shown; (3*S*,5*R*) diastereoisomer **11b** was prepared by using the D-tryptophan benzyl ester, and **11k**−**m** were obtained as racemic mixtures of *trans*-(3*R*,5*S*/3*S*,5*R*) diastereoisomers starting from the appropriate 5-substituted D/L-tryptophan esters **7**.

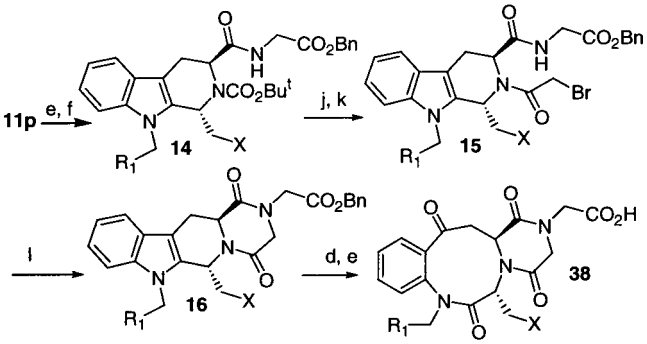
1,2,3,4-tetrahydro-β-carbolines (**11a,c**−**h,k**−**p**). Although the minor *cis*-(1*S*,3*S*) diastereoisomer of **8** was isolated and acetylation achieved using harsher conditions than those used to effect acylation of the *trans* adduct, subsequent base-mediated alkylation on the pyrrole nitrogen resulted in concomitant epimerization at the

Scheme 3. Synthesis of 2,7-Dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonines **20**−**37** and **41**−**44**[a,b]



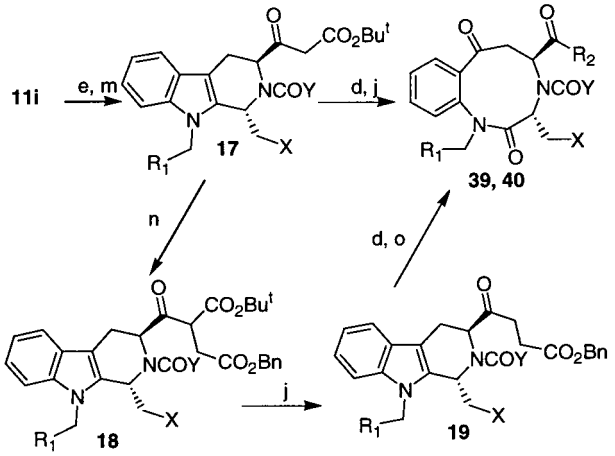
[a] (d) O_3, Me_2S, MeOH, CH_2Cl_2; (e) Pd−C, H_2, MeOH, THF; (f) amino acid ester ($H_2NCH_2CN_4$(SEM) for **43**), PyBroP, *i*-$PrNEt_2$, CH_2Cl_2, or EDCI, HOBt, DMAP, CH_2Cl_2; (g) $(Ph_3P)_4Pd$, $HNEt_2$, THF; (h) $MgBr_2{\cdot}Et_2O$, CH_2Cl_2; (i) EDCI, $MeSO_2NH_2$, CH_2Cl_2. [b] Same as for Scheme 2.

Scheme 4. Synthesis of 2,4,7,9-Tetraoxo-2,3,4,5,7,7a,8,9-octahydro-1*H*-pyrazino[1,6-*a*]benzo[*h*]-[1,4]diazonine **38**[a]



[a] (d−f) Same as for Scheme 3; (j) CF_3CO_2H, CH_2Cl_2; (k) $BrCH_2COCl$, NEt_3, CH_2Cl_2; (l) Cs_2CO_3, DMF.

Scheme 5. Synthesis of 2,7-Dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonines **39** and **40**[a]



[a] (d,e,j) Same as for Schemes 3 and 4; (m) CDI, CH_2Cl_2, CH_3CO_2t-Bu, LiN(*i*-Pr)$_2$, THF; (n) NaH, $BrCH_2CO_2Bn$, DMF; (o) Pd−C, H_2, MeOH, THF, TPAP, NMO, MeCN, CH_2Cl_2.

C-3 position to afford the thermodynamically more stable *trans*-(1*S*,3*R*) diastereoisomer. Alternatively when *N*′-benzyl-substituted L-tryptophan benzyl esters **9** were used in the Pictet−Spengler reaction (Scheme 2, method B) a single *trans*-(1*R*,3*S*) diastereoisomer (**10**) was obtained which was readily acylated on the pyrido nitrogen to afford **11i,j,n**,**o**. Comparison of the outcome of attempted oxidation of the 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles **11** under various conditions established that while most methods yielded mixtures of products, the 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo-[*h*][1,4]diazonine ring system (**12**) was the principal product formed using either singlet oxygen or ozone (Scheme 3). Ozonolysis followed by reductive workup was the preferred method, since it was less limited by scale and avoided the long reaction times necessary to effect the transformation using singlet oxygen. Removal of the benzyl ester protecting group of intermediates **12** by hydrogenolysis enabled coupling of the appropriate amino acid derivatives to the acids **13** under standard active ester coupling conditions. Where the terminal substituent was a carboxylic acid group this component was most conveniently incorporated as its benzyl ester derivative (examples **20**−**23, 25**−**37**). However, in some instances hydrogenolysis resulted in concomitant reduction of the aryl ketone group, thus requiring use of an allyl ester protected amino acid (**41**). Using the same route the (3*R*,5*S*) enantiomer **24** was also prepared staring from D-tryptophan. Compound **42** was obtained by coupling of **13a** with glycine methyl ester. The tetrazole analogue **43** was prepared by coupling of intermediate **13j** with SEM-protected *C*-(tetrazol-5-yl)-methylamine, followed by removal of the SEM protecting group by Lewis acid-promoted cleavage. The acylsulfonamide derivative **44** was prepared from **31** by treatment with methanesulfonamide using EDCI activation of the terminal acid group.

Synthesis of the tricyclic pyrazino[1,6-*a*]benzo[*h*][1,4]-diazonine **38** is shown in Scheme 4. The benzyl ester protecting group of **11p** was removed by hydrogenation and the carboxylic acid obtained coupled with glycine benzyl ester **14.** The *tert*-butyloxycarbonyl protecting group of **14** was removed and replaced by a bromoacetyl group to give **15**. Base promoted ring closure afforded the pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole **16** which was ozonized and deprotected to obtain **38**.

The ketomethylene derivatives **39** and **40** were prepared starting from **11i** (Scheme 5). Following removal of the benzyl ester protecting group and treatment with 1,1′-carbonyldiimidazole, the imidazolide obtained was reacted with *tert*-butyl lithioacetate.[27] The β-keto ester **17** obtained was alkylated directly with benzyl bromoacetate to afford **18** followed by decarboxylation of the *tert*-butyl-protected acid with trifluoroacetic acid to give a γ-keto ester **19**. Oxidation of the β-keto *tert*-butyl ester derivative **17** and treatment with trifluoroacetic acid using standard conditions afforded **40**. Ozonolysis of **19** gave the protected 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine from which the carboxylic acid group of the γ-keto benzyl ester group was unmasked by hydrogenolysis. This was accompanied by reduction of the aryl ketone group, thus requiring reoxidation with TPAP to obtain **39**.

Molecular Modeling

By consideration of the most amenable sites for substitution on the 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine ring system, potential target compounds were examined using the method of field-

point-based analysis described previously.[11,12] New ligands were chosen through an iterative process, based on the overlay energy of each conformation within 15 kcal mol^{-1} of the global minimum with a selected low-energy conformation of **3**. The outcome of this process, when applied to the representative ligand **32**, is illustrated in Figure 1.

Discussion

The compounds were assessed as CCK_2 receptor antagonists by their ability to inhibit pentagastrin-stimulated acid secretion in an isolated perfused rat stomach assay[28] and to displace the binding of [^{125}I]-CCK-8S to CCK_2 sites in mouse cerebral cortex homogenates[29] (Table 1). While not considered an optimum structure in terms of its comparison with **3**, our initial compound **13a** did at least display weak affinity for CCK_2 receptors, with a higher affinity estimate being obtained in the radioligand binding assay. Differences of this type in cross-tissue affinity estimates at CCK_2 receptors have also been observed for other more fully characterized antagonists such as **1**. This behavior has been ascribed to the existence of CCK_2 receptor subtypes which are considered to be differentially expressed within these tissues.[29] It was therefore a further objective to obtain compounds that did not discriminate between CCK_2 receptor subtypes. Thus, compound **13a** was deficient in this regard, being at least 10-fold less potent in the isolated rat stomach assay than in the mouse cortex assay. However, both increased receptor affinity, and parity in the estimates between the two assays was achieved by attachment of amino acids to the carboxylate of **13a** to generate analogues **20**−**23**. From molecular modeling analysis it appeared that the terminal carboxylic acid group was positioned in a location more like that of **3** (see Figure 1c). This increase in receptor affinity was greatest for the glycine derivative **20** and diminished on further chain lengthening in the form of the *β*-alanine homologue **21**. The affinity was also subject to conformational influence since the L- and D-alanine derivatives **22** and **23**, respectively, exhibited different behavior. Compound **24**, the (3*S*,5*R*) enantiomer of **20**, was significantly less potent, indicating that the (3*R*,5*S*) configuration, and more particularly the disposition of the 1-adamantylmethyl and glycine substituents that this stereochemistry confers, is the preferred configuration for the *trans* diastereoisomers of this series. The two additional possible *cis* diastereoisomers were not accessible using the existing synthetic route due to the ready epimerization at C-3 to the thermodynamically more stable *trans* diastereoisomers (vide supra).

