Abstract

CHARLES ERIC BALLARD. (I) Development of an Inexpensive Carbohydrate Derivative Used as a Chiral Auxiliary in the Synthesis of α-Hydroxy Carboxylic Acids. (II) Synthesis of a Potential Carrier for Copper Ions Designed to Be Transported by P-Glycoprotein. (Under the direction of Professor Binghe Wang)

1. Development of an Inexpensive Carbohydrate Derivative Used as a Chiral Auxiliary in the Synthesis of α-Hydroxy Carboxylic Acids

Protected α-hydroxy carboxylic acids were synthesized in moderate yield and high diastereoselectivity by alkylation of glycolate (α-hydroxy acetate) enolates using a D-fructose-derived chiral auxiliary. The new chiral center was assigned the *R* configuration based on comparisons of optical rotations and on one crystal structure analysis. This alkylation methodology is compatible with several hydroxyl protecting groups. The free hydroxy acids were obtained upon removal of the protecting group from the hydroxyl functionality followed by saponification.

2. Synthesis of a Potential Carrier for Copper Ions Designed to Be Transported by P-Glycoprotein

Poisoning by heavy metals has traditionally been treated with a handful of nonspecific, highly polar chelating agents. Although the present set of chelators has proven to be valuable as therapeutics, their lack of specificity sometimes results in leaching of

essential minerals and their high polarity limits their excretion, such that the metal-chelate complexes are primarily removed by the kidneys.

We have developed a potential transporter for copper ions, consisting of a chelator conjugated to a P-glycoprotein transporter substrate. We hypothesize that upon complexation to copper, the complex can be removed by the P-glycoprotein active transporter. Assays that will determine the metal-binding and biological transport properties of the conjugates are planned for later.

(I) Development of an Inexpensive Carbohydrate Derivative Used as a Chiral Auxiliary in the Synthesis of α-Hydroxy Carboxylic Acids

(II) Synthesis of a Potential Carrier for Copper Ions Designed to Be Transported by P-Glycoprotein

by Charles Eric Ballard

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Approved by:

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_____	_____
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Dedication

To my wife Jodi, my parents George and Betty, and my sister Ellen.

I appreciate all of your love, encouragement, patience, and support.

Biography

The author was born on July 7, 1973, in Covington, Kentucky. He grew up in Princeton, Kentucky. Upon graduating from Caldwell County High School, Eric attended the University of Kentucky on a Singletary Scholarship. There he earned a BS in Chemical Engineering in 1995. In 1997 he began his graduate education with Professor Binghe Wang at North Carolina State University. Here he worked on a variety on projects, including ones involving molecular recognition, asymmetric synthetic methodology, and biological transport.

Acknowledgments

My advisor, Professor Binghe Wang, provided guidance, patience, and financial support during my graduate studies. North Carolina State University Department of Chemistry and the Burroughs Wellcome Fund also provided financial support. I also thank the National Institutes of Health and the American Heart Association for funding this research.

Dr. Hongwu Yu and Ms. Michelle Ferro also worked on the fructose auxiliary project. Dr. Paul Boyle determined the two crystal structures related to that project. Ms. Xinhui Lou and Dr. Yanling Zhang worked with me on the chelator project.

I also thank the other former and current members of the Wang group, especially Dr. Greg Springsteen, Dr. Wenqian Yang, and Dr. Wei Wang.

The members of my committee made suggestions and comments during my graduate studies. These faculty members are Professors Daniel Comins, Jon Lindsey, and Suzanne Purrington.

Dr. Sabapathy Sankar helped with 2D and variable-temperature NMR experiments.

I am grateful to my fellow graduate students and postdocs within the department, especially the Comins group, for their camaraderie.

Several faculty members discussed possible career paths with me. Among these I especially thank Professors Alton Banks and Maria Oliver-Hoyo for their advice and suggestions.

Mr. Robert Morse and Professor Joe Wilson sparked my interest in organic chemistry. Professor Eric Grulke encouraged me to attend graduate school.

Members of the support staff provided prompt assistance with regard to

equipment repairs and administrative matters. These persons include Mr. Leonard Page, Mr. Eddie Barefoot, Mr. Tony Radford, Ms. Jan Singhass, Mr. Glenn Hennessee, Mrs. Sara Rose, Mr. Jeff Cable, Ms.Crissy Williams Brown, Ms. Cynthia Martin, Ms. Joyce Dunn, and Ms. Brenda Burgess.

A free trial period of Advanced Chemistry Development online software was used to estimate the physical properties of the target compounds in the chelator project.

Table of Contents Page

List of Figures Page

List of Tables Page

List of Schemes

List of Abbreviations

μ: ionic strength

ABC: adenosine triphosphate-binding cassette

ATP: adenosine triphosphate

Bn: benzyl

br: broad

Boc: *tert*-butoxycarbonyl

BOM: benzyloxymethyl

cLogD: predicted common logarithm of the octanol/water partition coeffient as a function of pH

cLogP: predicted common logarithm of the octanol/water partition coeffient at zero ionic strength

CPTA: *N*-(*p*-toluic acid)-1,4,8,11-tetraazacyclotetradecane

cyclam: 1,4,8,11-tetraazacyclotetradecane

CYP 3A4: cytochrome P450 3A4

d: doublet

de: diastereomeric excess

DCC: 1,3-dicyclohexylcarbodiimide

DCM: dichloromethane

DEA: diethylamine

DFOA: desferrioxamine

DIEA: *N,N*-diisopropylethylamine

DMAP: 4-(dimethylamino)pyridine

DMPU: 1,3-dimethylpropyleneurea; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*) pyrimidinone

DMF: *N,N*-dimethylformamide

DMSA: *meso*-2,3-dimercaptosuccinic acid

DMSO: dimethyl sulfoxide

DPA: D-penicillamine

EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

EDTA: ethylenediaminetetraacetic acid

eq.: equivalent

FABMS: fast-atom bombardment mass spectrometry

Fmoc: 9-fluorenylmethoxycarbonyl

Gly: glycine

His: histidine

HOBt: 1-hydroxybenzotriazole

HMDS: hexamethyldisilazide; bis(trimethylsilyl)amide

HMPA: hexamethylphosphoric triamide

HPLC: high-pressure liquid chromatography

HRFABMS: high resolution fast-atom bombardment mass spectroscopy

IR: infrared

K: formation constant

LDA: lithium diisopropylamide

Lys: lysine

MDR: multidrug resistance

MEK: methyl ethyl ketone

MOM: methoxymethyl

MRP: multidrug resistance protein

MS: molecular sieves

NMR: nuclear magnetic resonance

p: pentet

P-gp: P-glycoprotein

Ph: phenyl

psi: pound per square inch

q: quartet

rt: room temperature

s: singlet

t: triplet

TBS: *tert*-butyldimethylsilyl

TBDPS: *tert*-butyldiphenylsilyl

TEA: triethylamine

tert: tertiary

TES: triethylsilyl

TETA: triethylenetetramine

TFA: trifluoroacetic acid

TfOH: trifluoromethanesulfonic acid

THF: tetrahydrofuran

TIPS: triisopropylsilyl

TLC: thin layer chromatography

TMEDA: *N,N,N',N'*-tetramethylethylenediamine

TMP: 2,2,6,6-tetramethylpiperidide

UV: ultraviolet

Z: benzyloxycarbonyl

Chapter 1. Development of an Inexpensive Carbohydrate Derivative as a Chiral Auxiliary for the Asymmetric Synthesis of α-Hydroxy Acids.

1.1. Contribution

The goal of this project was to develop a new synthetic methodology for the asymmetric synthesis of α-hydroxy acids. A glycolate alkylation approach using a fructose derivative was undertaken. My contributions were as follows: optimization of the methylation of glycolate **3a**; preparation of acids **2a-g,k**, glycolates **3a-g**,**k** and **15** and methylated products **4a, 5a, 6a, 7a, 8a, 9a, 10a, 14a,** and **16;** preparation of pseudo-racemic standards **4a** and **16**; deprotection and hydrolysis of esters **13e** and **13g**; and preparation of the pseudo-racemates corresponding to **19a,b**. Dr. Hongwu Yu conducted the initial allylations with glycolate **3a**; prepared the acids **2a,h,i**, glycolates **3a,h-j**, the alkylated products **4a-e**, **11a-c, 12a-c,** and **13a-g**, and their pseudo-racemic standards; deprotected and hydrolyzed compounds **13** to the free acids **18**; and prepared the samples submitted for crystallographic analysis. Dr. Paul Boyle determined both X-ray crystal structures. I have included experimentals for all compounds; the ones that I did not prepare are marked with an asterisk in the experimental section. The following chapter describing the work is taken, with slight modification, from "An Inexpensive Carbohydrate Derivative Used as a Chiral Auxiliary in the Synthesis of α-Hydroxy Carboxylic Acids," Yu, H.; Ballard, C.E.; Boyle, P.D.; Wang, B.; *Tetrahedron* **2002**, *58*, 7663-7679.

1.2. Introduction

α-Hydroxy carboxylic acids are important building blocks for the synthesis of depsides and depsipeptides, natural products that often exhibit significant biological activity.[1-16] Depsipeptides such as the potent antibiotic vancomycin have been developed into therapeutic agents. One way to make progress in this area is to make analogs of these natural products containing unnatural hydroxy acids. Development of synthetic routes to hydroxy acids will be key to these efforts.

Reported enantioselective routes to α-hydroxy acids[17,18] include hydroxylation of enolates,[19,20] reduction of α-ketoacid derivatives or their precursors,[21-28] Horner-Wittig reaction of aldehydes with a dialkoxymethyl phosphine oxide followed by Sharpless dihydroxylation,[29] carbonyl-ene reactions of glyoxylates,[30,31] addition of cyanide to aldehydes and ketones,[32,33] nucleophilic alkylation of aldehydes[34] or α-oxo acid derivatives,[35-37] Friedel-Crafts reactions of aromatic compounds with glyoxylates,[38] O-H insertions of diazoacetates,[39] condensation of *trans*-1,3-dithiane-1,3-dioxide with aldehydes,[40] reduction of chiral hemiacetals,[41,42] dihydroxylation followed by a second oxidation,[43] nucleophilic alkylation of oxazin-4-ones,[44] [2,3] Wittig rearrangement of propargyloxy acetates,[45] dynamic kinetic resolution of hydroxy esters,[46] and enzymatic resolution of hydroxy acids.[47]

Another straightforward method is the stereoselective alkylation of glycolates (α-hydroxy acetates).[48-55] This strategy relies on a chiral auxiliary to direct the approach of the incoming electrophile to one face of the glycolate enolate. In addition, the enolate should have a single *E*/*Z* geometry. The most notable of these reports used a *trans*-2,5-disubstituted pyrrolidine,[56] menthone[57] or camphorsulfonamide[58], or Evans's oxazolidinone[59] as chiral

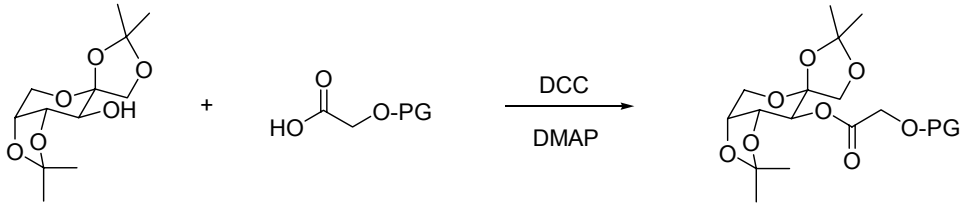
auxiliaries. The first three strategies provided excellent yield and good to excellent diastereomeric excess (de) for the alkylation even with less reactive electrophiles (*e.g.,* butyl iodide), but they suffer the limitation of being cleaved under harshly acidic conditions. The oxazolidinone auxiliary gave excellent yields and diastereoselectivities, but it was only studied with reactive electrophiles, mainly allylic or propargylic iodides. However, no auxiliary that can be removed by basic hydrolysis has been reported to efficiently alkylate glycolates with a wide variety of electrophiles.

One readily available source of inexpensive chiral auxiliaries is carbohydrates. Enolate alkylations using carbohydrate auxiliaries have met with mixed results.[60,61] Costa,[62,63] Mulzer,[64] and Koll[65] achieved moderate yields and selectivities with their systems. Recently Enders used a glucose-derived auxiliary for efficient α-alkylation of sulfonates.[66] We investigated 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (D-fructose diacetonide)[67] because it has proven valuable in asymmetric synthesis. It has been used as an auxiliary in Diels-Alder cycloadditions,[68] and it is the precursor to an epoxidation catalyst developed by Shi and co-workers.[67] Earlier we outlined our preliminary results using D-fructose diacetonide as an auxiliary in glycolate alkylation.[69] Herein we report our complete studies of asymmetric glycolate alkylation.