As with the bicyclic heteroaromatic series, exemplified by **3**, a 1-adamantylmethyl group appeared to be the optimum hydrophobic substituent at C-3, since its substitution in **20** with other less bulky groups, **25**−**27**, resulted in a reduction in receptor affinity. The cycloheptylmethyl analogue **27** was closest to **20** in receptor affinity but only in the functional bioassay. This trend was also observed for analogues of **3** and increases the likelihood that these structurally distinct classes of ligands interact with same domain of the CCK_2 receptor. This assertion is reinforced by the apparent requirement for an aromatic substituent at the N-1 position of the benzodiazonine ring. The molecular modeling-derived superposition overlays the indole group of **3** with the 1-benzyl group of the benzodiazonine ring (Figure 1c).

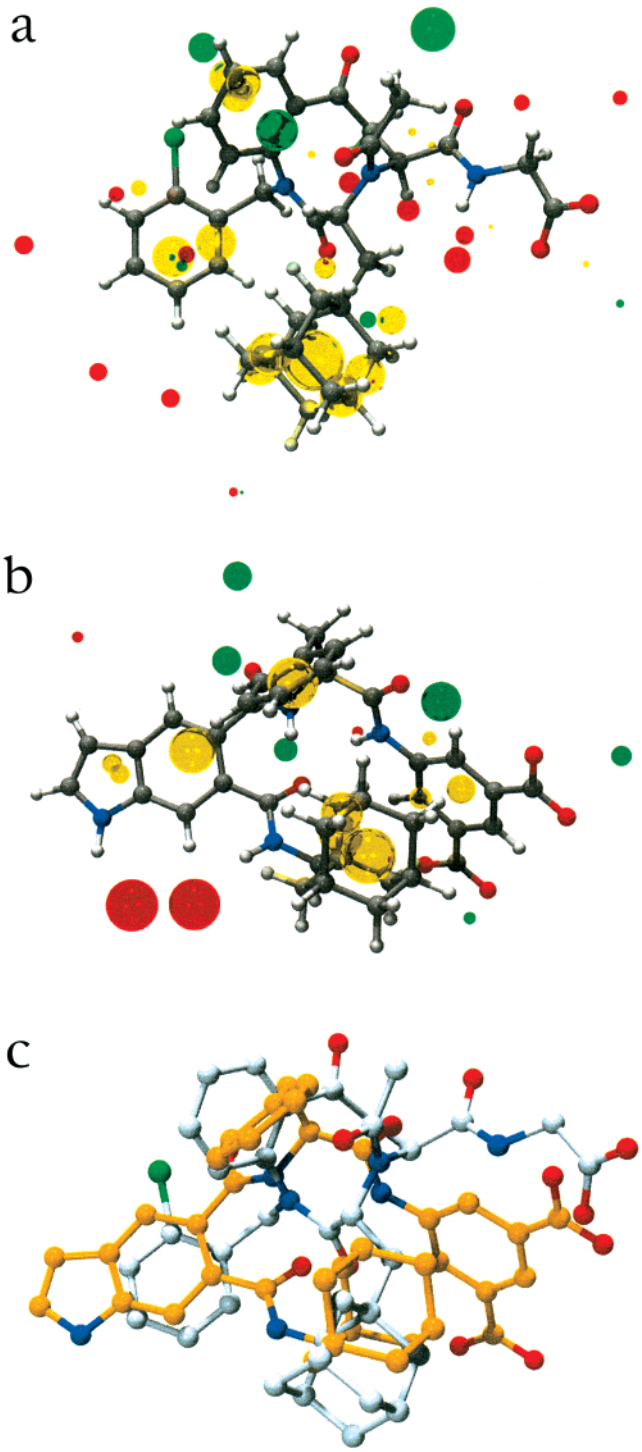
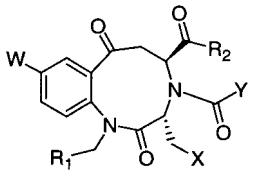


Figure 1. Composite molecular fields of **32** and **3** (JB93182): (a) conformation of compound **32** which achieved the greatest overlay energy with **3**; (b) conformation of **3** used for the comparison, with its related composite fields; (c) depiction of steric overlay of **32** and **3** arising from the fieldpoint-based superimposition of panels a and b, in which the hydrogen atoms have been omitted for clarity (**3** is shown in yellow and **32** is shown in white). Green spheres represent negative electrostatic fieldpoints, red spheres represent electropositive fieldpoints, and yellow spheres depict the hydrophobic or 'sticky points'. The size of the each sphere is directly related to the magnitude of the fieldpoint.

Table 1. In Vitro CCK$_2$ Receptor Affinity Estimates for 2,7-Dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonines



no.[a]	W	R_1	X	R_2	Y	CCK_2[b]	CCK_2[c]
13a	H	Ph	1-Ad	OH	Me	4.88 ± 0.19	6.03 ± 0.01
20	H	Ph	1-Ad	$NHCH_2CO_2H$	Me	6.79 ± 0.25	6.76 ± 0.08
21	H	Ph	1-Ad	$NH(CH_2)_2CO_2H$	Me	6.10 ± 0.33	6.05 ± 0.09
22	H	Ph	1-Ad	(*S*)-$NHCH(Me)CO_2H$	Me	6.84 ± 0.32	6.73 ± 0.08
23	H	Ph	1-Ad	(*R*)-$NHCH(Me)CO_2H$	Me	6.27 ± 0.34	6.29 ± 0.09
24[d]	H	Ph	1-Ad	$NHCH_2CO_2H$	Me	ia[e]	5.29 ± 0.04
25	H	Ph	*t*-Bu	$NHCH_2CO_2H$	Me	5.76 ± 0.35	5.31 ± 0.03
26	H	Ph	*c*-C_6H_{11}	$NHCH_2CO_2H$	Me	6.30 ± 0.38	5.37 ± 0.03
27	H	Ph	*c*-C_7H_{13}	$NHCH_2CO_2H$	Me	6.78 ± 0.32	5.57 ± 0.04
28	H	H	1-Ad	$NHCH_2CO_2H$	Me	ia[e]	<5
29	H	4-F-C_6H_4	1-Ad	$NHCH_2CO_2H$	Me	5.54 ± 0.41	5.68 ± 0.03
30	H	3-F-C_6H_4	1-Ad	$NHCH_2CO_2H$	Me	6.42 ± 0.31	6.66 ± 0.05
31	H	2-F-C_6H_4	1-Ad	$NHCH_2CO_2H$	Me	6.93 ± 0.29	7.01 ± 0.04
32	H	2-Cl-C_6H_4	1-Ad	$NHCH_2CO_2H$	Me	6.74 ± 0.27	6.99 ± 0.05
33[f]	OMe	Ph	1-Ad	$NHCH_2CO_2H$	Me	6.86 ± 0.21	6.93 ± 0.05
34[f]	Me	Ph	1-Ad	$NHCH_2CO_2H$	Me	7.11 ± 0.15	6.92 ± 0.05
35[f]	F	Ph	1-Ad	$NHCH_2CO_2H$	Me	7.66 ± 0.63	6.39 ± 0.10
36	H	2-Cl-C_6H_4	1-Ad	$NHCH_2CO_2H$	OMe	6.02 ± 0.32	6.23 ± 0.03
37	H	2-Cl-C_6H_4	1-Ad	$NHCH_2CO_2H$	Et	6.48 ± 0.28	5.79 ± 0.02
38	H	Ph	1-Ad	$-N(CH_2CO_2H)CH_2-$		ia[e]	5.52 ± 0.04
39	H	2-F-C_6H_4	1-Ad	$(CH_2)_2CO_2H$	Me	ia[e]	5.58 ± 0.01
40	H	2-F-C_6H_4	1-Ad	CH_2CO_2H	Me	6.75 ± 0.32	6.48 ± 0.10
41	H	2-Cl-C_6H_4	1-Ad	(*S*)-$NHCH(Me)CO_2H$	Me	7.47 ± 0.19	7.33 ± 0.11
42	H	Ph	1-Ad	$NHCH_2CO_2Me$	Me	7.24 ± 0.31	5.66 ± 0.06
43	H	2-Cl-C_6H_4	1-Ad	$NHCH_2CN_4H$	Me	7.49 ± 0.38	7.01 ± 0.19
44	H	2-F-C_6H_4	1-Ad	$NHCH_2CONHSO_2Me$	Me	6.61 ± 0.49	6.43 ± 0.01
1, L-365,260						7.54 ± 0.03	8.40 ± 0.01
3, JB93182						9.90 ± 0.18	8.95 ± 0.24

[a] All compounds have (3*R*,5*S*) configuration except: [d](3*S*,5*R*) and [f](3*S*,5*R*/3*R*,5*S*). [b] pK_B ± SEM values, estimated from single shifts of pentagastrin concentration−effect curves in the isolated, lumen-perfused immature rat stomach. [c] pK_{iI} ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for CCK_2 binding sites in mouse cortex homogenates from at least three separate experiments. [e] Inactive at concentration tested (between 10^{-4} and 3×10^{-5} M).

While removal of the aromatic ring of this substituent, as in compound **28**, leads to a marked reduction in receptor affinity with respect to **20**, the variation in affinity observed on introduction of substituents into this ring is consistent with it occupying the same region of the indole of **3**: for instance, the 4-fluoro derivative **29** in which the location of an electronegative substituent, presumably in a region of the receptor more suited to the electropositive pyrrolo nitrogen group, is reflected in the reduced affinity of **29** and to a lesser extent in the 3-fluoro derivative **30**. In contrast, receptor affinity is maintained in the 2-substituted derivatives **31** and **32**, in which the inductive effect of the fluoro and chloro substituents, respectively, generates a net positive charge, albeit smaller in density than that generated by the pyrrole in **3**, on the opposite edge of the aromatic ring to the 2-halo substituent (Figure 1a). The CCK_2 receptor affinity in the bicyclic heteroaromatic series was shown to be sensitive to the fieldpoint distribution around the pyrrolo ring of the indole substituent, with the 10-fold lower potency of the indole regioisomer of **3** being ascribed to the reversal of polarity around this ring. Moreover the magnitude of the positive fieldpoints in this region of **3** is strengthened by electron delocalization through the 5,6-dicarbonyl substituents of the fused aromatic ring. Although it may be envisaged that introduction of a 1-(6-indolomethyl) group in place of the 1-benzyl substituent of the benzodiazonine ring would generate an electropositive fieldpoint of greater magnitude than that arising from the 2-halo-substituted benzyl substituent in the benzodiazonines, the absence of additional delocalization derived from conjugation with the 5,6-dicarbonyl moiety, which occurs in the indole of **3**, would not be reproduced and would therefore be unlikely to have such a significant influence on the receptor affinity. In addition, introduction of an indole substituent in this position is incompatible with the existing synthetic route. On the other hand, the apparent insensitivity of the affinity to the presence or nature of substituents on the fused aromatic ring in examples **33**−**35** was mirrored in the high degree of tolerance of substituents in the phenylalanine-derived aromatic ring of **3** and its analogues, which corresponds to the benzo-fused aromatic ring of **32** in the superposition (Figure 1c).

The structure−activity relationships (SAR) of the fused bicyclic heteroaromatic-based and benzodiazonine-based series were consistent with the superposition predicted by a fieldpoint-generated molecular modeling comparison, and as such the opportunity for achieving a further increase in the receptor affinity of the benzodiazonines, by consideration of **3**, was limited. Alternatively constraint of those substituents already present was considered to achieve more favorable entropy on receptor binding.

Within the family of low-energy conformations of benzodiazonines, there occurred conformations in which the *N*-acetyl carbonyl group appeared to act as a

hydrogen bond acceptor for the amide NH on the C-3 side chain (data not shown). These conformations were generally not the global minimum conformation but were sufficiently energetically low lying to likely exist at body temperature. To ascertain whether such conformations were biologically relevant, the tricyclic compound **38** was prepared as an unrefined probe of their significance. This change significantly reduced the receptor affinity, although the difference in ring size between this compound and that resulting from formation of a putative hydrogen bond in **20**, as well as the realignment of the carbonyl group, makes this an imperfect analogue. Substitution of the acetyl group of **32** by bulkier substituents, as in examples **36** and **37**, which might be expected to influence their ability to participate in intramolecular hydrogen bonding, results in a reduction in affinity with respect to the acetyl derivative. However, these more subtle changes resulted in a less pronounced reduction in affinity with respect to **32** than that resulting from the preparation of tricyclic compound **38**. Furthermore in the γ-keto acid derivative **39**, in which the amide of the side chain is replaced with a ketomethylene moiety, which is unable to act as a hydrogen bond donor, it was found that the receptor affinity was similarly diminished with respect to **31**. This effect can be attributed to the increased entropy arising from having a methylene substituent in place of an amide nitrogen. The β-keto acid derivative **40**, in which the entropic component to receptor binding would be expected to less, has comparable affinity to **31**, at least in the functional assay. That this is so may be considered surprising in view of the different lengths of the respective side chains of **40** and **31**, but it is consistent with ionic interactions, in which the carboxylic acid would be expected to partake, being influenced by spatial as well as directional relationships. At first glance the requirement for a carboxylic acid in this position would appear to be unnecessary since the methyl ester derivative **42** is as potent in the isolated rat stomach assay as the corresponding acid containing compound **20.** However, this compound was approximately 10-fold less potent in the radioligand binding assay and as such fell short of our requirements. The carboxylic acid group could be replaced by other acid mimics such as tetrazole (**43**) and acylsulfonamide (**44**) without a substantial loss of affinity in both assays.

Consideration of the foregoing results and their interpretations prompted preparation of **41**, which is the most potent example of this class of compounds and has matching affinity estimates in both of the CCK_2 assays. Compound **41** was at least 100-fold selective for CCK_2 over CCK_1 receptors as judged by its displacement of 20 pM [^{125}I]BH-CCK-8S to CCK_1 binding sites on guinea pig pancreatic cells,[30] in which **41** and all other benzodiazonines examined, were ineffective ($pK_i \leq 5$). In addition, several of the benzodiazonines were effective in vivo by intravenous administration in a Ghosh and Schild rat model of pentagastrin-stimulated gastric acid secretion.[11] For instance, although apparently of lower receptor affinity than compounds **1** and **3**, **32** was effective in this assay at intermediate doses compared to that required to achieve inhibition by the reference compounds and, moreover, displayed dose-dependent behavior (Table 2).

Table 2. Inhibition of Pentagastrin-Stimulated Acid Secretion in Anesthetized Rats

no.	dose[a]	inhibition[b]
1 (L-365,260)	1.0	46 ± 10 (3)
3 (JB93182)	0.025	97 ± 11 (4)
32	0.1	35 ± 5 (4)
	0.3	67 ± 10 (4)

[a] Compound dose in μmol/kg. *N*-Methyl-D-glucamine salts of **3** and **32** were administered in 0.9% saline solution and **1** in aqueous 2-hydroxypropyl-β-cyclodextrin solution (45% w/v). [b] Peak percentage inhibition ± SEM (number of replicates) relative to submaximal acid secretory infusion dose of pentagastrin (0.1 μg/kg/min). Values obtained by comparison with the acid output of the stimulated preparation prior to dosing with the test compounds.

Conclusion

A practical route to 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonines has been developed. Fieldpoint-based comparison with the prototypical CCK_2 receptor antagonist **3** identified this uncommon ring system as a potential chemical template, and through further structural manipulation it has been possible to reproduce, in part, some of the properties of **3** in a novel series of benzodiazonines. There remains a variance of approximately 100-fold in CCK_2 receptor affinity between the most potent examples of the benzodiazonine series and **3**, which can at least, in part, be attributed to differences in magnitude and distribution of the respective fieldpoint patterns. Selectivity over CCK_1 receptors has been retained, and examples of this series inhibited gastric acid secretion in an in vivo assay. Although the benzodiazonines do not display substantially greater potency in vivo than **3** even when allowing for their inferior receptor affinity, this work has enhanced further the value of fieldpoints as a method of comparing conformations of different molecules and by a rational sequence has enabled us, in this instance, to devise a novel and effective chemical template, structurally much removed from the starting hormone and distinct from other CCK_2 receptor antagonists.

Experimental Section

General. All the compounds, except for compounds **1** and **42**, were tested as either *N*-methyl-D-glucamine or sodium salts. The salts were prepared by stirring an aqueous mixture of the compound with 1 equiv of *N*-methyl-D-glucamine or 0.1 M sodium hydroxide, until a solution was obtained (a minimum amount of 1,4-dioxan was added if necessary to complete dissolution) and the solutions freeze-dried. The isolated perfused rat stomach assay and the method of analysis were conducted as previously described.[28] For testing, the compounds were dissolved in dimethyl sulfoxide at a single concentration between 10^{-4} and 3×10^{-5} M, and at least six separate experiments were used to obtain pK_B estimates for each compound. The mouse cerebral cortex[29] and guinea pig pancreas[30] assays were used as previously described, in which each of the compounds were dissolved in dimethylformamide to give stock concentrations of 10 mM and further dilutions made in HEPES−NaOH buffer. Details of the anesthetized rat preparation used have been described previously.[11]

NMR spectra were recorded on a Bruker DRX 300 spectrometer with chemical shifts reported in ppm relative to tetramethylsilane used as internal standard. Elemental analyses were determined at the London School of Pharmacy and are within 0.4% of the theoretical values. Optical rotations were measured using an Optical Activity Ltd., AA-10 polarimeter. Merck silica gel 60 (40−63 μm) was used for column chromatography.