1.3. Results and Discussion

1.3.a. Initial Results

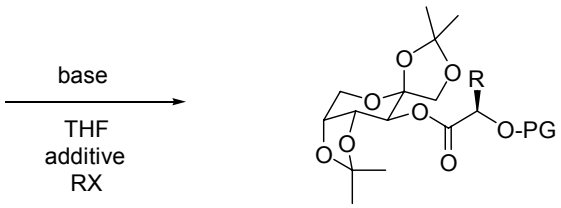
The auxiliary **1** was obtained from D-fructose in one step.[67] Its free 3-hydroxyl group



1

2a PG = Bn
2b PG = $CH_2C_6H_4NO_2(p)$
2c PG = $CH_2C_6H_4OMe(p)$
2d PG = $CH_2C_6H_4F(p)$
2e PG = Me
2f PG = MOM
2g PG = BOM
2h PG = TBS
2i PG = TBDPS
2k PG = TIPS

3a PG = Bn
3b PG = $CH_2C_6H_4NO_2(p)$
3c PG = $CH_2C_6H_4OMe(p)$
3d PG = $CH_2C_6H_4F(p)$
3e PG = Me
3f PG = MOM
3g PG = BOM
3h PG = TBS
3i PG = TBDPS
3j PG = TES
3k PG = TIPS



4a PG = Bn, R = Me
4b PG = Bn, R= allyl
4c PG = Bn, R = Bn
4d PG = Bn, R = Et
4e PG = Bn, R = $PhCH_2CH_2$

5a PG = $CH_2C_6H_4NO_2(p)$, R = Me

6a PG = $CH_2C_6H_4OMe(p)$, R = Me

7a PG = $CH_2C_6H_4F(p)$, R =Me
8a PG = Me, R = Me

9a PG = MOM, R = Me

10a PG = BOM, R = Me

11a PG = TBS, R = Me
11b PG = TBS, R = allyl
11c PG = TBS, R =Bn

12a PG = TBDPS, R = Me
12b PG = TBDPS, R = allyl
12c PG = TBDPS, R = Bn

13a PG = TES, R = Me
13b PG = TES, R = allyl
13c PG = TES, R = Bn
13d PG = TES, R = Et
13e PG = TES, R = $PhCH_2CH_2$
13f PG = TES, R = $CH_3(CH_2)_4$
13g PG = TES, R = 2-naphthylmethyl

14a PG = TIPS, R = Me

Scheme 1.1. General route for the synthesis and alkylation of glycolates **3**.

was esterified with benzyloxyacetic acid **2a** using 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to give glycolate **3a** (Scheme 1.1). Initial alkylations were conducted with two reactive halides (allyl bromide and allyl iodide) to determine the feasibility of using D-fructose diacetonide as a chiral auxiliary (Scheme 1.1).Tetrahydrofuran (THF) was used as the solvent for these reactions. Table 1.1 summarizes the findings of these experiments. Comparison of entry 4 with entries 1-3 shows that lithium bis(trimethylsilyl)amide (LiHMDS) (2 eq.) was the optimal base in combination with the more reactive allyl iodide. In an effort to maximize the de by performing the alkylation at lower temperature, entry 5 shows that a higher yield was obtained, but that the diastereoselectivity was slightly lower.

Since these initial results were encouraging, we tried to optimize the reaction with respect to a variety of factors, including solvent, additives, base, cation, and hydroxyl protecting group. The next studies examined the reaction as a function of solvent polarity and coordination power. The more Lewis basic solvents were expected to coordinate the cation of the enolate more strongly, giving a more reactive intermediate.[70] The coordination of the enolate with solvent and additives greatly affects the degree of aggregation of the enolate in solution, which can significantly influence its reactivity and selectivity.[71] Some reports have shown that aprotic polar additives such as hexamethylphosphoric triamide (HMPA) can erode[53,72] or even reverse[63,73] stereoselectivity. However, entry 6 of Table 1.1 shows that addition increased the yield of the reaction by 22% without decreasing the stereoselectivity.

Table 1.1. Influences of base and temperature on the alkylation of **3a** to **4b** in THF.

Entry	RX	Base	Temp. (°C)	Yield (%)	de (%)
1	allyl bromide	LDA (1.5 eq)	-78	59	66
2	allyl iodide	LiHMDS (1.5 eq)	-78	51	92
3	allyl iodide	NaHMDS (1.5 eq)	-78	41	81
4	allyl iodide	LiHMDS (2 eq)	-78	54	92
5	allyl iodide	LiHMDS (2 eq)	-92	78	86
6	allyl iodide (5% HMPA)	LiHMDS (2 eq)	-78	76	92

1.3.b. Optimization of the Alkylation Conditions

These factors were optimized using glycolate **3a** with MeI as the alkylating agent (Scheme 1.1 and Table 1.2). The initial conditions (entry 1) were the same as those used for Table 1.1, entry 4: 2 equivalents of LiHMDS at –78 °C. The moderate yield and de for this reaction indicate that this is an ideal reaction for optimization studies. If one of the reaction conditions makes an important positive or negative impact on the alkylation, the yield and/or selectivity data should be significantly different from the data in this baseline experiment. In addition, this product offers the advantage that its de can be determined by ^{1}H NMR.

The data in Table 1.2 indicate that the baseline conditions were close to optimal, besides the use of HMPA as an additive and lowering the reaction temperature. Comparison of entries 1 and 2 shows that adding HMPA did not significantly affect the reaction. However, with electrophiles besides MeI, a large increase in yield was seen with the addition of HMPA.[69] For example, the addition of HMPA increased the yield of the alkylation by 22% when allyl iodide was the electrophile (Table 1.1, entries 4 and 6). Comparison of entries 2 and 3 shows that lowering the reaction temperature improved both the yield and de.

Table 1.2. Reaction conditions, yields, and de's for the optimization of the methylation of **3a** to **4a** (PG = Bn, R = Me).

Entry	Solvent	Additive[a]	Base[b]	Reaction temp. (°C)	Yield (%)	de (%)
1	THF	none	LiHMDS	-78	61	83
2	THF	HMPA	LiHMDS	-78	64	79
3	THF	HMPA	LiHMDS	-95	73	86
4	THF	DMPU	LiHMDS	-95	72	73
5	THF	TMEDA	LiHMDS	-95	51	86
6	THF	HMPA	KHMDS	-95	73	78
7	THF	HMPA	LiHMDS (1 eq.) + *n*-BuLi (1 eq.)	-95	43	69
8	THF	HMPA	LiTMP	-95	36	91
9	PhMe	HMPA	LiHMDS	-95	21	87
10	DME	HMPA	LiHMDS	-78	52	83
11	THF	HMPA + $MgBr_2$ (2.4 eq.)	LiHMDS	-95	51	92
12	THF	HMPA + LiBr (2.0 eq.)	LiHMDS	-95	40	91
13	THF	HMPA+ LiCl (2.2 eq.)	LiHMDS	-95	40	93

[a] 5% (v/v)
[b] 2 eq.

Comparison of HMPA with the other aprotic polar solvents 1,3-dimethylpropyleneurea (DMPU) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in entries 4 and 5 shows that DMPU gives a comparable yield with slightly lower de while TMEDA gives a much lower yield with comparable stereoselectivity. Comparison of the different bases in entries 6-8 shows that only KHMDS (2 eq.) gave a comparable yield, but with a slight sacrifice of de. The bulky base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) gave a very low yield but a quite high de for the methylation. Comparison of THF with the other solvents listed in entries 9 and 10, toluene and 1,2-dimethoxyethane (DME), show that THF is superior. These solvents vary widely in their ability to coordinate cations, and various reports have shown each has been tested in certain examples of enolate chemistry.[53] The addition of various metal additives[71,74] in entries 11-13 gave much lower yields but good de's. With the lithium halide salts, about half of the starting material was recovered unreacted.

1.3.c. Effect of the Hydroxyl Protecting Group on the Alkylation

After these optimization studies had been completed, the compatibility of other hydroxyl protecting groups (PG's) besides benzyl with these methylation conditions was studied (Scheme 1.1 and Table 1.3). The alkylation conditions used were LiHMDS (2 eq.) in THF/5% HMPA at –95 ºC. Substrates in entries 2-11 were prepared by DCC/DMAP coupling of the appropriately protected glycolic acid with the auxiliary **1**, except for glycolate **3j**, which was prepared by hydrogenolysis of **3a** followed by reprotection with the triethylsilyl group. These protecting groups cover a large range of electronic and steric characteristics. The overall impression from this table is that the choice of protecting group had relatively little effect on the stereoselectivity of the alkylation, but that it significantly affected the yield. This was expected because the directing influence of the reaction was assumed to arise almost entirely from the chiral auxiliary. The differences in yield probably arise from differences in reactivity of the enolates.

Entry 1 of Table 1.3 is the same as entry 3 of Table 1.2 and served as a baseline for this study. Entries 2-4 include substituted benzyl groups and were included for comparison with entry 1. The literature indicates that the protons of an α-oxy carbonyl compound are more acidic than those of an α-unsubstituted carbonyl compound by about 2 pK_a units.[75,76] We hypothesized that altering the electronics of the protecting group would affect the yield of the reaction.

To test if this hypothesis were true for the subtly different cases of unsubstituted and *p*-substituted benzyl groups, we prepared substrates **3b**, **3c**, and **3d**. The reaction in entry 2

seems to represent an odd case because during the addition of base, the solution of substrate

Table 1.3. Compatibility of different protecting groups with the optimal conditions.

Entry	Substrate	PG	Product (R = Me)	Reaction temp. (°C)	Yield (%)	de (%)
1	**3a**	Bn	**4a**	-95	73	86
2	**3b**	$CH_2C_6H_4NO_2$ (*p*)	**5a**	-95	19	89
3	**3c**	$CH_2C_6H_4OMe$ (*p*)	**6a**	-95	66	91
4	**3d**	$CH_2C_6H_4F$ (*p*)	**7a**	-95	75	93
5	**3e**	Me	**8a**	-95	66	92
6	**3f**	MOM	**9a**	-95	65	91
7	**3g**	BOM	**10a**	-95	68	87
8	**3h**	TBS	**11a**	-78	76	84
9	**3i**	TBDPS	**12a**	-78	83	89
10	**3j**	TES	**13a**	-78	77	88
11	**3k**	TIPS	**14a**	-95	70	84

3b turned dark red in color, unlike those of the other substrates, which were pale yellow. Based on the low pK_a of *p*-nitrotoluene (20.4),[77] competitive deprotonation at the benzylic position may be occurring. Comparison of entries 3 and 4 with entry 1 indicates that the *p*-substituent had only a small effect on the yield of the alkylation. The compound with the electron-withdrawing fluorine (entry 4) gave a slightly greater yield than that for the electron-donating methoxy (entry 3). A possible explanation is that the electron-donating group destabilizes the enolate, so that it undergoes more side reactions.

Entries 5-7 include more alkyl hydroxyl protecting groups: methyl, methoxymethyl (MOM), and benzyloxymethyl (BOM). The yields for these alkylations were slightly lower.

The most successful reactions were carried out with silyl protecting groups (entries 8-11). The groups tested included the *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS), triethylsilyl (TES), and triisopropylsilyl (TIPS) groups. The less bulky groups (TBS, TBDPS, and TES) provided the best yields and selectivities of any protecting group, allowing for the different reaction temperatures. The TIPS group gave a slightly lower yield,

with slightly lower selectivity. TIPS may be too large to allow for efficient approach of the electrophile to the enolate.

To confirm the conclusions from these studies, additional electrophiles were tested with substrates **3a**,**h-j** (PG = Bn, TBS, TBDPS, and TES, respectively, Scheme 1.1 and Table 1.4). Generally substrate **3a** showed lower yield than the other substrates. The TBDPS- and TES-protected substrates (**3i** and **3j**, respectively) gave comparably high yields and selectivity. The TES glycolate **3j** was chosen for further studies with a wide range of electrophiles, including many less reactive iodides (entries 10-12). Moderate yields and good de's were also obtained with these substrates.

Table 1.4. Yields and de's for the conversion of esters **3a, h-j** to **4, 11-13** in the presence of HMPA at –78 ºC.

Entry	Substrate	Electrophile (RX)[a]	Product	Yield (%)[b]	de (%)[c]
1	**3a**	BnBr	**4c**	58	98
2	**3a**	CH_3CH_2I	**4d**	74	76
3	**3a**	$PhCH_2CH_2I$	**4e**	52	79
4	**3h**	$CH_2=CHCH_2I$	**11b**	88	85
5	**3h**	BnBr	**11c**	88	86
6	**3i**	$CH_2=CHCH_2I$	**12b**	78	89
7	**3i**	BnBr	**12c**	89	94
8	**3j**	$CH_2=CHCH_2I$	**13b**	71	91
9	**3j**	BnBr	**13c**	75	96
10	**3j**	CH_3CH_2I	**13d**	83	88
11	**3j**	$PhCH_2CH_2I$	**13e**	61	60
12	**3j**	$CH_3(CH_2)_4I$	**13f**	58	83
13	**3j**	2-(bromomethyl) naphthalene	**13g**	71	91

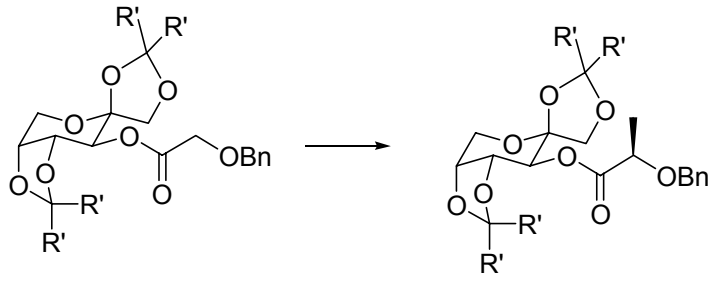
[a] 5 eq.

[b] Isolated yield after silica gel chromatography

[c] Determined by HPLC on a Nova-Pak silica column (3.9 x 150 mm) using hexanes/EtOAc or by 300 or 400 MHz ^{1}H NMR

1.3.d. Importance of the Protecting Groups on the Auxiliary

To test the importance of the bulkiness of the fructose diol protecting groups, substrate **15** was prepared (Scheme 1.2). Methylation of **15** proceeded in comparable yield and selectivity at –95 ºC (71% yield, 85% de) compared with **3a** (73% yield, 86% de). The similarity of the results indicates that the alkyl substituents of the ketals have little effect on the selectivity. A possible explanation may be that the dioxolane rings of the ketals favor a particular conformation of the auxiliary that leads to high asymmetric induction. Therefore, the steric hindrance provided by the alkyl groups on the ketal is less important than the conformational bias provided by the ketals or the steric hindrance provided by the dioxolane portionsof the ketals.



3a R' = Me
15 R'= Et

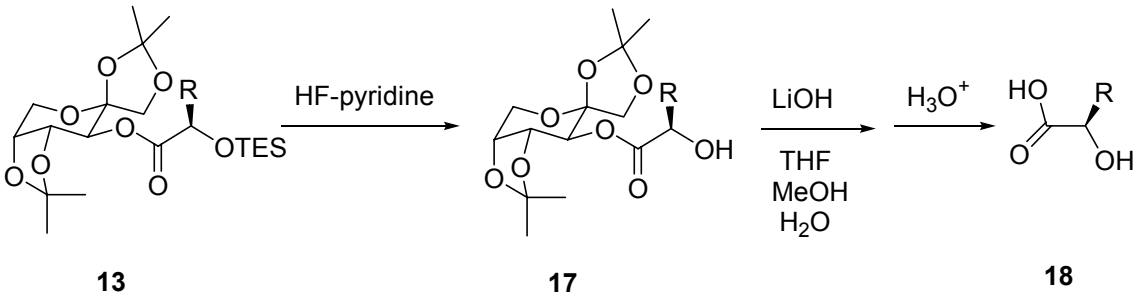
4a R' = Me
16 R' = Et

Scheme 1.2. Methylation of the glycolate **15** bearing larger protecting groups on the auxiliary.

1.3.e. Deprotection and Hydrolysis of the Alkylated Products to Generate Free α-Hydroxy Carboxylic Acids

The configuration of the newly generated stereocenter was determined by the optical rotation of the free acids. Compounds **4a,c** were hydrolyzed in LiOH/THF/H_2O to give the

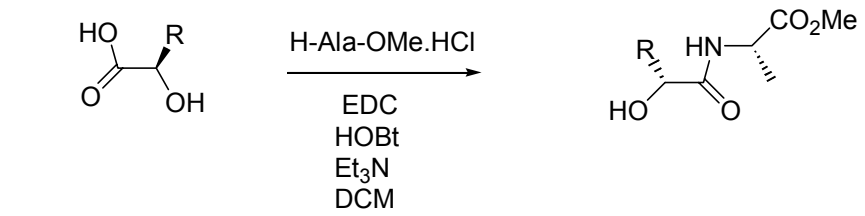
hydroxyl-protected acid. Upon comparing their specific rotations with the literature values,[78,79] they were concluded to have the *R* configuration. In addition, the absolute configurations of the enolate alkylation products **13** were assigned by comparisons of the specific rotations of the α-hydroxy carboxylic acids **18** obtained upon cleavage of the protecting group with hydrogen fluoride-pyridine followed by saponification (Scheme 1.3) to those in the literature. The results are listed in Table 1.5. These results indicated that the newly formed chiral center had the *R* configuration.



Scheme 1.3. Deprotection and hydrolysis of the esters **13** to give the free acids **18**.

To determine if racemization had occurred during the deprotection or the saponification, a modification of Cavelier's method (Scheme 1.4) was followed.[80] Alkylated products **13c,e** were deprotected with hydrogen fluoride-pyridine. ^{1}H NMR of the crude compounds **17** indicated that they had the same de (within experimental error, 5%) as compounds **13**. These crude compounds **17** were saponified as above to give the free acids **18b,d**, respectively. These acids were coupled to H-Ala-OMe, using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt), to give the amides **19** (Scheme 1.5). The de of the amides as determined by ^{1}H NMR was the same (within experimental error, 5%) as that of **13** and **17**,

respectively. The deprotection, saponification, and amidation steps were all high yielding (>86%), minimizing any effects of kinetic resolution.



18b R = Bn
18d R = $PhCH_2CH_2$

19a R = Bn
19b R = $PhCH_2CH_2$

Scheme 1.4. The modified Cavelier's method for determining if racemization had occurred during the deprotection or hydrolysis of **13.**

Table 1.5. Specific optical rotations of the α-hydroxy carboxylic acids **18**.

α-hydroxy carboxylic acid	$[\alpha]_D$ (°)	absolute configuration
2-hydroxypropionic acid (**18a**)	-12.7 (c 0.33, EtOH)	
2-hydroxy-3-phenylpropionic acid (**18b**)	+12.7 (c 0.43, EtOH)	*R*[a]
2-hydroxybutanoic acid (**18c**)	-10.4 (c 0.12, EtOH)	
2-hydroxy-4-phenylbutanoic acid (**18d**)	-13.3 (c 0.45, EtOH)	*R*[a]
2-hydroxyheptanoic acid (**18e**)	-12.3 (c 0.41, $CHCl_3$)	*R*[81]
2-hydroxy-3-naphthalen-2-yl-propionic acid (**18f**)	-18.0 (c 0.74, EtOH)	

[a]Comparison with data from the Aldrich Chemical catalog

1.3.f. Crystallographic Studies

To probe the factors responsible for the high stereoselectivity of these alkylations and to confirm the assignment of the *R* configuration at the α-center, glycolate **3a** and product **4c** were subjected to crystallographic analysis. The stereoview of **3a** (Figure 1.1) shows the pyranose ring in a boat conformation. The acyl group lies in a chain. The stereoview of **4c** (Figure 1.2) shows that the alkylated acyl chain lies roughly perpendicular to the acetonide protecting groups on the carbohydrate. The pyranose ring is still in a boat-like conformation. More importantly, it is seen that the new stereocenter has the *R* configuration.

In both structures the side closer to the 4,5-acetonide appears to be more open. This is confirmed by analysis of the crystal structures. In the starting material **3a** the distance of closest approach of a hydrogen atom on the α-carbon to the 1,2-acetonide is 3.37 Å, while its distance of closest approach to the 4,5-acetonide is greater than 5.0 Å. In the product **4c** the distance of closest approach of a hydrogen atom on the α-carbon to the carbons of the 1,2-acetonide is 3.49 Å, while its distance of closest approach to the 4,5-acetonide is greater than 5.0 Å.

It is understood that these structures of the starting material and the product do not provide information about the conformation of the reactive intermediate, the enolate. The factors responsible for the high de of the alkylations are stereoselective formation of the enolate and selective approach of the electrophile to one face of the enolate. Yamamoto's work with α-oxy esters indicates that under the reaction conditions the enolate should have the *Z* geometry.[82,83] (This contrasts with Ireland's studies that showed that esters not bearing a heteroatom at the α position should form the *E* emolate under these conditions.[84]) If the general conformation of the enolate is similar to that of the starting material and the product, the *Z* enolate is consistent with the *R* configuration of the new chiral center.

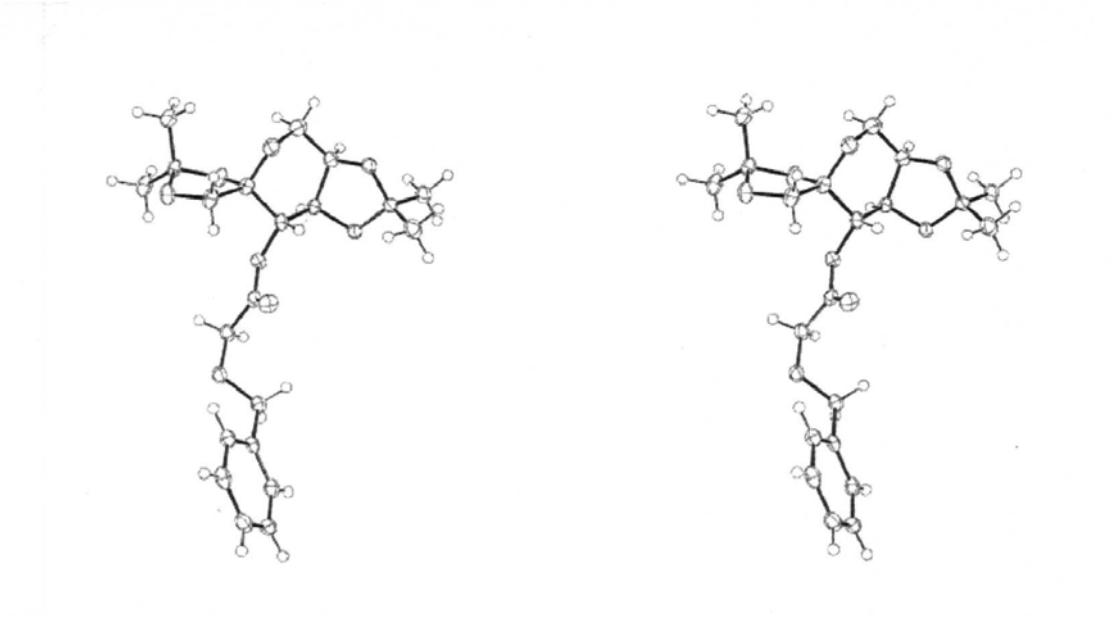


Figure 1.1. Stereoview of glycolate **3a**.

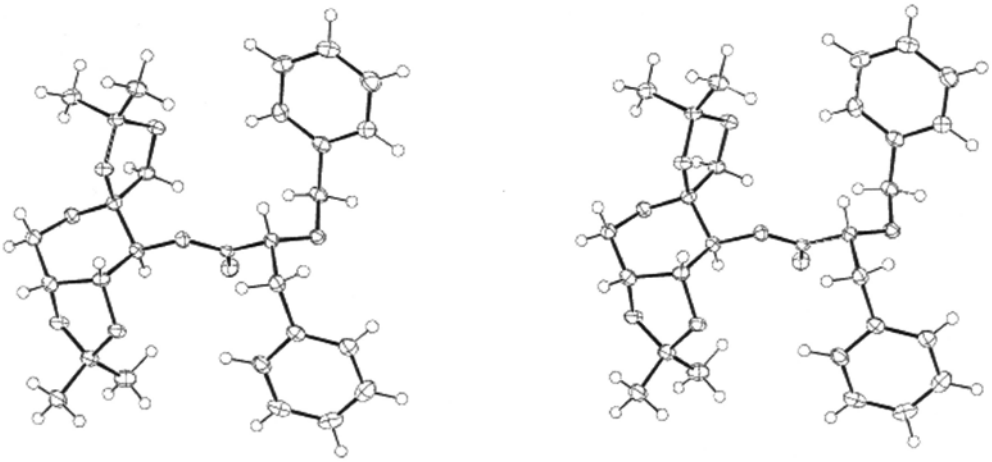


Figure 1.2. Stereoview of alkylated ester **4c.**

1.4. Conclusion

The synthesis of α-hydroxy carboxylic acids using auxiliary **1** has been successfully executed. The following features were notable: (1) the crystalline auxiliary 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose **1** was easily obtained on a large scale from an inexpensive starting material, D-fructose; (2) the enolate alkylation proceeded in high de; (3) the addition of HMPA increased the yield without sacrificing diastereoselectivity; (4) the alkylation was compatible with several hydroxyl protecting groups; and (5) the other enantiomer of the auxiliary is readily available.[67,85] It is difficult to compare this auxiliary with the others that have been reported in the literature, partly because different electrophiles were used in each study. However, on the whole, it seems that D-fructose diacetonide is comparable with or better than most other auxiliaries that have been used for glycolate alkylation. The fructose auxiliary gave slightly lower yields and stereoselectivity than Katsuki's pyrrolidine[56] and Uang's[58] and Pearson's[57] dioxolanone auxiliaries. It is not quite as selective as the Evans auxiliary,[59] but it gave good yields with a variety of electrophiles. However, none of these other systems were tested with the range of alkylating agents that were used in this study. With the Evans auxiliary only especially reactive electrophiles were examined. D-Fructose diacetonide offers competitive selectivity and reactivity compared to these proven auxiliaries. Furthermore, the D-fructose auxiliary offers the advantage of low cost. Further development of chiral auxiliaries available from inexpensive carbohydrates will broaden the arsenal of tools available for the preparation of α-hydroxy acids in a variety of situations.

Chapter 2. Synthesis of a Potential Carrier for Copper Ions Designed to Be Transported by P-Glycoprotein

2.1. Contribution

The goal of this project was to design, synthesize, and preliminarily evaluate a series of compounds that might increase the excretion of excess copper(II) ions *in vivo*. My contributions to the project included designing the target molecules, synthesizing the targets, and determining their binding constants with copper(II). The targets still need to be evaluated for transport in an *in vitro* biological system and tested for any effect they might have on the transport of copper(II) in the same biological model. These experiments will be performed by my coworkers.