Abbreviations: 1-Ad (adamantan-1-yl), PyBroP (bromotrispyrrolidinophosphonium hexafluorophosphate), CDI (1,1′-carbonyldiimidazole), DCM (dichloromethane), EDCI (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride), DMAP (4-(dimethylamino)pyridine), HOBt (1-hydroxybenzotriazole), NMO (4-methylmorpholine *N*-oxide), PCC (pyridinium chlorochromate), SEM (2-(trimethylsilyl)ethoxymethyl), TPAP (tetrapropylammonium perruthenate), pTSA (*p*-toluenesulfonic acid monohydrate).

Adamantan-1-ylacetaldehyde, cyclohexylacetaldehyde, and 3,3-dimethylbutyraldehyde were prepared by PCC oxidation[31] of the corresponding commercially available alcohols. Cycloheptylacetaldehyde was similarly prepared from 2-cycloheptylethanol.[32] The 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole intermediates **11a**−**p** were prepared by either of the two methods described below (Scheme 2).

Method A: Benzyl (1*R*,3*S*)-1-[(1-Adamantyl)methyl]-2-acetyl-9-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (11a). Step a: Trifluoroacetic acid (0.27 mL, 3.5 mmol) was added to a solution of L-tryptophan benzyl ester (10.23 g, 34.8 mmol) and adamantan-1-ylacetaldehyde (6.2 g, 34.8 mmol) in dry CH_2Cl_2 (300 mL) with 3A molecular sieves (46.5 g) at −10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 7 h. The mixture was cooled to 0 °C, trifluoroacetic acid (5.6 mL, 72.7 mmol) added, and stirring continued at room temperature for 16 h. The reaction mixture was filtered, washed with saturated $NaHCO_3$ (200 mL), brine (2 × 200 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product as a mixture of diastereoisomers. Benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate was obtained by isolation of the more polar component by chromatography using EtOAc−CH_2Cl_2 (1:40) as eluant (6.2 g, 39%): ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H, NH), 7.48 (m, 1H, Ar H), 7.33−7.27 (m, 5H, Ar H), 7.17−7.07 (m, 3H, Ar H), 5.20 (s, 2H, CH_2Ar), 4.41 (d, J = 6.9 Hz, 1H, H-1), 4.01 (dd, J = 7.2 and 5.1 Hz, 1H, H-3), 3.13 (dd, J = 15.6 and 5.1 Hz, 1H, H-4), 3.01 (dd, J = 15.6 and 7.2 Hz, 1H, H-4), 2.01 (br s, 3H, 3 × CH), 1.78−1.59 (m, 13H, 6 × CH_2 and CHC*H*HAd), 1.48 (m, 1H, CHC*H*HAd).

Step b: Acetyl chloride (1.2 mL, 16.9 mmol) was added to a solution of benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (6.24 g, 13.7 mmol) and NEt_3 (1.9 mL, 13.6 mmol) with DMAP (30 mg) in dry CH_2Cl_2 (120 mL) at −20 °C under nitrogen. The solution was allowed to warm to room temperature and after stirring for a further 2 h was washed with 10% citric acid solution (100 mL), brine (2 × 100 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave an oil which on trituration with EtOAc afforded benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-2-acetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate as a white amorphous solid (6.3 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H, NH), 7.51 (m, 1H, Ar H), 7.36−7.27 (m, 5H, Ar H), 7.21−7.09 (m, 3H, Ar H), 5.29 (d, J = 11.1 Hz, 1H, C*H*HAr), 5.12 (m, 2H, C*H*HAr and H-1), 4.16 (m, 1H, H-3), 3.38 (dd, J = 15.9 and 10.5 Hz, 1H, H-4), 3.03 (dd, J = 15.9 and 4.2 Hz, 1H, H-4), 2.22 (s, 3H, $COCH_3$), 1.92 (br s, 3H, 3 × CH), 1.74−1.51 (m, 14H, 6 × CH_2 and CH_2Ad).

Step c: A solution of benzyl (1*R*,3*S*)-1-[(1-adamantyl)-methyl]-2-acetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (6.3 g, 12.7 mmol) in dry DMF (50 mL) was added to a suspension of NaH (60% dispersion in oil/0.56 g, 14 mmol) in dry DMF (20 mL) under nitrogen at room temperature. The reaction mixture was stirred for 15 min at room temperature whereupon a solution of benzyl bromide (1.6 mL, 13.5 mmol) in DMF (10 mL) was added. The reaction was stirred for a further 1 h, diluted with EtOAc (150 mL), washed with 2 N HCl (150 mL), brine (3 × 150 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave (**11a**) as a yellow foam (7.45 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 1H, Ar H), 7.39−7.14 (m, 12H, Ar H), 6.83 (m, 1H, Ar H), 5.48 (d, J = 17.1 Hz, 1H, C*H*HAr), 5.30 (d, J = 12.3 Hz, 1H, C*H*HAr′), 5.10 (m, 2H, C*H*HAr and C*H*HAr′), 4.84 (d, J = 10.5 Hz, 1H, H-1), 4.22 (m, 1H, H-3), 3.37 (m, 1H, H-4), 3.07 (m, 1H, H-4), 1.90 (br s, 3H, 3 × CH), 1.71−1.42 (m, 17H, 6 × CH_2, $COCH_3$ and CH_2Ad).

Method B: Benzyl (1*R*,3*S*)-1-[(1-Adamantyl)methyl]-2-acetyl-9-(2-fluorobenzyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (11i). *N* ′-(2-Fluorobenzyl)-L-tryptophan was prepared by reacting L-tryptophan with sodamide and 2-fluorobenzyl bromide in liquid ammonia according to a literature method.[33] The product was esterified using benzyl alcohol and pTSA in toluene, to afford *N* ′-(2-fluorobenzyl)-L-tryptophan benzyl ester as the *p*-toluenesulfonate salt.

N ′-(2-Fluorobenzyl)-L-tryptophan benzyl ester (23.06 g, 57.3 mmol) was reacted with adamantan-1-ylacetaldehyde according to **step a** to give benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-9-(2-fluorobenzyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate as a red fluffy solid (30.01 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.53 (m, 1H, Ar H), 7.41−7.08 (m, 10H, Ar H), 6.89 (m, 1H, Ar H), 6.38 (m, 1H, Ar H), 5.32−5.21 (m, 4H, CH_2Ar), 4.35 (d, J = 9.9 Hz, 1H, H-1), 4.07 (dd, J = 10.5 and 4.5 Hz, 1H, H-3), 3.18 (dd, J = 15.3 and 4.5 Hz, H-4), 2.91 (dd, J = 15.3 and 10.5 Hz, H-4), 2.20−2.00 (br s, 1H, NH), 1.94 (br s, 3H, 3 × CH), 1.72−1.57 (m, 13H, 6 × CH_2 and CHC*H*HAd), 1.23 (d, J = 15 Hz, 1H, CHC*H*HAd).

Benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-9-(2-fluorobenzyl)-1,2, 3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (18.81 g, 33.4 mmol) was reacted according to **step b** to give **11i** as a white amorphous solid (16.65 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 1H, Ar H), 7.35−7.11 (m, 10H, Ar H), 6.93 (m, 1H, Ar H), 6.27 (m, 1H, Ar H), 5.32 (m, 3H, CH_2Ar and C*H*HAr), 5.12 (d, J = 12.3 Hz, 1H, C*H*HAr), 4.93 (d, J = 10.5 Hz, 1H, H-1), 4.24 (dd, J = 11.7 and 4.5 Hz, 1H, H-3), 3.40 (dd, J = 11.7 Hz, 1H, H-4), 3.05 (dd, J = 15.9 and 4.5 Hz, H-4), 1.86 (br s, 6H, 3 × CH and $COCH_3$), 1.81−1.50 (m, 13H, 6 × CH_2 and CHC*H*HAd), 1.41 (d, J = 15.0 Hz, 1H, CHC*H*HAd).

Benzyl (3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]-diazonine-5-carboxylate (12a). Step d: Ozone was bubbled through a solution of **11a** (7.45 g, 12.7 mmol) in MeOH (200 mL) at −78 °C until a blue color persisted. Nitrogen was then bubbled through the solution until it turned clear, followed by the addition of Me_2S (6.0 mL, 81.7 mmol). The solution was allowed to warm to room temperature stirred for a further 2 h, and evaporated to dryness. The crude product was purified by chromatography on silica gel using EtOAc−CH_2Cl_2 (1:19) as eluant, affording **12a** as a colorless oil (5.8 g, 72%): ^{1}H NMR ($CDCl_3$) δ 7.43−7.22 (m, 13H, Ar H), 6.75 (m, 1H, Ar H), 5.63 (d, J = 14.1 Hz, 1H, C*H*HAr), 5.16 (d, J = 12.3 Hz, 1H, C*H*HAr′), 5.05 (d, J = 12.3 Hz, 1H, C*H*HAr′), 4.03−3.99 (m, 3H, H-3, H-5 and H-6), 3.90 (d, J = 14.1 Hz, 1H, C*H*HAr), 3.05 (dd, J = 6.6 and 2.1 Hz, 1H, H-6), 2.46 (dd, J = 14.4 and 11.7 Hz, 1H, C*H*HAd), 1.91 (br s, 3H, 3 × CH), 1.71−1.55 (m, 6H, 3 × CH_2), 1.48−1.28 (m, 6H, 3 × CH_2), 1.16 (s, 3H, $COCH_3$), 1.08 (d, J = 14.4 Hz, 1H, C*H*HAd).