2.2. Introduction

Toxicity due to heavy metals has been known for many centuries. Toxicity can be due to inhaling exhaust fumes from leaded gasoline, eating mercury-laden fish, or due to inhalation of gasoline exhaust fumes containing lead. However, it can also be related to other diseases. Wilson's disease is a metabolic disorder related to the poor metabolism of copper, leading to a buildup of the metal in the liver, brain, and kidneys.[86] It afflicts about one in one million individuals. Symptoms of Wilson's disease include liver disease and nerve damage.[86] A more widespread problem is the iron poisoning that afflicts the sufferers of hereditary hemochromatosis, in which the cellular uptake of iron is unregulated, and that affects a smaller number of those who have transfusion-dependent anemias.[87] As many as

one in 200 persons may be homozygous for hereditary hemochromatosis.[87] Iron overload due to transfusions in anemia patients is much less common.[87]

The treatment for these poisonings is injection of a chelating agent to sequester the metal followed by the elimination of the complex. The set of clinically used chelating agents is quite small. A sample is shown in Figure 2.1.[88] The first two chelators, triethylenetetramine (TETA, **20**)[89,90] and D-penicillamine (DPA, **21**),[91] are used primarily for the treatment of copper poisoning. Ethylenediaminetetraacetic acid (EDTA, **22**) is used to treat a wide range of metal poisonings.[92] Desferrioxamine (DFOA, **23**) is used to treat iron overload.[93] *Meso*-2,3-dimercaptosuccinic acid (DMSA, **24**) is a newer chelator that is used primarily for the removal of lead.[94] These chelators display a variety of Lewis basic functionalities: amines, sulfides, carboxylates, and hydroxamates. The specific Lewis basic functionalities and the geometric constraints between them impart a relatively modest degree of selectivity to which metals they bind. Because of this modest degree of selectivity, essential metals sometimes can be leached to dangerously low levels, especially in the case of EDTA **22**.[88]

These chelators act by sequestering the metal in a tight complex. The polar complex is excreted from the body by the kidneys. A negative result can be nephrotoxicity (kidney poisoning).[88] This toxicity could be reduced if excretion of the complex occurred by a different pathway.

Excretion of the chelator-metal complex through the intestines is an attractive alternative. Such a pathway should reduce nephrotoxicity and increase the rate of excretion, due to the large surface area of the intestines. Normally, excretion through the intestine is prevented by the hydrophilicity of the complexes.[95] Our design was chosen to take

advantage of a problematic efflux transporter in drug delivery research for the excretion of metals through the small intestine. The targeted efflux transporter is the so-called P-glycoprotein (P-gp).[96] Due to the large surface area of the intestines, such an excretion pathway should drastically help to increase excretion efficiency and lower organ toxicity.

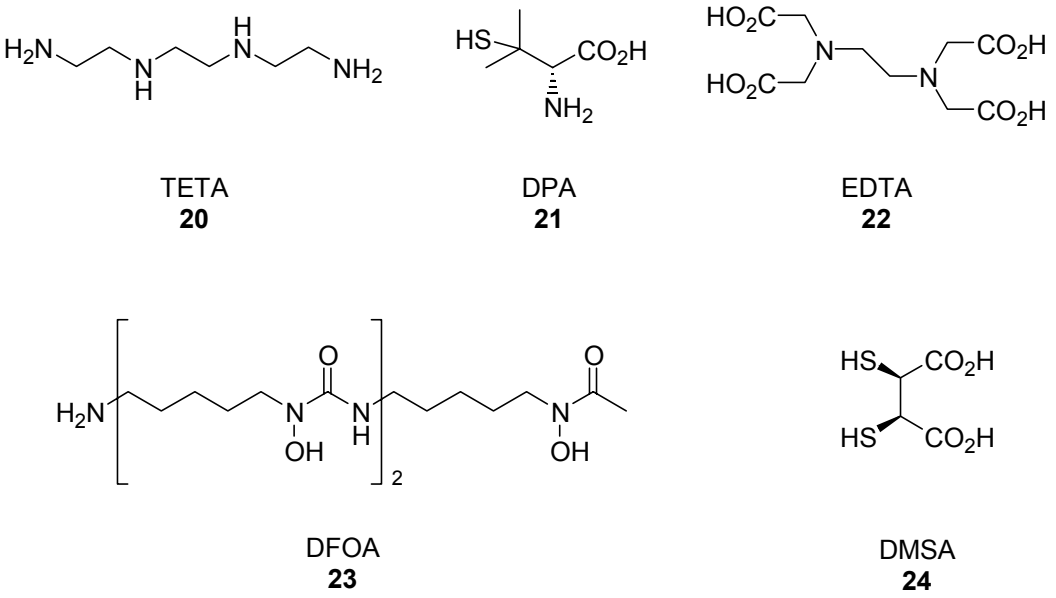


Figure 2.1. A sample of clinically used chelators **20**-**24**.

P-gp is an example of an adenosine triphosphate (ATP)-binding cassette (ABC) protein.[97] P-gp is encoded by the ABCB1 (MDR1) gene.[98,99] Its gross structure is illustrated in Figure 2.2. It consists of 12 transmembrane domains and two ATP-binding sites.[100] Solid state structures of P-gp and related ABC transporters have been determined down to 1.5 Å resolution.[101-104] This active transporter moves a wide variety of substances outside the cell membrane. Upon binding of a substrate to a particular transmembrane region,[105] hydrolysis of one molecule of ATP forces a conformational change that releases the substrate in or

beyond the outer edge of the cell membrane.[106,107] Hydrolysis of a second equivalent of ATP resets the enzyme for another cycle.[108]

Normally ABC transporters are expressed in the brain, testis, and placenta to prevent the accumulation of xenobiotics in those particular organs. They are also expressed in the

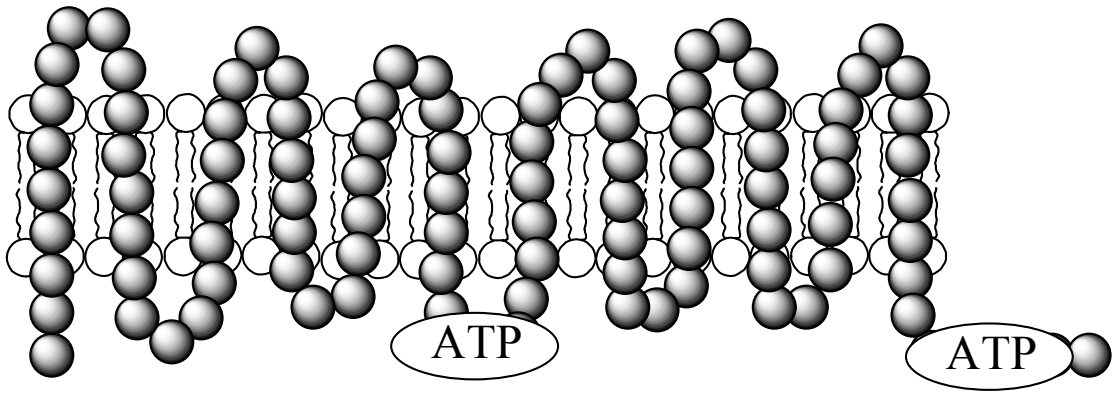
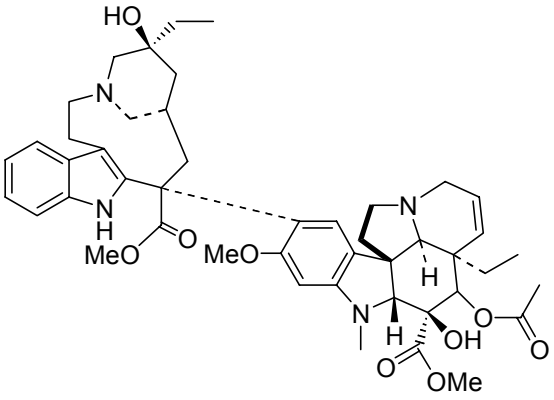


Figure 2.2. Cartoon illustrating the structure of P-gp.

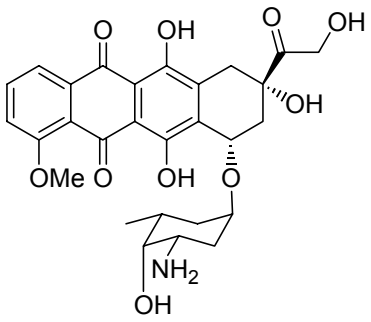
intestine, liver, kidney, and blood-brain barrier to protect the entire body.[97,105] P-gp is localized on the apical side of the intestinal mucosa.[109] It is involved in the secretion of both orally and intravenously administered drugs.[110] Another ABC transporter, MRP1, is located on the basolateral side of the intestinal mucosa and transports substrates into the bloodstream.[111]

It is also overexpressed in several cancer cells upon the initiation of chemotherapy. It is one cause of multidrug resistance (MDR). MDR is the tolerance to a broad spectrum of chemotherapies developed by cancer cells upon treatment with one of a variety of drugs that are P-gp substrates. Among the substrates of P-gp are the chemotherapeutics shown in Figure 2.3.[105,112,113] These substrates encompass a wide variety of chemical structures and biological mechanisms of action. Vinblastine **25**, a vinca alkaloid, and doxorubicin **26**, an

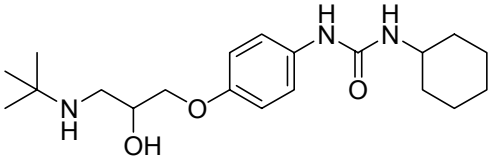
anthracycline antibiotic, are powerful anticancer drugs. Talinonol **27** and verapamil **28** are antiarrhythmic agents. Nicardipine **29** is an antianginal and antihypertensive agent. Phenytoin **30** is an anticonvulsant and antiepileptic drug.



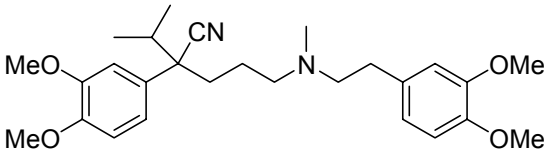
vinblastine
25



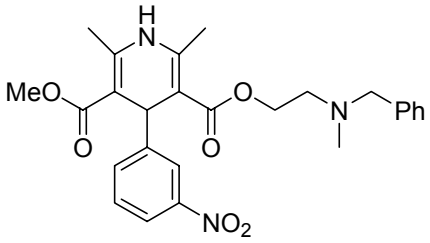
doxorubicin
26



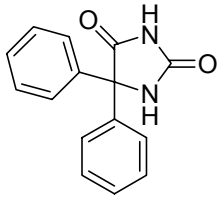
talinolol
27



verapamil
28



nicardipine
29



phenytoin
30

Figure 2.3. Examples of the wide range of drugs that are substrates of P-gp.

2.3. Design

We hypothesized that conjugation of a chelator to a P-gp transporter substrate would increase the excretion of the chelator-metal complex through the intestine. A cartoon of the design is shown in Figure 2.4. One P-gp substrate was selected. The linker was varied between one or eleven methylene units. Two chelating units were chosen.

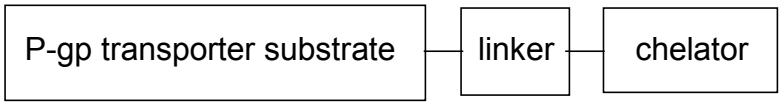


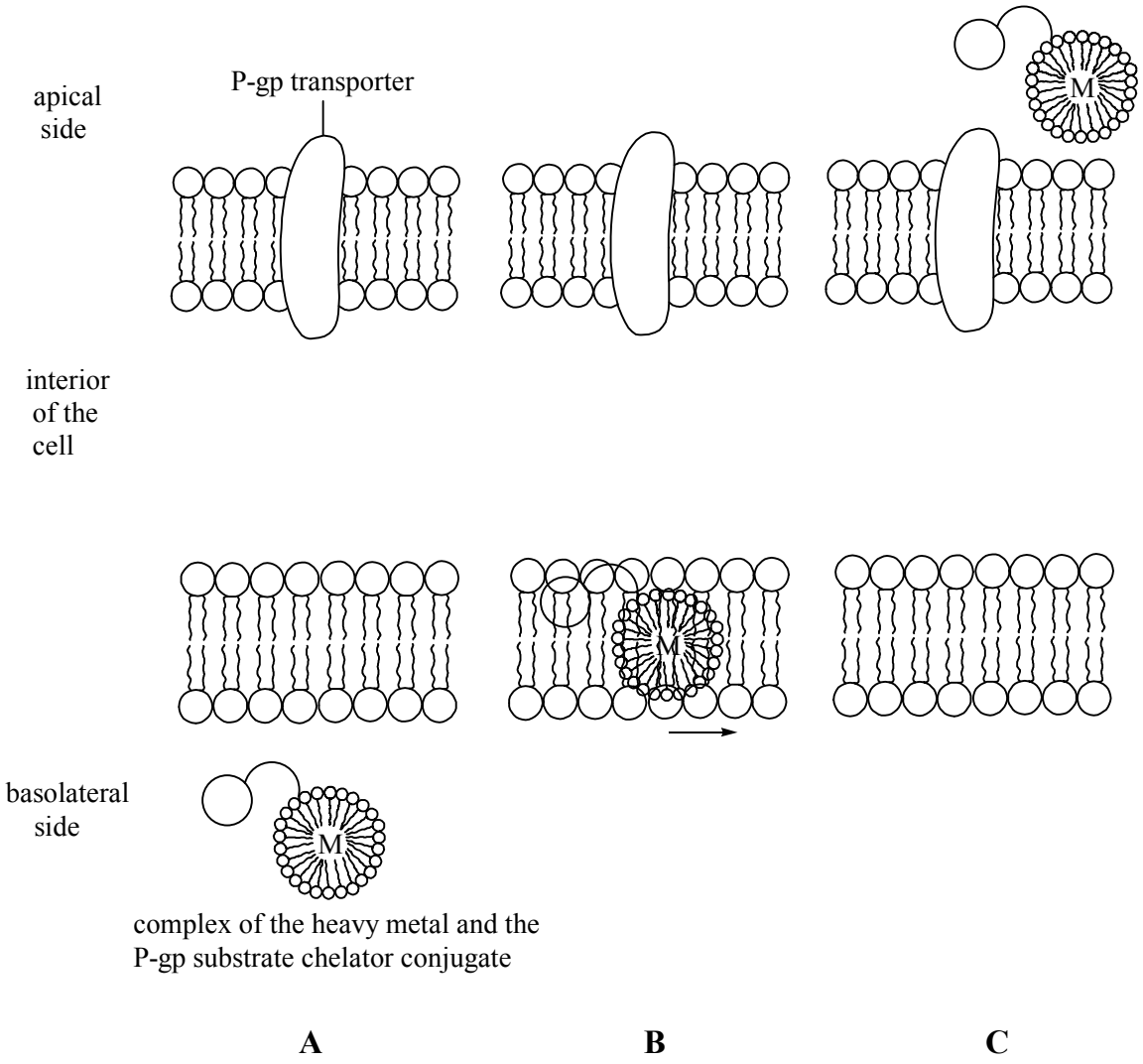
Figure 2.4. Conceptual design for the P-gp substrate-chelator conjugates.

The active transport of the P-gp substrate-chelator conjugate complexed with a metal out of the body is shown in Scheme 2.1. First, as in **A**, the complex passively diffuses into the epithelial cell from the basolateral side (bloodstream). The complex passively diffuses to the apical side of the cell through the lipid bilayer as illustrated in **B**. The P-gp transporter binds to the complex and transports it out of the cell into the intestinal tract as shown in **C**.

This concept is elegant because it takes advantage of a transporter that usually limits the influx of drugs. This concept can also be viewed as an enhancement of the body's natural defenses against xenobiotics. As a result of two acts of molecular recognition, the coordination of the metal to the chelator moiety and the binding of the substrate motif to P-gp, the desired removal of the heavy metal can occur.

After the general design of the target molecules had been determined, the specific transporter substrate and chelator moieties had to be selected. The literature provided a wide number of choices for each unit. The criteria used for the selection process included

expected ease of synthesis and literature precedent indicating that the substrate and chelator units would retain their respective properties upon incorporation into the targeted carriers.



Scheme 2.1. Active transport of the P-gp substrate-chelate complexed to a metal from the body.

A sample of known P-gp substrates is shown in Figure 2.5.[112] Phenothiazine **31** is used as an insecticide and in the manufacture of pharmaceuticals. Fluphenazine **32**,

perphenazine **33**, thioridazine **34**, trifluprom azine **35**, trifluperazine **36** are antipsychotic drugs.

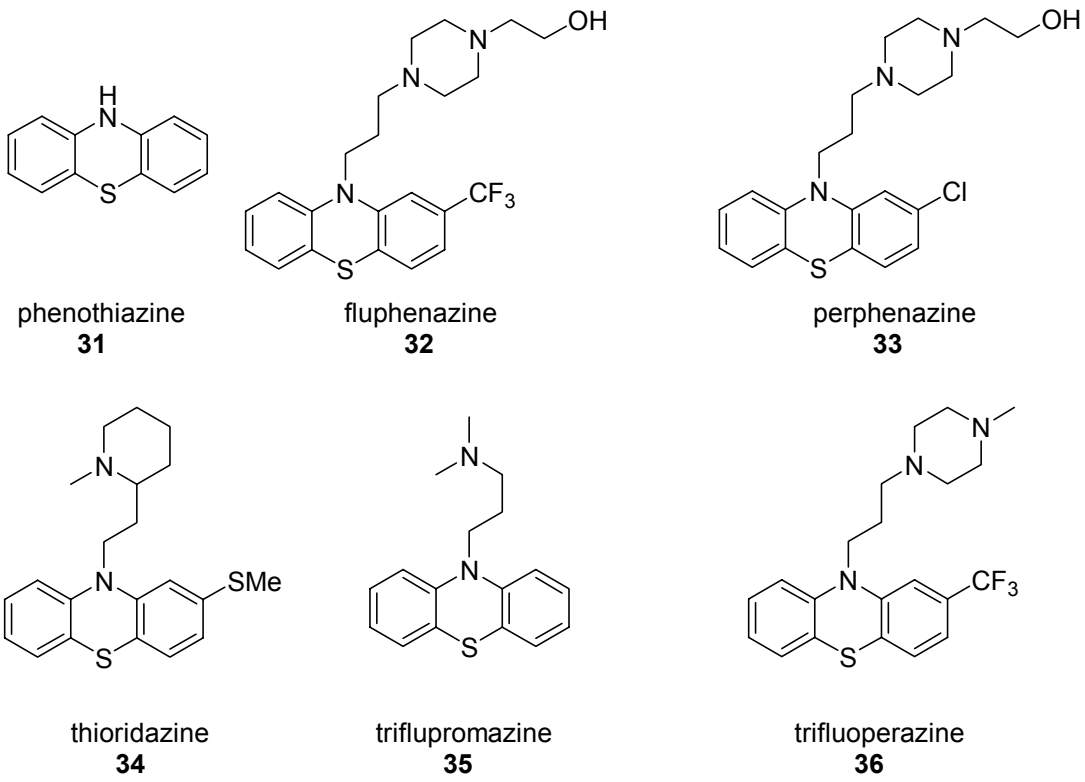


Figure 2.5. Several P-gp substrates **31**-**36** containing the phenothiazine moiety.

Phenothiazine **31** was chosen because of its appearance in a number of P-gp substrates (Figure 2.5), structural simplicity, and low cost. Another practical advantage is that the unit is a strong chromophore. The proton on the nitrogen provided a handle for selectively derivatizing the substrate moiety. Compounds **31**-**36** illustrate that the core is tolerant to a wide variety of modifications.

Besides being concerned about interactions of our substrate-chelator conjugates with P-gp, we were also concerned about their interactions with cytochrome P450 enzymes.[114]

There is a large degree of overlap in substrate specificity between P-gp and P450 3A4 (CYP 3A4). More than half of the total P450 in the human liver can be CYP 3A4. Our concern in using a P-gp substrate is that the substrate-chelator conjugates may also be substrates of CYP 3A4. However, a recent report examining the overlap of these enzymes' specificities possibly indicates that the phenothiazine-based targets are not CYP 3A4 substrates.[114] The paper examined 27 compounds known to be substrates of P-gp and/or CYP 3A4. Among the ten compounds that were selective for P-gp was fluphenazine **32**. Since fluphenazine contains a phenothiazine moiety, we gained a modest degree of confidence that our targets would not be CYP 3A4 substrates. No other phenothiazine-based compounds were included in that study.

A model describing the essential features of a P-gp substrate has recently been proposed[113] and a computational model of the P-gp substrate pharmacophore has been presented.[115] According to this model, P-gp substrates contain one or more type I or type II units. Type I units contain two electron donor groups separated by 2.5 ± 0.3 Å. Type II units contain two electron donors separated by 4.6 ± 0.6 Å or three electron donors, with the outer two separated by 4.6 ± 0.6 Å. Considering the nitrogen and sulfur atoms of phenothiazine as electron donors shows that this model is valid for phenothiazine. Combined with the observation that the phenothiazine-based compounds shown in Figure 2.5 are also P-gp substrates, the model indicates that *N*-alkylated phenothiazines should also be P-gp substrates. The linker was varied between either one or eleven methylene units. The eleven-methylene linker was included to give target compounds that were amphiphilic. The amphiphilic compounds are expected to have the best passive transport through the lipid bilayer of the cell membrane. In case the passive transport into the intestinal epithelial cells

was the limiting step of excretion, these surfactant-like compounds were expected to have the best transport properties across the intestinal lining.

The next step in the design was the somewhat arbitrary choice of an amide bond to join the linker to the chelating moiety. An amide was chosen because amide formation is usually quite dependable. Additionally, we felt that that we could functionalize our linker and our chelators with a carboxyl and an amino group, respectively, that we could use in the linking step. Phenothiazine **31** can be derivatized with a carboxylic acid to give **37** (n = 1) and **38** (n = 11) (Figure 2.6). These compounds can be conjugated to a chelating moiety bearing a free amine by forming an amide bond.

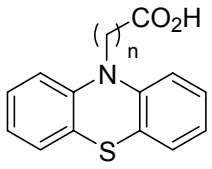


Figure 2.6. Phenothiazine derivatized with a carboxylic acid [**37** (n = 1) and **38** (n =11)] .

With the design of the P-gp substrate determined, the choice of chelator remained. Several chelating units have been reported to bind metals *in vivo*. Among these are the therapeutic chelators illustrated in Figure 2.1. None of these seemed to be applicable for our purpose because we found no literature precedent suggesting that we could conjugate these chelators to our P-gp substrate moiety without possibly disturbing their coordination properties.

Another set of chelators that coordinate lanthanides form complexes that are used as radiodiagnostics or radiopharmaceuticals.[116-119] Most of these chelators contain iminodiacetic acid moiety **39** (Figure 2.7). However, none of these iminodiacetic acids were reported to

bind copper. This eliminated them from our pool of candidates. However, two compounds that chelate copper very tightly even upon derivatization were chosen for our studies. As mentioned in the introduction, excess copper is associated with a recognized disorder, Wilson's disease.

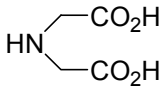


Figure 2.7. The iminodiacetic acid moiety **39**.

The tripeptide Gly-His-Lys **40** has been reported to coordinate copper(II) with a large formation constant (K, log K = 27).[120] The chelate of this tripeptide with copper(II) in the solid state[121] and the postulated structure of the solution state is illustrated in Figure 2.8. The amino terminus, an amide nitrogen, and the imidazole π-nitrogen form a tridentate complex with the copper. Two molecules of water also coordinate to the metal center to complete the square pyramidal geometry. Of special note is the observation that the ε-amino group does not coordinate to the metal. This implies that the ε-amino group could be used to link the tripeptide to another structural unit without affecting the metal chelation. In fact others have done this in the development of fluorescent sensors for copper.[122] Another indicator that the Lys side chain is not important for chelation is that the dipeptides Gly-His and Ala-His have almost the same affinity for copper as Gly-His-Lys.[120]

Conjugation of the phenothiazine acid with the side chain of Gly-His-Lys **40** resulted in the design of targets **41** (n =1) and **42** (n = 11) (Figure 2.9). In our case, D-amino acids

were substituted for the natural L-amino acids for the tripeptide synthesis to increase their *in vivo* stability against peptidases and proteases.

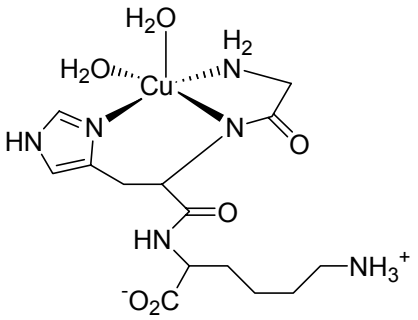


Figure 2.8. Structure of the chelate between Gly-His-Lys **40** and Cu^{2+}.

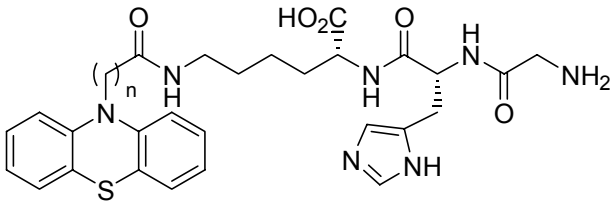
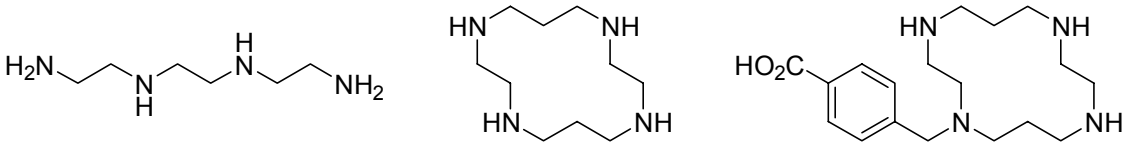


Figure 2.9. Targets **41** (n = 1) and **42** (n = 11) related to Gly-His-Lys.

The other chelator that was selected was 1,4,8,11-tetraazacyclotetradecane (cyclam, **43**, Figure 2.10). It is a cyclic analog of TETA (**20**, Figure 2.1), a clinical therapeutic for copper toxicity. The binding constant between TETA **20** and copper(II) has been reported as log K > 20.[123] The binding constant between cyclam and copper(II) has been reported as log K = 28;[124] apparently the cyclic structure of cyclam reduces the decrease in entropy that is associated with chelation, resulting in a greater binding constant.

A monosubstituted derivative of cyclam, *N*-(*p*-toluic acid)-1,4,8,11-tetraazacyclotetradecane (CPTA, **44**, Figure 2.10),[125] has also been demonstrated to bind

copper(II) tightly (log K = 24).[124] An X-ray structure of the CPTA-Cu^{2+} complex indicates that the pendant carboxylate does not participate in the chelation.[126] Further evidence of this claim comes from the biochemical literature. CPTA has been conjugated to a monoclonal antibody and has been shown to form a stable complex with copper.[127-130]



20 **43** **44**

Figure 2.10. Polyaza chelators **20**, **43**, and **44**.