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine-5-carboxylate (13a). Step e: 12a (5.8 g, 9.2 mmol) was stirred under an hydrogen atmosphere with 10% palladium on charcoal (500 mg) in MeOH−THF (100 mL/1:1) at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite and evaporated to dryness, affording **13a** as a white amorphous solid (4.75 g, 96%): ^{1}H NMR (DMSO-d_6) δ 7.50 (s, 3H, Ar H), 7.32−7.20 (m, 5H, Ar H), 7.00 (m, 1H, Ar H), 5.34 (d, J = 14.4 Hz, 1H, C*H*HAr), 4.00−3.71 (m, 4H, H-3, H-5, H-6 and C*H*HAr), 2.74 (m, 1H, H-6), 2.40 (m, 1H, C*H*HAd), 1.86 (br s, 3H, 3 × CH), 1.59 (m, 6H, 3 × CH_2), 1.49−1.26 (m, 6H, 3 × CH_2), 1.10 (m, 2H, C*H*HAd and $COCH_3$); $[\alpha]^{20}_D$ −82.0° (*c* 1.00, MeOH); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{36}N_2O_5 \cdot C_7H_{17}NO_5 \cdot 2.0H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (20). Step f: PyBroP (233 mg, 0.5 mmol) was added to a solution of **13a** (264 mg, 0.5

mmol), glycine benzyl ester *p*-toluenesulfonate (170 mg, 0.5 mmol) and *i*-Pr_2NEt (260 μL, 1.5 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 18 h, diluted with CH_2Cl_2 (20 mL), washed with 2 N HCl (25 mL), brine (25 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography with EtOAc−CH_2Cl_2 (3:7) as eluant. (3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-benzyloxycarbonylmethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine was obtained as a colorless oil (190 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 7.45−7.23 (m, 13H, Ar H), 6.76 (m, 1H, Ar H), 6.38 (br s, 1H, CONH), 5.63 (d, J = 14.1 Hz, 1H, C*H*HAr), 5.18 (s, 2H, CH_2Ar'), 4.14−3.98 (m, 5H, H-3, H-5, H-6 and CONHCH_2), 3.92 (d, J = 14.1 Hz, 1H, C*H*HAr), 3.07 (dd, J = 11.7 and 3.3 Hz, 1H, H-6), 2.73 (m, 1H, C*H*HAd), 1.95 (br s, 3H, 3 × CH), 1.74−1.38 (m, 12H, 6 × CH_2), 1.24 (m, 4H, $COCH_3$ and C*H*HAd).

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-benzyloxycarbonylmethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (190 mg, 0.28 mmol) was reacted according to **step e** affording **20** as a white amorphous solid (154 mg, 92%): ^{1}H NMR (DMSO-d_6) δ 12.54 (br s, 1H, CO_2H) 7.47 (s, 4H, Ar H), 7.27 (m, 5H, Ar H), 7.00 (s, 1H, CONH), 5.35 (d, J = 15.0 Hz, 1H, C*H*HAr), 3.99−3.76 (m, 3H, H-3, H-5 and H-6) 3.70−3.65 (m, 3H, C*H*HAr and CONHCH_2), 2.92 (m, 1H, H-6), 2.30 (m, 1H, C*H*HAd), 1.86 (br s, 3H, 3 × CH), 1.65−1.25 (m, 13H, 6 × CH_2 and C*H*HAd) 1.04 (s, 3H, $COCH_3$); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{39}N_3O_6$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

21−**23** were prepared by a similar sequence used to prepare **20** except that the appropriate amino acid benzyl esters were used in place of glycine benzyl ester *p*-toluenesulfonate in **step f**.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-(2-carboxyethyl)aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (21): ^{1}H NMR (DMSO-d_6) δ 7.49 (s, 3H), 7.28−7.23 (m, 5H), 7.06 (m, 1H), 7.00 (m, 1H), 5.35 (m, 1H), 3.98−3.88 (m, 3H), 3.61 (m, 1H), 3.21−3.16 (m, 3H), 2.89 (m,1H), 2.31 (m, 3H), 1.86 (s, 3H), 1.57−1.45 (m, 8H), 1.27 (m, 4H), 1.04 (s, 3H); $[\alpha]^{20}_D$ −56.0° (*c* 1.00, MeOH); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{41}N_3O_6$·$C_7H_{17}NO_5$·3.0H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-[(1*S*)-carboxyethyl]aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (22): ^{1}H NMR (DMSO-d_6) δ 7.49 (m, 3H), 7.30−7.21 (m, 5H), 7.11 (m, 1H), 7.00 (m, 1H), 5.38 (m, 1H), 4.20 (m, 1H), 4.01−3.87 (m, 3H), 3.65 (m, 1H), 2.89 (m, 1H), 2.40 (m, 1H), 1.87 (s, 3H), 1.62−1.31 (m, 9H), 1.27 (m, 4H), 1.19 (m, 3H), 1.06 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{41}N_3O_6$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-[(1*R*)-carboxyethyl]aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (23): ^{1}H NMR (DMSO-d_6) δ 7.49 (m, 3H), 7.41 (m, 1H), 7.30−7.22 (m, 5H), 7.00 (m, 1H), 5.38 (m, 1H), 4.06 (m, 1H), 3.99−3.86 (m, 3H), 3.62 (m, 1H), 3.00 (m, 1H), 2.40 (m, 1H), 1.86 (s, 3H), 1.62−1.31 (m, 9H), 1.27−1.24 (m, 7H), 1.06 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{41}N_3O_6$·C_7H_{17}-NO_5·3.0H_2O) C, H, N.

(3*S*,5*R*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (24): prepared by a similar sequence used to prepare **20** except that D-tryptophan benzyl ester was used in place of L-tryptophan benzyl ester in **step a**; ^{1}H NMR (DMSO-d_6) δ 12.54 (br s, 1H, CO_2H) 7.47 (s, 4H, Ar H), 7.27 (m, 5H, Ar H), 7.00 (s, 1H, CONH), 5.35 (d, J = 15.0 Hz, 1H, C*H*HAr), 3.99−3.76 (m, 3H, H-3, H-5 and H-6) 3.70−3.65 (m, 3H, C*H*HAr and CONHCH_2), 2.92 (m, 1H, H-6), 2.30 (m, 1H, C*H*HAd), 1.86 (br s, 3H, 3 × CH), 1.65−1.25 (m, 13H, 6 × CH_2 and C*H*HAd) 1.04 (s, 3H, $COCH_3$); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{39}N_3O_6$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

25−**27** were prepared by a similar sequence used to prepare **20** except that the appropriate acetaldehyde was used in place of adamantan-1-ylacetaldehyde in **step a**.

(3*R*,5*S*)-4-Acetyl-1-benzyl-5-carboxymethylaminocarbonyl-3-(2,2-dimethylpropyl)-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (25): ^{1}H NMR (DMSO-d_6) δ 7.47−7.12 (m, 9H), 6.97 (m, 1H), 5.43 (m, 1H), 3.96 (m, 3H), 3.61 (m, 3H), 2.90 (m, 1H), 2.48 (m, 1H), 1.56 (m, 1H), 1.05 (s, 3H), 0.84 (s, 9H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{33}N_3O_6$·$C_7H_{17}NO_5$·4.5H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-1-benzyl-5-carboxymethylaminocarbonyl-3-cyclohexylmethyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (26): ^{1}H NMR (DMSO-d_6) δ 7.43−7.20 (m, 8H), 6.73 (m, 1H), 6.62 (m, 1H), 5.66 (m, 1H), 4.15−3.93 (m, 6H), 3.07 (m, 1H), 2.45 (m, 1H), 1.74−0.90 (m, 15H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{35}N_3O_6$·$C_7H_{17}NO_5$·6.0H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-1-benzyl-5-carboxymethylaminocarbonyl-3-cycloheptylmethyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (27): ^{1}H NMR (DMSO-d_6) δ 7.43−7.20 (m, 8H), 6.73 (m, 1H), 6.62 (m, 1H), 5.66 (m, 1H), 4.16−3.92 (m, 6H), 3.07 (m, 1H), 2.45 (m, 1H), 1.62−1.26 (m, 13H), 1.10 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{37}N_3O_6$·$C_7H_{17}NO_5$·6.0H_2O) C, H, N.