A very closely related chelator (**45**, Figure 2.11) was chosen for use in our system. The secondary amines of the macrocycle can coordinate to copper(II). The free primary amine on the benzylic side chain will allow for conjugation to the carboxylic acid-terminated phenothiazine moiety. Conjugation of the phenothiazine acid with the primary amine of **45** resulted in the design of targets **46** (n = 1) and **47** (n = 11) (Figure 2.12).

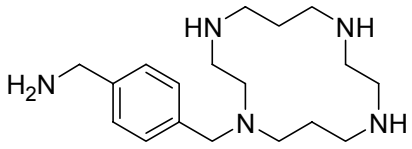


Figure 2.11. The targeted cyclam derivative **45**.

An advantage of targets **46** and **47** is that each contains a single amide bond. If the biological transport studies indicate that these compounds are not substrates of P-gp, this

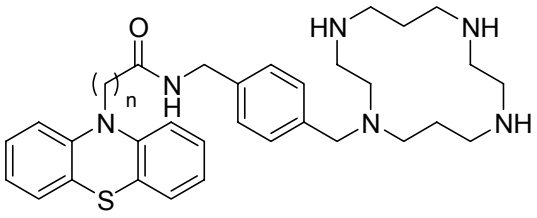


Figure 2.12. Targets **46** (n = 1) and **47** (n = 11) based on cyclam.

amide bond could be reduced to the secondary amine. For the case of n = 2, the reduction product would bear a greater resemblance to known P-gp substrates **32-36**, all of which bear a tertiary amine three methylene units from phenothiazine.

A further indication that the targets had the appropriate physical properties was the range of their calculated log D (cLogD) values (Table 2.1). The values were obtained using the Advanced Chemistry Development/Interactive Lab Web service (ACD/LogD 6.0). The cLogD value is the common logarithm of the octanol/water partition coefficient as a function of pH. It is similar to the calculated log P (cLogP), which is the common logarithm of the octanol/water partition coefficient at zero ionic strength. cLogD is more appropriate for discussing the physical properties of compounds that are ionic; cLogP is indicative of the physical properties of neutral molecules. The cLogP values of the cyclam- and tripeptide-based compounds are included for comparison (Tables 2.1 and 2.2), although they are not the most appropriate values for estimating the physical properties under physiological conditions. As shown in Table 2.1, there is sometimes a large discrepancy between the cLogD and cLogP values for ionizable compounds. The cLogP values were obtained from ChemDraw 5.0 using both Crippen's[131] and Viswanadhan's[132] fragmentations.

Table 2.1. The predicted partition coefficients for the cyclam-based targets **46** and **47**.

Cyclam-based target	cLogD	cLogP (Crippen)	cLogP (Viswanadhan)
46 (n = 1)	-0.3 ± 1.0	2.94 ± 0.47	3.14 ± 0.49
(n = 2)	-0.1 ± 1.0	3.23 ± 0.47	3.32 ± 0.49
(n = 3)	0.2 ± 1.0	3.51 ± 0.47	3.57 ± 0.49
(n = 4)	0.6 ± 1.0	3.93 ± 0.47	3.97 ± 0.49
(n = 5)	1.0 ± 1.0	4.35 ± 0.47	4.36 ± 0.49
(n = 6)	1.5 ± 1.0	4.76 ± 0.47	4.76 ± 0.49
47 (n = 11)	4.1 ± 1.0	Could not be calculated	Could not be calculated

Table 2.2. The predicted partition coefficients for the tripeptide-based targets **41** and **42**.

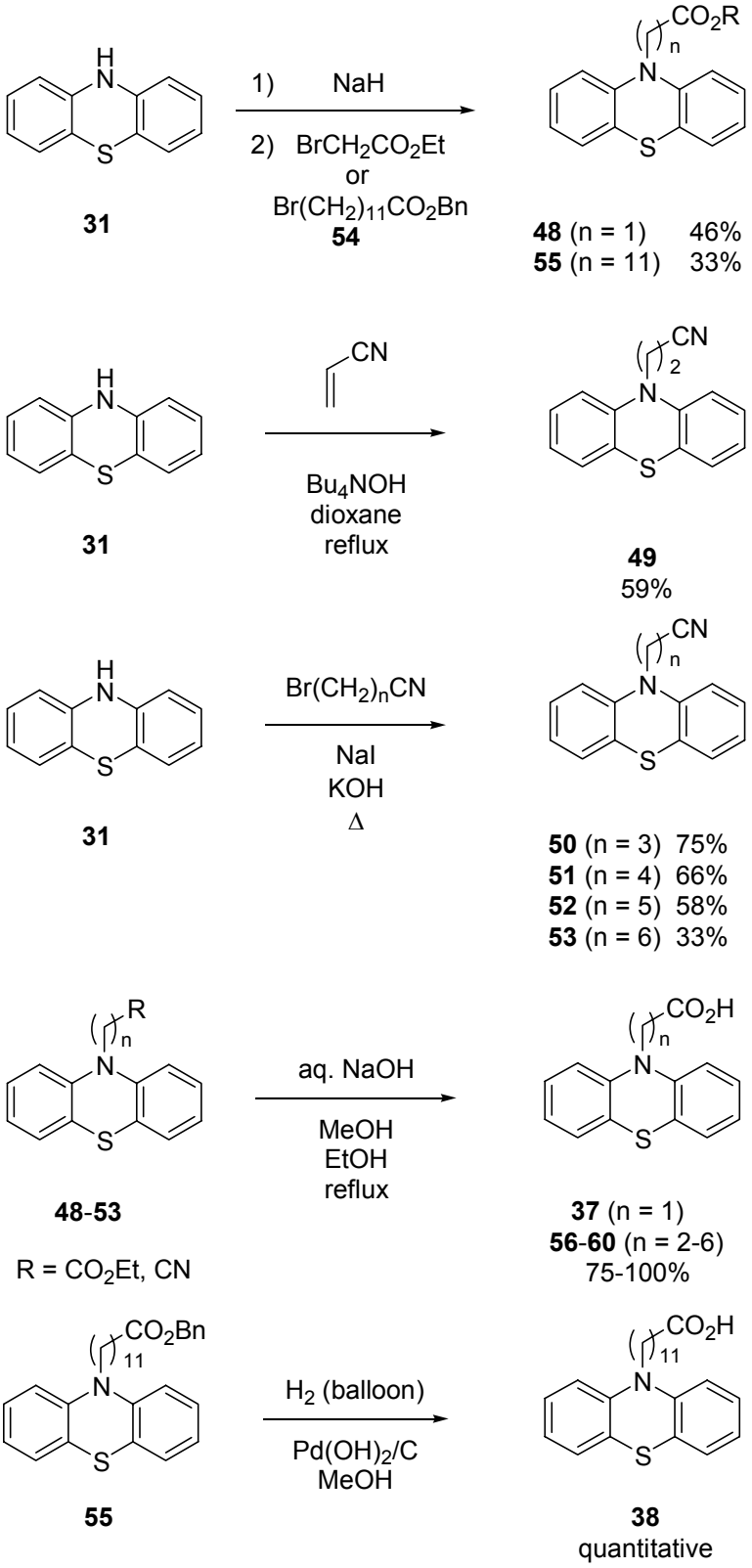
Tripeptide-based target	cLogP (Crippen)	cLogP (Viswanadhan)
41 (n = 1)	-1.02 ± 0.47	-0.12 ± 0.49
(n = 2)	-0.73 ± 0.47	0.06 ± 0.49
(n = 3)	-0.45 ± 0.47	0.31 ± 0.49
(n = 4)	-0.03 ± 0.47	0.71 ± 0.49
(n = 5)	0.39 ± 0.47	1.11 ± 0.49
(n = 6)	0.81 ± 0.47	1.50 ± 0.49
42 (n = 11)	Could not be calculated	Could not be calculated

The targeted carriers are expected to be substrates of P-gp. These compounds do not exactly parallel the structures of the P-gp substrates in Figure 2.5, in that our compounds contain an amide in the side chain of an amine. However, they all contain the phenothiazine unit **31**, which itself is a P-gp substrate. In addition, at pH 7.4, the designed compounds will be cationic. All of the other phenothiazine-based substrates (**32-36**) are cationic at neutral pH.

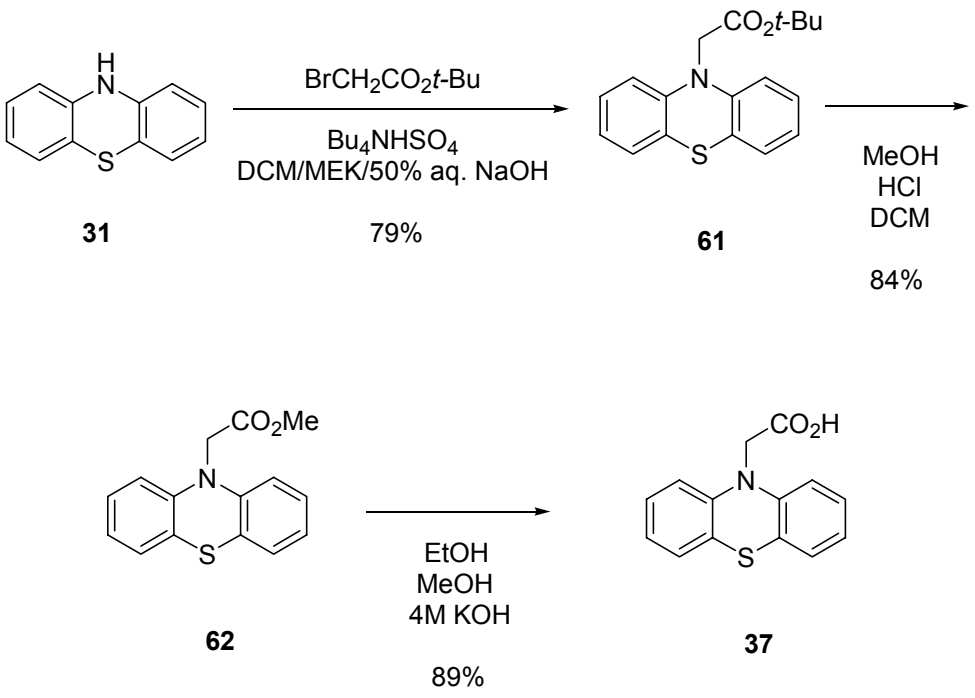
2.4. Synthesis

With the design of the target molecules in hand, the synthetic work began with modification of the P-gp substrate phenothiazine **31**. The bond to the linker was formed by alkylating phenothiazine under basic conditions in *N*,*N*-dimethylformamide (DMF) (Scheme 2.2). In addition to generating the acids for the making the one- and eleven-methylene linker compounds, additional linkers between two and six methylene units were produced for the synthesis of additional analogs. For compound **48** (n = 1), phenothiazine **31** was deprotonated with NaH and then ethyl bromoacetate was added.[133] Compound **49** (n = 2) was prepared by a literature Michael addition.[134] For compounds **50**-**53** (n = 3-6), a mixture of phenothiazine **31**, the appropriate ω-bromonitrile, sodium iodide, and potassium hydroxide were stirred while being heated.[135] Compound **54** (n = 11) was prepared in a manner similar to that of **48** (n = 1), using benzyl 12-bromododecanoate (**55**).[136] Compounds **48**-**53** were hydrolyzed in a mixture of refluxing aqueous sodium hydroxide, methanol, and ethanol to generate the free acids **37** and **56**-**60** (n = 1-6). Yields for the hydrolysis were >88%, except for **49** (n = 2, 75% yield), which (according to TLC) underwent a retro-Michael side reaction. The free acid **38** was obtained from **54** (n = 11) upon hydrogenolysis with $Pd(OH)_2/C$. The resulting carboxylic acids **37**-**38** and **56**-**60** could be coupled to a free amine on a chelator unit to generate the targeted carrier molecules.

An alternative preparation of acid **57** is shown in Scheme 2.3. Phase-transfer catalyzed alkylation of phenothiazine **31** with *tert*-butyl bromoacetate yielded ester **61**.[137] Direct deprotection of the ester could not be achieved. Treatment with trifluoroacetic acid (TFA) with or without the cation scavenger Et_3SiH[138] resulted in decomposition of **61**.



Scheme 2.2. Preparation of the phenothiazine-based free acids **37-38** and **56-60**.



Scheme 2.3. An alternative route to acid **37**.

However, a one-pot deprotection-esterification in methanolic HCl proceeded to give **62** in good yield. Saponification of the methyl ester yielded acid **37**.

Alkylation using bromoacetonitrile according to the procedure used to prepare **50**-**53** proceeded in low yield (5-10%). We suspected that single electron transfer reactions might be responsible, given the electron-rich nature of phenothiazine and the electron-poor nature of bromoacetonitrile. Even when the bromoacetonitrile and reaction mixture were thoroughly degassed, the reaction did not proceed in higher yield.

The targeted protected tripeptide **63** is shown in Figure 2.13. The *N*- and *C*-termini protecting groups were chosen to be labile to hydrogenolysis; therefore, the benzyloxycarbonyl (Z) carbamate and benzyl (Bn) ester were included at the ends of the molecule. The deprotection of the *N*-and *C*-termini would be the last step of the synthesis. Hydrogenolysis was expected to give a very high yielding and clean deprotection of the

penultimate compounds. The ε-amino group was protected orthogonally with the acid-sensitive *tert*-butoxycarbonyl (Boc) group. The synthetic plan involved deprotecting the side chain amine in order to couple it to the carboxylic acid of the transporter substrate moiety **37-38**. The 9-fluorenylmethoxycarbonyl (Fmoc) group was used to protect the α-amino group intermittently during the peptide synthesis.

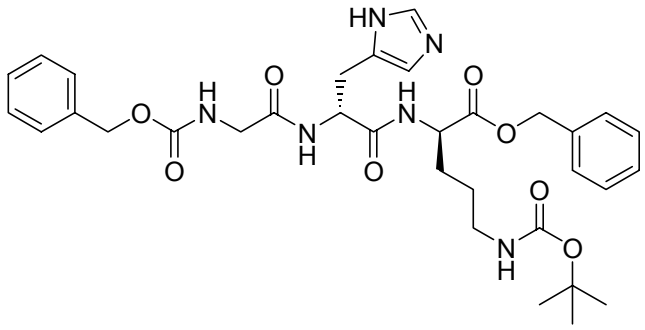
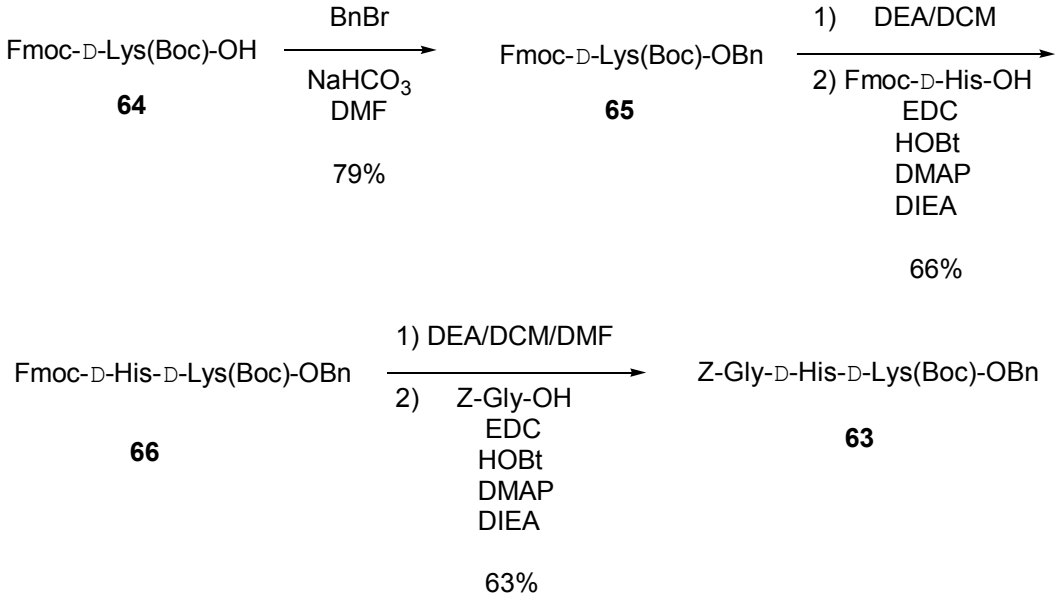


Figure 2.13. The targeted tripeptide Z-Gly-D-His-D-Lys(Boc)-OBn **63**.

The peptide synthesis proceeded as illustrated in Scheme 2.4. Commercially available Fmoc-D-Lys(Boc)-OH **64** was protected at its *C*-terminus with the benzyl group. The Fmoc group of **65** was removed with diethylamine (DEA)/DCM.[139] The crude free amine was immediately coupled with the acid Fmoc-D-His-OH activated by DCC and HOBt in the presence of DMAP and *N,N*-diisopropylethylamine (DIEA) to give the dipeptide **66**.[140] The α-amino terminus of the dipeptide was deprotected with DEA/DCM/DMF.[139] The crude free amine was coupled to the activated acid of Z-Gly-OH to give the triprotected peptide **63**.[140]

To couple the tripeptide chelator to the phenothiazine (P-gp transporter substrate) moiety (Scheme 2.5), first the side chain amine was deprotected with TFA. The ammonium salt was coupled to the activated acid of the phenothiazine moiety to give **67** and **68**. Because of losses during purification, the yields of these amidations are low.



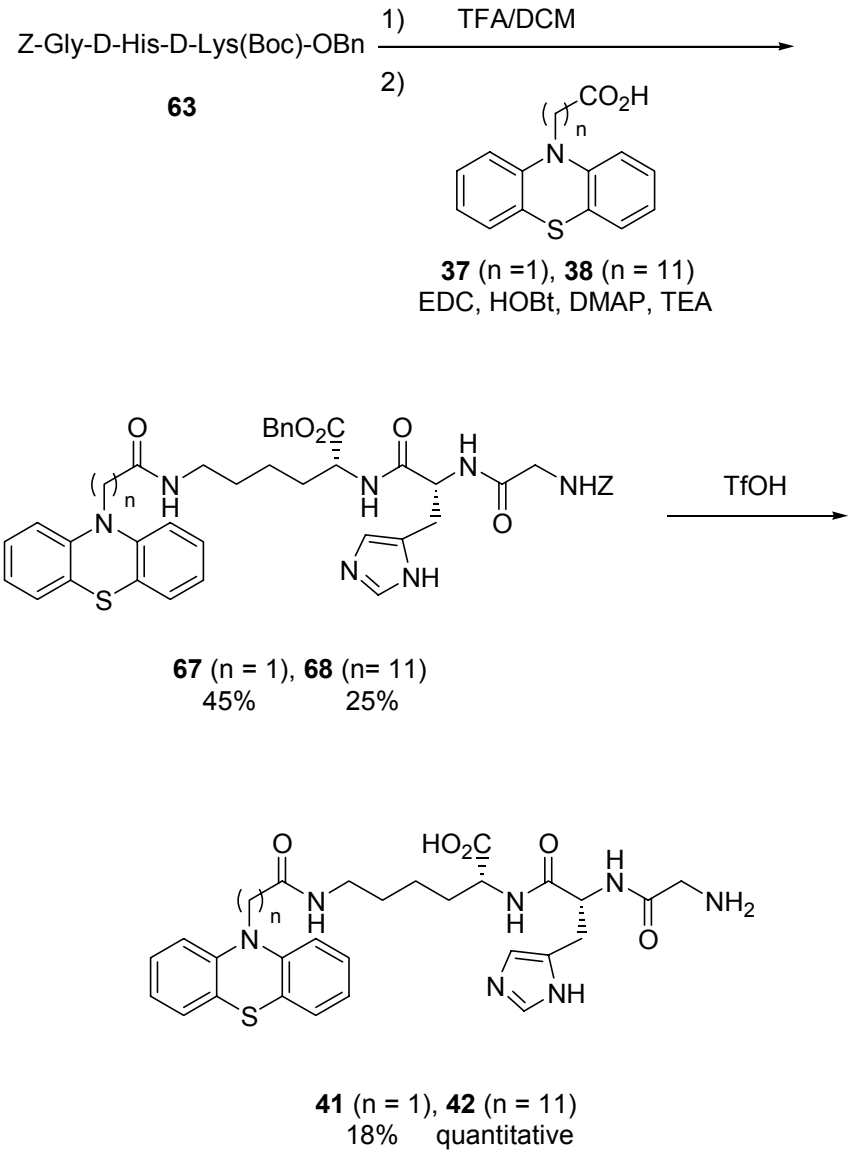
Scheme 2.4. Synthesis of the tripeptide **63**.

Attempts to deprotect the benzyl ester and benzyl carbamate with Pd/C[141] or $Pd(OH)_2/C$[142] in the presence or absence of a small quantity of acetic acid or HCl with a hydrogen pressure of up to 45 psi failed to remove both protecting groups. Transfer hydrogenation using formic acid as the hydrogen donor[143] also failed to give complete deprotection. At best only one protecting group was cleaved, tentatively judged as the benzyl ester based on analysis of TLC data and ^{1}H NMR spectra.

Another approach was required for the deprotection. Greene's compilation on protecting groups[144] listed two other approaches that seemed promising: strong acid and

dissolving metal reduction. The former approach seemed more attractive for two reasons: its operational simplicity and because of a report of the instability of phenothiazine under dissolving metal conditions.[145]

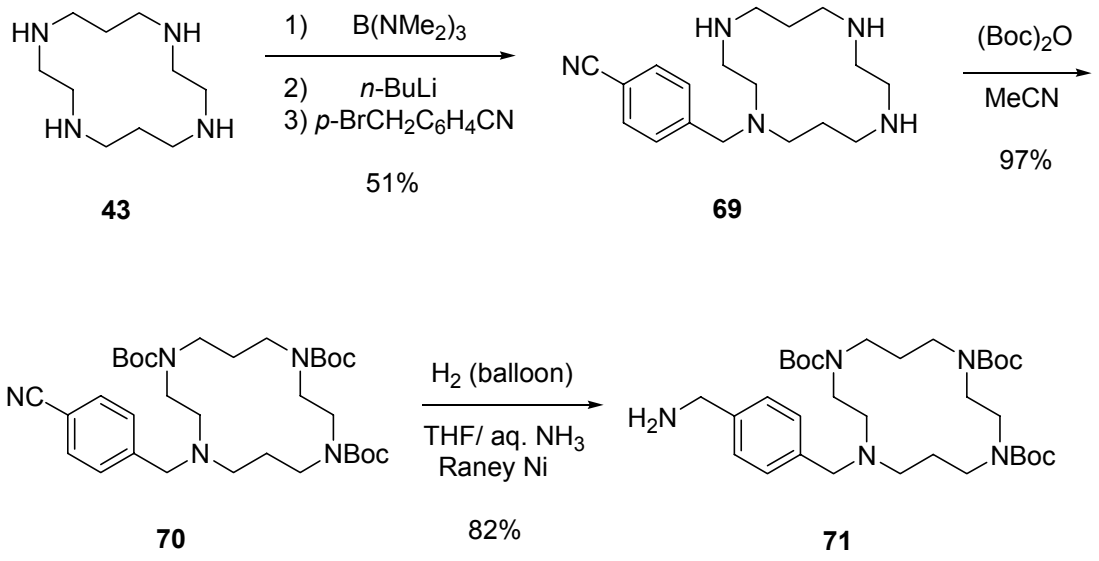
Acidolysis of the benzyl ester and benzyl carbamate with trifluoromethanesulfonic acid (TfOH) was reported by Kawatani.[146] Aware of the instability of the phenothiazine core



Scheme 2.5. Preparation of the tripeptide-phenothiazine carriers **41** and **42**.

to 25% TFA ($pK_a = 0.23$)[147] in DCM, a model study using methyl ester **62** was conducted to test stability of the phenothiazine moiety to the more acidic TfOH ($pK_a = -11$).[148] These experiments showed that **62** was stable upon treatment with 10 eq. of TfOH. Model studies with the amino acids H-Gly-OBn and Z-His-OH indicated that the same conditions could remove both protecting groups cleanly. However, it revealed that the chloroform that was used as the reaction solvent must contain no ethanol, which is usually present as a stabilizer. The ^{1}H NMR spectrum of the products indicated that a side reaction might have occurred. In stabilizer-free chloroform deprotection of **67** and **68** with TfOH proceeded to give **41** and **42** (Scheme 2.5).

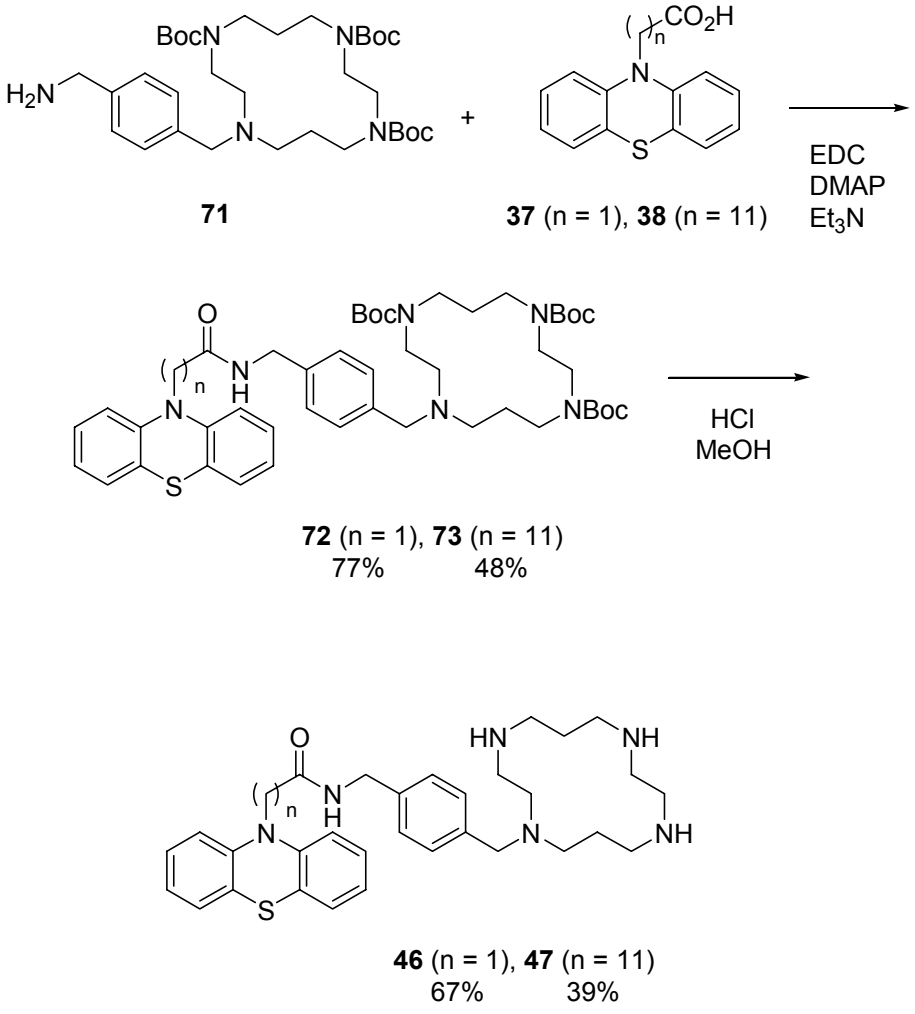
The synthesis of the cyclam-based chelator was executed as shown in Scheme 2.6. Commercially available cyclam **43** was monolalkylated with *p*-cyanobenzyl bromide using a temporary protecting group strategy.[149,150] The secondary amines of **69** were protected with the Boc group.[151] The nitrile functionality of **70** was selectively reduced with hydrogen



Scheme 2.6. Preparation of the targeted cyclam **71**.

under basic conditions to give the primary amine **71**.[152]

The conjugation of the polyazamacrocycle **71** and the P-gp transporter substrate unit is illustrated in Scheme 2.7. Coupling of the free amine of **71** with the carboxylic acid of **37** and **38** in the presence of EDC gave the amides **72** and **73**. Deprotection of the Boc groups with methanolic HCl[153] gave the hydrochloride salt of the target compounds **46** and **47**. The compounds could be obtained in their free amine form upon washing with potassium hydroxide.