28−**30** were prepared by a similar sequence used to prepare **20** except that either methyl iodide or the appropriate fluoro-substituted benzyl bromides were used in place of benzyl bromide in **step c**.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-methyl-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (28): ^{1}H NMR (DMSO-d_6) δ 7.65 (m, 2H), 7.52 (m, 1H), 7.45 (m, 1H), 7.36 (m, 1H), 4.01−3.91 (m, 2H), 3.67−3.53 (m, 3H), 3.07 (s, 3H), 2.89 (m, 1H), 2.40 (m, 1H), 1.90 (s, 3H), 1.62 (s, 6H), 1.57−1.48 (m, 3H), 1.38−1.30 (m, 4H), 1.07 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{35}N_3O_6$·$C_7H_{17}NO_5$·3.0H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(4-fluorobenzyl)-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (29): ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5H), 6.95 (m, 2H), 6.72 (m, 1H), 5.73 (m, 1H), 5.26 (s, 1H), 4.26 (m, 1H), 4.05 (m, 4H), 3.31 (m, 1H), 2.63 (m, 1H), 2.35 (m, 1H), 1.88(s, 3H), 1.73−1.24 (m, 12H), 1.23 (s, 3H), 1.08 (m, 1H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}FN_3O_6$·$C_7H_{17}NO_5$·1.4H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(3-fluorobenzyl)-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (30): ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (m, 5H), 7.03 (m, 3H), 6.76 (m, 1H), 5.77 (m, 1H), 4.02 (m, 4H), 3.63 (m, 1H), 2.64 (m, 1H), 2.37 (m, 1H), 1.90 (s, 3H), 1.90−1.20 (m, 12H), 1.24 (s, 3H), 1.10 (m, 1H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}FN_3O_6$·$C_7H_{17}NO_5$·1.3H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-fluorobenzyl)-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (31): prepared from **11i** by the same sequence used to obtain **20** from **11a;** ^{1}H NMR ($CDCl_3$) δ 7.47−7.24 (m, 5H), 7.04 (m, 3H), 6.37 (m, 1H), 5.40 (m, 1H), 4.10 (m, 1H), 4.35 (m, 2H), 4.03 (m, 2H), 3.07 (m, 1H), 2.64 (m, 1H), 2.35 (m, 1H), 1.88 (s, 3H), 1.73−1.24 (m, 12H) 1.22 (s, 3H), 1.15 (m, 1H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}$-FN_3O_6·$C_7H_{17}NO_5$·1.2H_2O) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-carboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (32): prepared by the same route used to prepare **31** except that *N* ′-(2-chlorobenzyl)-L-tryptophan benzyl ester was used in place of *N* ′-(2-fluorobenzyl)-L-tryptophan benzyl ester in **step a**; ^{1}H NMR ($CDCl_3$) δ 7.42−7.12 (m, 6H), 7.10 (m, 1H), 6.86 (m, 1H), 6.46 (br s, 1H), 5.64 (m, 1H), 4.25−4.10 (m, 5H), 3.10 (m, 1H), 2.69 (m, 1H), 1.95 (s, 3H), 1.74−1.40 (m, 12H), 1.25 (m, 6H);

further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}ClN_3O_6 \cdot C_7H_{17}NO_5$) C, H, N.

33−**35** were prepared by a similar sequence used to prepare **20** except that the appropriate 5-substituted D/L-tryptophan benzyl ester was used in place of L-tryptophan benzyl ester in **step a**.

(±)-*trans*-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-carboxymethylaminocarbonyl-2,7-dioxo-9-methoxy-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (33): ^{1}H NMR ($CDCl_3$) δ 7.30−7.20 (m, 6H), 6.88 (m, 2H), 6.65 (m, 1H), 6.45 (br s, 1H), 5.60 (m, 1H), 4.15 (m, 1H), 4.00 (m 3H), 3.92 (m, 1H), 3.85 (s, 3H), 3.04 (m, 1H), 2.72 (m, 1H), 1.94 (s, 3H), 1.73−1.54 (m, 9H), 1.38 (m, 3H), 1.34 (s, 3H,), 1.18 (m, 1H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{41}N_3O_7 \cdot C_7H_{17}NO_5 \cdot 2.0H_2O$) C, H, N.

(±)-*trans*-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-carboxymethylaminocarbonyl-2,7-dioxo-9-methyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (34): ^{1}H NMR ($CDCl_3$) δ 7.27−7.18 (m, 7H), 6.65 (m, 1H), 6.50 (br s, 1H), 5.60 (m, 1H), 4.11−3.89 (m, 5H), 3.04 (m, 1H), 2.70 (m, 1H), 2.37 (s, 3H), 1.93 (s, 3H), 1.78−1.53 (m, 12H), 1.38 (m, 3H), 1.24 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{41}N_3O_6 \cdot C_7H_{17}NO_5 \cdot 3.0H_2O$) C, H, N.

(±)-*trans*-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-carboxymethylaminocarbonyl-2,7-dioxo-9-fluoro-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (35): ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 3H), 7.27 (m, 2H), 7.20 (m, 1H), 6.70 (m, 1H), 6.42 (m, 1H), 5.60 (m, 1H), 4.08 (m, 1H), 4.04 (m, 4H), 3.86 (m, 1H), 3.05 (m, 1H), 2.72 (m, 1H), 2.10 (s, 3H), 1.58 (m, 6H), 1.38 (m, 6H), 1.32 (s, 3H), 1.20 (m 1H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}FN_3O_6 \cdot C_7H_{17}NO_5 \cdot 1.5H_2O$) C, H, N.

36 and **37** were prepared by a similar sequence used to obtain **32** except that methyl chloroformate and propionyl chloride, respectively, were used in place of acetyl chloride in **step b**.

(3*R*,5*S*)-4-Methoxycarbonyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-carboxymethylcarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (36): ^{1}H NMR (DMSO-d_6) δ 7.56 (m, 1H), 7.45−7.20 (m, 7H), 6.84 (m, 1H), 5.43 (m, 1H), 4.40 (m, 1H), 4.07 (m, 1H), 3.75 (m, 1H), 3.61 (m, 2H), 3.01 (m, 1H), 2.20 (m, 1H), 1.86 (s, 3H), 1.57−1.30 (m, 11H), 1.22 (m, 5H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{38}ClN_3O_7 \cdot C_7H_{17}NO_5 \cdot 1.0H_2O$) C, H, N.

(3*R*,5*S*)-4-Ethylcarbonyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-carboxymethylcarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (37): ^{1}H NMR (DMSO-d_6) δ 7.62−7.19 (m, 7H), 6.98 (m, 1H), 5.45 (m, 1H), 4.06 (m, 5H), 3.68 (m, 3H), 3.01 (m, 1H), 2.25 (m, 1H) 1.88 (s, 3H), 1.67−1.14 (m, 13H), 0.55 (m, 3H); $[\alpha]^{20}_D$ −83.3° (*c* 0.66, MeOH); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{40}ClN_3O_6 \cdot C_7H_{17}NO_5 \cdot 2.0H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-[(1*S*)-carboxyethyl]aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (41). Compound **13j** was reacted according to **step f** except that L-alanine allyl ester was used in place of glycine benzyl ester *p*-toluenesulfonate to give (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)-methyl]-1-(2-chlorobenzyl)-5-[(1*S*)-allyloxycarbonylethyl]aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]-diazonine.

Step g: Et_2NH (0.9 mL, 8.7 mmol) was added to a solution of (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-[(1*S*)-allyloxycarbonylethyl]aminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (1.06 g, 1.6 mmol) and $(Ph_3P)_4Pd$ (200 mg, 0.17 mmol) in dry THF (60 mL) and the mixture stirred under argon for 17 h. The reaction mixture was diluted with EtOAc (40 mL), washed with 5% $KHSO_4$ (80 mL), brine (60 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography with HOAc−MeOH−CH_2Cl_2 (1:3:40) as eluant. **41**was obtained as a pale yellow solid (971 mg, 96%): ^{1}H NMR (DMSO-d_6) δ 12.60 (br s, 1H), 7.46−7.13 (m, 7H), 7.00 (m, 1H), 5.45 (m, 1H), 4.19−3.95 (m, 4H), 3.60 (m, 1H), 3.00 (m, 1H), 2.29 (m, 1H), 1.88 (s, 3H), 1.63−1.28 (m, 13H), 1.19 (m, 3H), 1.08 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{40}ClN_3O_6 \cdot C_7H_{17}NO_5 \cdot 3.0H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-methoxycarbonylmethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (42): prepared by a similar sequence used to prepare **20** except that glycine methyl ester was used in place of glycine benzyl ester *p*-toluenesulfonate in **step f**, and the final deprotection **step e** was omitted; ^{1}H NMR ($CDCl_3$) δ 7.45−7.23 (m, 8H), 6.77 (m, 1H), 6.30 (m, 1H), 5.60 (m, 1H), 4.10−4.00 (m, 4H), 3.90 (m, 1H), 3.76 (m, 3H), 3.09 (m, 1H), 2.70 (m, 1H), 1.74 (s, 3H), 1.73−1.40 (m, 13H), 1.15 (s, 3H). Anal. ($C_{35}H_{41}N_3O_6 \cdot 0.5H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-(tetrazol-5-yl)methylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (43). *N*-Benzyloxycarbonyl-*C*-(2*H*-tetrazol-5-yl)methylamine (obtained from *N*-benzyloxycarbonylaminoacetonitrile by modification of a literature method)[34] (7.81 g, 34 mmol) and Cs_2CO_3 (16.55 g, 51 mmol) in MeOH−H_2O (4:1/175 mL) was stirred at room temperature for 2 h. The mixture was evaporated to dryness, re-evaporated from EtOH (2 × 150 mL) and the residual oil suspended in dry DMF (180 mL). SEM-chloride (7.0 mL, 38 mmol) was added, and the mixture stirred at room temperature for 18 h. The reaction mixture was poured into EtOAc−H_2O (2:1/450 mL), the organic layer separated, washed with 5% $KHSO_4$ (150 mL), 10% Na_2CO_3 (150 mL), brine (2 × 100 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent gave *N*-benzyloxycarbonyl-*C*-(SEM-2*H*-tetrazol-5-yl)-methylamine as a colorless oil (12.18 g, 100%).

A mixture of *N*-benzyloxycarbonyl-*C*-(SEM-2*H*-tetrazol-5-yl)methylamine (12.18 g, 34 mmol) and 10% palladium on charcoal (0.93 g) in MeOH−THF (40:1/205 mL) was stirred under hydrogen at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite and evaporated to dryness to give the crude product as a colorless oil. The oil was dissolved in a saturated solution of HCl in MeOH and evaporated to dryness. The crude product was dissolved in H_2O, washed with Et_2O and the aqueous solution freeze-dried to give *C*-(SEM-2*H*-tetrazol-5-yl)methylamine hydrochloride as a white fluffy solid (5.79 g, 65%).

Compound **13j** was reacted according to **step f** except that *C*-(SEM-2*H*-tetrazol-5-yl)methylamine hydrochloride was used in place of glycine benzyl ester *p*-toluenesulfonate to give (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-[2-(2-trimethylsilylethoxy)methyl-2*H*-tetrazol-5-yl]methylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]-diazonine.

Step h: (3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-chlorobenzyl)-5-[2-(2-trimethylsilylethoxy)methyl-2*H*-tetrazol-5-yl]-methylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo-[*h*][1,4]diazonine (977 mg, 1.3 mmol) and $MgBr_2 \cdot Et_2O$ (2.33 g, 9.1 mmol) in dry CH_2Cl_2 (50 mL) were stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% $KHSO_4$ (100 mL), brine (2 × 100 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography using MeOH−CH_2Cl_2 (1:5) as eluant. **43** was obtained as a white amorphous solid (725 mg, 89%): ^{1}H NMR (DMSO-d_6) δ 7.63 (m, 1H), 7.47−7.12 (m, 7H), 7.00 (m, 1H), 5.46 (m, 1H), 4.41 (m, 2H), 4.14−3.93 (m, 3H), 3.80 (m, 1H), 3.00 (m, 1H) 2.69 (m, 1H), 2.40 (m, 1H) 1.88 (s, 3H), 1.70−1.32 (m, 13H), 1.04 (s, 3H); further characterized as the sodium salt. Anal. ($C_{34}H_{37}ClN_7O_4 \cdot Na \cdot 2.5H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-benzyl-5-methanesulfonamidocarboxymethylaminocarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (44). Step i: Methanesulfonamide (40 mg, 0.4 mmol) was added to a solution of **31** (194 mg, 0.32 mmol), EDCI (77 mg, 0.40 mmol), and DMAP (50 mg, 0.4 mmol) in dry CH_2Cl_2 (20 mL), and the reaction mixture stirred at room temperature

for 18 h. The solution was diluted with CH_2Cl_2 (10 mL), washed with 5% $KHSO_4$ (2 × 20 mL), brine (2 × 20 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography using HOAc−MeOH−CH_2Cl_2 (1:20:200) as eluant. **44** was obtained as a yellow fluffy solid (102 mg, 47%): ^{1}H NMR (DMSO-d_6) δ 11.48 (s, 1H), 7.53−7.42 (m, 4H), 7.30−7.21 (m, 5H), 7.00 (m, 1H), 5.34 (m, 1H), 4.00−3.87 (m, 4H), 3.74 (m, 2H), 3.21 (s, 3H), 2.90 (m, 1H), 2.40 (m, 1H), 1.87 (s, 3H), 1.64−1.27 (m, 13H), 1.06 (s, 3H); further characterized as the sodium salt. Anal. ($C_{35}H_{40}FN_4O_7S\cdot Na\cdot H_2O$) C, H, N.

(3*R*,7a*S*)-3-[(1-Adamantyl)methyl]-1-benzyl-6-carboxymethyl-2,4,7,9-tetraoxo-2,3,4,5,7,7a,8,9-octahydro-1*H*-pyrazino[1,6-*a*]benzo[*h*][1,4]diazonine (38). Benzyl (1*R*,3*S*)-1-[(1-adamantyl)methyl]-9-benzyl-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11p)** was obtained by a similar sequence used to prepare **11a** except that di-*tert*-butyl dicarbonate was used in place of acetyl chloride in **step b**. (1*R*,3*S*)-1-[(1-Adamantyl)methyl]-9-benzyl-3-benzyloxycarbonylmethylaminocarbonyl-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole **(14)** was obtained by treatment of **11p** according to **steps e** and **f**: ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 1H, Ar H), 7.39−7.15 (m, 12H, Ar H), 7.00 (m, 1H, Ar H), 5.60 (m, 1H, C*H*HAr), 5.36−5.09 (m, 5H, H-1, CH*H*Ar and CH_2Ar'), 4.30−4.15 (m, 3H, H-3 and CONHCH_2CO), 3.60 (m, 1H, H-4), 3.33 (m, 1H, H-4), 1.94 (br s, 3H, 3 × CH), 1.74−1.30 (m, 23H, 6 × CH_2, CH_2Ad and C(CH_3)$_3$).

Step j: 14 (921 mg, 1.31 mmol) in trifluoroacetic acid (20 mL) was stirred at room temperature in a lightly stoppered flask for 2 h. The reaction mixture was evaporated to dryness and re-evaporated from ether (2 × 40 mL). The solid obtained was dissolved in CH_2Cl_2 (40 mL), washed with saturated $NaHCO_3$ (40 mL), brine (2 × 40 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent gave (1*R*,3*S*)-1-[(1-adamantyl)methyl]-9-benzyl-3-benzyloxycarbonylmethylaminocarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole as a yellow solid (741 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 1H, CONH), 7.57 (m, 1H, Ar H), 7.36−7.11 (m, 12H, Ar H), 6.90 (m, 1H, Ar H), 5.35−5.19 (m, 4H, CH_2Ar and CH_2Ar'), 4.28 (d, J = 10.8 Hz, 1H, H-1), 4.20−4.13 (dd, J = 14.1, 5.7 Hz, 2H, CONHCH_2CO), 3.89 (dd, J = 11.1, 5.1 Hz, H-3), 3.47 (dd, J = 15.9, 4.8 Hz, 1H, H-4), 3.33 (dd, J = 15.9, 11.4 Hz, 1H, H-4), 1.97 (br s, 3H, 3 × CH), 1.70−1.56 (m, 13H, 6 × CH_2 and C*H*HAd), 1.27(m, 1H, CH*H*Ad).

Step k: (1*R*,3*S*)-1-[(1-Adamantyl)methyl]-9-benzyl-3-benzyloxycarbonylmethylaminocarbonyl-2-bromoacetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**15**) was obtained on treatment of (1*R*,3*S*)-1-[(1-adamantyl)methyl]-9-benzyl-3-benzyloxycarbonylmethylaminocarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole according to **step b** using bromoacetyl bromide in place of acetyl chloride: ^{1}H NMR ($CDCl_3$) δ 7.59 (m, 1H, Ar H), 7.36−7.13 (m, 12H, Ar H), 6.92 (m, 1H, Ar H), 5.56 (m, 1H, C*H*HAr), 5.33 (m, 3H, CH*H*Ar and CH_2Ar'), 5.20 (s, 2H, $COCH_2Br$), 5.07 (m, 1H, H-1), 4.97 (m, 1H, CONH), 4.17 (m, 1H, H-3), 4.03 (m, 2H, CONHCH_2CO), 3.55 (m, 1H, H-4), 3.35 (m, 1H, H-4), 1.89 (br s, 3H, 3 × CH), 2.02 (m, 1H, CH*H*Ad), 1.66−1.27 (m, 13H, 6 × CH_2, and C*H*HAd).

Step l: 15 (690 mg, 0.95 mmol) and Cs_2CO_3 (311 mg, 0.95 mmol) in DMF 910 mL) were heated at 100 °C for 2 h. On cooling, the mixture was diluted with H_2O (30 mL), and extracted with EtOAc (2 × 30 mL). The combined extracts were washed with 10% citric acid (30 mL), saturated $NaHCO_3$ (30 mL), brine (2 × 30 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography with EtOAc−DCM (1:40) as eluant to give **16** as an oil (196 mg, 33%): ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 1H, Ar H), 7.45 (m, 4H, Ar H), 7.33−7.25 (m, 3H, Ar H), 7.13 (m, 3H, Ar H), 7.02 (m, 2H, Ar H), 6.10 (m, 1H, Ar H), 5.30−5.17 (m, 5H, CH_2Ar, H-1 and CH_2Ar'), 4.70 (m × 2, 2H, H-3 and COC*H*HN), 4.28 (m, 1H, NC*H*HCO$_2$Bn), 3.95 (m, 1H, COCH*H*N), 3.83 (m, 1H, NCH*H*CO$_2$Bn), 3.35 (m, 1H, H-4), 3.00 (m, 1H, H-4), 1.91 (br s, 3H, 3 × CH), 1.73−1.43 (m, 1H, 13H, 6 × CH_2, and C*H*HAd), 1.28 (m, 1H, CH*H*Ad).

Reaction of **16** according to **step d** gave (3*R*,7a*S*)-3-[(1-adamantyl)methyl]-1-benzyl-6-benzyloxycarbonylmethyl-2,4,7,9-tetraoxo-2,3,4,5,7,7a,8,9-octahydro-1*H*-pyrazino[1,6-*a*]benzo[*h*][1,4]diazonine: ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 1H, Ar H), 7.58 (m, 1H, Ar H), 7.38 (m, 6H, Ar H), 7.27 (m, 3H, Ar H), 7.10 (m, 2H, Ar H), 6.98 (m, 1H, Ar H), 5.21−5.09 (m, 4H, C*H*HAr, H-3 and CH_2Ar'), 4.44 (m × 2, 2H, CH*H*Ar and H-5), 4.32 (m, 1H, COC*H*HN), 3.77 (m, 1H, COCH*H*N), 3.67 (m, 1H, NC*H*HCO$_2$Bn), 3.43 (m × 2, 2H, NCH*H*CO$_2$Bn and H-6), 4.97 (m, 1H, CONH), 4.17 (m, 1H, H-3), 4.03 (m, 2H, CONHCH_2-CO), 2.99 (m, 1H, CH*H*Ad), 2.50 (m, 1H, H-6), 1.93 (br s, 3H, 3 × CH), 1.70−1.34 (m, 12H, 6 × CH_2), 0.93 (m, 1H, C*H*HAd).

38 was obtained as a white amorphous solid by deprotection of (3*R*,7a*S*)-3-[(1-adamantyl)methyl]-1-benzyl-6-benzyloxycarbonylmethyl-2,4,7,9-tetraoxo-2,3,4,5,7,7a,8,9-octahydro-1*H*-pyrazino[1,6-*a*]benzo[*h*][1,4]diazonine according to **step e**: ^{1}H NMR (DMSO-d_6) δ 7.70−7.03 (m, 9H), 5.06 (m, 1H), 4.95 (m, 1H), 4.34 (m, 1H), 4.24 (m, 1H), 3.90 (m, 2H), 3.55 (m, 2H), 2.95 (m, 1H), 2.30 (m, 1H), 1.85 (s, 3H), 1.63−1.24 (m, 12H), 0.99 (m, 1H); $[\alpha]^{20}_D$ +67.4° (*c* 0.89, MeOH); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{37}N_3O_6\cdot C_7H_{17}NO_5\cdot 2.0H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-fluorobenzyl)-5-carboxyethylcarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (39). Step m: The benzyl protecting group of **11i** was removed according to **step e**, and the resultant acid reacted with *tert*-butyl lithioacetate using a literature method[27] to give (1*R*,3*S*)-1-[(1-adamantyl)methyl]-2-acetyl-1-(2-fluorobenzyl)-3-*tert*-butyloxycarbonylmethylcarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole **(17):** ^{1}H NMR ($CDCl_3$) δ 7.57 (m, 1H, Ar H), 7.27−7.12 (m, 5H, Ar H), 6.93 (m, 1H, Ar H), 6.23 (m, 1H, Ar H), 5.36 (m, 2H, CH_2Ar), 5.00 (d, J = 9.9 Hz, 1H, H-1), 4.36 (m, 1H, H-3), 3.69 (d, J = 15.0 Hz, 1H, COC*H*HCO), 3.30 (d, J = 15.0 Hz, 1H, COCH*H*CO), 3.20 (m, 1H, H-4), 3.12 (m, 1H, H-4), 2.02 (br s, 3H, 3 × CH), 1.90 (s, 3H, $COCH_3$), 1.79−1.50 (m, 14H, 6 × CH_2 and CH_2-Ad), 1.48 (s, 9H, C(CH_3)$_3$).

Step n: A solution of **17** (663 mg, 1.1 mmol) in dry THF (20 mL) was added dropwise over 10 min to a suspension of NaH (60% dispersion in mineral oil/51 mg, 1.3 mmol) in dry THF (5 mL) under argon at 0 °C. After stirring at 0 °C for 20 min, benzyl bromoacetate (0.2 mL, 1.2 mmol) was added, and the mixture stirred at room temperature for 2 h. The reaction mixture was poured into EtOAc−H_2O (1:1/60 mL), the organic layer separated, washed with brine (30 mL), and dried (Na_2SO_4). Filtration and evaporation of the solvent gave **18** as a yellow foam (864 mg, 100%): ^{1}H NMR ($CDCl_3$) δ 7.57 (m, 1H, Ar H), 7.38−7.15 (m, 10H, Ar H), 6.94 (m, 1H, Ar H), 6.25 (m, 1H, Ar H), 5.37 (m, 2H, CH_2Ar), 5.22 (s, 2H, CH_2Ar'), 5.05 (m, 1H, H-1), 4.55 (m, 1H, H-3), 4.30 (m, 1H, COC*H*(CH_2CO_2Bn)-CO), 3.29−3.20 (m, 2H, COCH(C*H*$_2$CO$_2$Bn)CO), 3.09 (m, 1H, H-4), 2.83 (m, 1H, H-4), 2.01 (br s, 3H, 3 × CH), 1.90 (s, 3H, $COCH_3$), 1.77−1.48 (m, 14H, 6 × CH_2 and CH_2Ad), 1.42 (s, 9H, C(CH_3)$_3$).

Step o: A solution of (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)-methyl]-1-(2-fluorobenzyl)-5-benzyloxycarbonylethylcarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (obtained on reacting **18** according to **steps j** and **d**) (232 mg, 0.35 mmol) was stirred under hydrogen with palladium on charcoal (75 mg) at room temperature for 17 h. The reaction mixture was filtered through a pad of Celite and the filtrate evaporated to give (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)methyl]-1-(2-fluorobenzyl)-5-carboxyethylcarbonyl-7-hydroxy-2-oxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine as a white solid (200 mg, 95%): ^{1}H NMR (DMSO-d_6) δ 7.43 (m, 1H, Ar H), 7.36−7.12 (m, 6H, Ar H), 6.90 (m, 1H, Ar H), 5.60 (m, ex. D_2O, 1H, OH), 5.47 (d, J = 10.2 Hz, 1H, C*H*HAr), 5.00 (br s, 1H, ArC*H*OH), 5.13 (m, 2H, CH_2Ar'), 4.99 (m, 1H, H-1), 4.10 (m, 1H, H-3), 3.22 (m, 1H, H-4), 3.08 (m, 1H, H-4), 2.97 (m, 1H, COC*H*HCH$_2$CO$_2$Bn), 2.84 (m, 2H, COCH$_2$C*H*$_2$CO$_2$Bn), 2.63 (m, 1H, COCH*H*CH$_2$CO$_2$Bn), 2.01 (br s, 3H, 3 × CH), 1.88 (s, 3H, $COCH_3$), 1.78−1.53 (m, 13H, 6 × CH_2 and C*H*HAd), 1.45 (m, 1H, CH*H*Ad).

A mixture of (3*R*,5*S*)-4-acetyl-3-[(1-adamantyl)methyl]-1-(2-fluorobenzyl)-5-carboxyethylcarbonyl-7-hydroxy-2-oxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (187 mg, 0.31 mmol), NMO (60 mg, 0.5 mmol), TPAP (19 mg, 0.05 mmol) and crushed 4A molecular sieves (206 mg) was stirred in MeCN−CH_2Cl_2 (1:4/5 mL) at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 5% $KHSO_4$ (20 mL), brine (20 mL), and dried (Na_2SO_4). Filtration and evaporation of the solvent gave **39** as a pale solid which was purified by preparative HPLC (Dynamax-60A C18, 65% MeCN−H_2O (containing 0.5% HOAc), t_R 17.7min) (48 mg, 26%): ^{1}H NMR (MeOH-d_4) δ 7.53 (m, 3H), 7.32 (m, 2H), 7.06 (m, 3H), 5.38 (m, 1H), 4.29−4.10 (m, 3H), 3.86 (m, 2H), 2.95 (m, 1H), 2.59 (m, 1H), 1.90 (m, 3H), 1.60 (m, 6H), 1.45 (m, 6H), 1.23 (m, 3H), 1.18 (s, 3H); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{39}FN_2O_6 \cdot C_7H_{17}NO_5 \cdot 0.5H_2O$) C, H, N.

(3*R*,5*S*)-4-Acetyl-3-[(1-adamantyl)methyl]-1-(2-fluorobenzyl)-5-carboxymethylcarbonyl-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine (40): obtained as a yellow solid by treatment of **17** according to **steps d** and **j**; ^{1}H NMR (DMSO-d_6) δ 7.55 (m, 3H), 7.32 (m, 2H), 7.13 (m, 3H), 5.21 (m, 1H), 4.25 (m, 1H), 3.99 (m, 1H), 3.89 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 3.14 (m, 1H), 2.76 (m, 1H), 2.40 (m, 1H), 1.92 (s, 3H), 1.65−1.25 (m, 13H), 1.04 (s, 3H); $[\alpha]^{20}_D$ −78.4° (*c* 0.60, MeOH); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{37}FN_2O_6 \cdot C_7H_{17}NO_5 \cdot 0.25H_2O$) C, H, N.

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