Scheme 2.7. Preparation of the cyclam-phenothiazine carriers **46**-**47**.

Future evaluation of the compounds in the model *in vitro* system of Caco-2 cells (a model of the intestinal mucosa) will show if targets **41**, **42**, **46**, and **47** are true substrates of P-gp.[154] If preferential transport occurs in the basolateral to apical direction compared to the basolateral to apical direction, then this will indicate that the compounds are truly substrates of the P-gp transporter. If necessary, further studies can be conducted to determine if the substrate-chelator conjugates increase the transport of copper *in vitro*.

2.5. Conclusion

The design and synthesis of four potential carriers of copper(II) have been executed. The design of these compounds is based on the conjugation of a P-gp substrate moiety with a known chelator unit. The chosen P-gp substrate is phenothiazine, and the two chelating units are GHL and cyclam. In each compound the transporter substrate and each chelator were linked by one-methylene and eleven-methylene bridges. The compounds will be carried on to further chemical and biological assays to determine if they perform as designed.

Experimental Section

General

All air- and/or water-sensitive reactions were performed under dry argon or dry nitrogen in flame-dried or oven-dried glassware (>120 °C, >4 h) that was cooled under vacuum. Most reagents were purchased from Aldrich or Fisher/Acros. Amino acids were purchased from Bachem or Novabiochem. Some reagents were purified according to standard procedures[155] as noted below. Dichloromethane (DCM) and triethylamine (TEA) were distilled from calcium hydride under inert gas; TEA was then stored over activated 4Å molecular sieves (MS). THF was distilled from sodium and benzophenone. HMPA, DMPU, and DMF were distilled under vacuum from calcium hydride before use and were stored over activated 4Å MS. DEA was distilled from KOH pellets and stored over KOH pellets. TMEDA and DIEA were used as received (redistilled, Aldrich Sure-Seal™ bottle). LiHMDS was purchased as a 1.0 M solution in THF (Aldrich Sure-Seal™ bottle) and was titrated.[156] NaHMDS was used as a 1.0 M solution in THF (Aldrich Sure-Seal™ bottle). KHMDS was used as a 0.5 M solution in toluene (Aldrich Sure-Seal™ bottle). *n*-BuLi was purchased as a 1.6 M solution in hexanes or as a 2.0 M solution in cyclohexane (Aldrich Sure-Seal™ bottle) and was titrated.[157] MS were activated by drying them in a 220 ºC oven for at least 24 h. Reaction temperatures are the temperatures of heating or cooling baths.

Analytical thin layer chromatography (TLC) was performed with Scientific Adsorbents plastic-backed TLC silica gel 60F hard layer plates. TLC plates were visualized with a 5% (w/v) solution of phosphomolybdic acid in ethanol or UV light (254 nm). For most compounds, flash chromatography was performed with Scientific Adsorbents silica gel (flash, 32-63 μm). For some compounds, including the polyazamacrocycles, flash

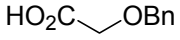
chromatography was conducted on Fisher or Aldrich basic alumina (60-325 or ~150 mesh, respectively). Column chromatography was followed by combining appropriate fractions, rotary evaporatorping, and drying under oil pump vacuum.

Mass spectrometry analyses were performed by the Mass Spectrometry Laboratories of North Carolina State University and the University of Kansas. Partial funding for the NCSU facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation. ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded with a Varian Gemini 300, GE Omega 300, Varian Mercury 300, or Varian Mercury 400 NMR spectrometer. Chemical shifts (δ) for my spectra were given in ppm relative to TMS (δ 0.00) for ^{1}H spectra and relative to residual solvent ($CDCl_3$: δ 77.23; CD_3OD: δ 49.15) for ^{13}C spectra. TFA (δ –76.6) was used an external standard for ^{19}F NMR. IR spectra were recorded of thin films of each compound on sodium chloride plates unless otherwise stated. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, Georgia.

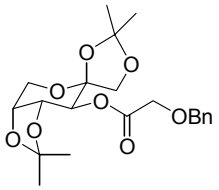
All melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Specific rotations were determined on an AUTOPOL III automatic polarimeter.

A Shimadzu high-pressure liquid chromatography (HPLC) system consisting of an SPD-10AV UV-visible detector, an SCL-10A system controller, and two LC-10AS pumps was used for the chiral auxiliary project. The de's of some of the alkylated products were determined on a Nova-Pak® silica column (3.9 x 150 mm) using hexanes:EtOAc.

Part (I) Preparation of the Chiral Glycolates, Their Alkylation, Their Deprotection, and Their Hydrolysis.



Benzyloxyacetic acid (2a).[158] In a 2-neck 250 mL round bottom flask sodium hydride (7.08 g, 177 mmol, 60% dispersion in mineral oil) was washed with hexanes (3 x 20 mL), and the remaining solvent was removed under oil pump vacuum for 15 min. Into a rapidly stirred suspension of this solid in dry THF (60 mL) at rt was cannulated a solution of benzyl alcohol (15.0 mL, 145 mmol, freshly distilled) in 50 mL dry THF (5 mL rinse) over 25 min. Additional benzyl alcohol (2.0 mL, 19 mmol, freshly distilled) was added neat. After the mixture had stirred at rt for 5 min, 15-crown-5 (0.10 mL, 0.50 mmol) and sodium iodide (600 mg, 4 mmol, oven-dried) were added. Into this white suspension, a solution of chloroacetic acid (7.30 g, 77.2 mmol, freshly recrystallized from $CHCl_3$) in dry THF (30 mL, 5 mL rinse) was cannulated over 10 min. The reaction flask was insulated with aluminum foil and heated to reflux. After 12 h, heating was discontinued. After the mixture had cooled at rt for 3 h, it was poured onto crushed ice and washed with EtOAc (4 x 40 mL). The aqueous layer was cooled with crushed ice and acidified with concentrated HCl until white material oiled out. The aqueous layer was extracted with EtOAc (5 x 40 mL). (The aqueous layer was reacidified after each extraction.) These combined organic layers were washed with saturated sodium chloride (10 mL), dried (magnesium sulfate), filtered, rotary evaporated, and dried under vacuum to give an orange liquid (12.7 g). It was purified on a flash silica column (2% to 10% MeOH/DCM). Fractions were combined, rotary evaporated, and dried under vacuum to give **2a** as a pale yellow liquid (11.4 g, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H), 4.66 (s, 2H), 4.14 (s, 2H).

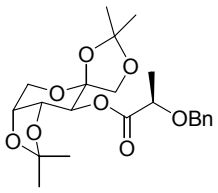


General esterification procedure for the preparation of the chiral glycolates. 1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl benzyloxyacetate (3a). To a solution of benzyloxyacetic acid (**2a**, 2.70 g, 14.5 mmol) in dry DCM (25 ml) were added DCC (3.18 g, 14.5 mmol), 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose **1** (2.00 g, 7.68 mmol) and DMAP (0.4 g, 3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for 45 h. DCM was removed on the rotary evaporator. The residue was resuspended in EtOAc and kept in the freezer for 30 min before the solid was filtered off. The organic solution was washed with saturated sodium bicarbonate, 10% citric acid, and saturated sodium chloride and dried (magnesium sulfate). Upon filtration and rotary evaporatorping, the residue was purified by flash chromatography on silica gel (hexanes:EtOAc 5:1 to 4:1) to afford **3a** as a white solid (4.9 g, 78%). mp 103-104 ºC. $[\alpha]_D$ = -128.7˚ (c 0.46, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.37 (m, 5H), 5.22 (d, *J* = 8.1 Hz, 1H), 4.31-4.10 (m, 6H), 4.65 (d, *J* = 1.5 Hz, 2H), 3.98 (d, *J* = 9.2 Hz, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.3, 137.2, 128.7, 128.3, 128.2, 112.3, 109.9, 103.7, 74.9, 73.9, 73.5, 72.1, 71.1, 67.2, 60.8, 28.0, 26.5, 26.4, 26.3. IR: ν 2990, 2931, 2884, 1760, 1737, 1454, 1384, 1372, 1221, 1195, 1127, 1085, 1028, 976, 914, 886, 851, 824, 809, 744, 698 cm^{-1}. EIMS: 408 (M^+). Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.48; H, 6.80.

General procedure for the alkylation. To a solution of LiHMDS (2 mmol) in dry THF (6 mL) (Method A) or in dry THF (6 mL) and HMPA (5 or 10% v/v) (Method B) was

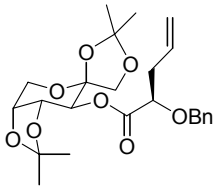
added dropwise a solution of substrate (1 mmol) in dry THF (4 mL) in 5 min at –78 °C. The resulting mixture was stirred at –78°C for 30 min, neat alkyl halide (5 mmol, purified by passage through a small plug of alumina[155]) was added. The reaction mixture was stirred at –78 °C until starting material had disappeared by TLC (hexanes:EtOAc 3:2 or hexanes:Et_2O 4:1). The reaction was quenched at –78 °C with saturated ammonium chloride. After the temperature of the mixture had reached about 0 °C, the mixture was transferred to a separatory funnel and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with saturated sodium chloride and dried (magnesium sulfate). Upon removing solvent on the rotary evaporator, the residue was purified by flash chromatography on silica gel (hexanes:Et_2O) to afford the product.

Method C was the same as Method B except that the reaction temperature was maintained at –95 °C.

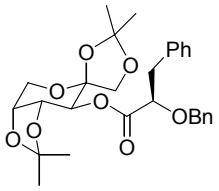


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)propionate (4a). The product was obtained in 73% yield using alkylation Method C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 5.19 (d, J = 8.1 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.31 (dd, J = 5.1, 7.8 Hz, 1H), 4.23 (dd, J = 1.5, 5.1 Hz, 1H), 4.18-4.08 (m, 3H), 3.99 (d, J = 9.6 Hz, 1H), 3.86 (d, J = 9.6 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.48 (d, J = 7.5 Hz, 3H), 1.38 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.3, 137.7, 128.6, 128.3, 128.0, 112.3, 109.9, 103.8, 74.9, 74.2, 73.9, 72.2, 72.1, 71.1, 60.8, 28.0, 26.6,

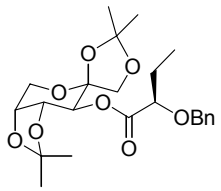
26.5, 26.4, 19.0. IR: ν 3031, 2987, 2936, 2885, 1755, 1496, 1454, 1372, 1326, 1296, 1240, 1220, 1194, 1140, 1085, 1066, 1028, 976, 912, 888, 862, 851, 836, 810, 741, 699 cm^{-1}. EIMS: 421 ($M\text{-}H^+$). Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.69; H, 7.11.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)-4-pentenoate (4b).* (All procedures marked with an aterisk were conducted by Dr. Hongwu Yu.) The product was obtained in 76% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 5.92-5.78 (m, 1H), 5.21-5.09 (m, 3H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.30 (dd, *J* = 5.1, 8.1 Hz, 1H), 4.23 (dd, *J* = 1.5, 5.1 Hz, 1H), 4.15 (dd, *J* = 2.4, 14.1 Hz, 1H), 4.12 (m, 1H), 4.05 (d, *J* = 6.6 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 8.7 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.2, 137.6, 133.0, 128.5, 128.3, 128.0, 112.3, 109.8, 103.8, 77.9, 74.8, 73.9, 72.3, 72.2, 72.1, 71.2, 60.8, 37.5, 28.0, 26.6, 26.4. IR: ν 2990, 2931, 2884, 1755, 1643, 1454, 1372, 1337, 1220, 1190, 1112, 1085, 1026, 976, 913, 888, 851, 837, 810, 738, 698 cm^{-1}. FABMS: 447 ($M\text{-}H^+$). Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.16.

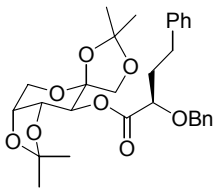


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)-3-phenyl-propionate (4c).* The product was obtained in 58% yield using alkylation Method A. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (d, *J* = 7.7 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.27-4.15 (m, 3H), 4.14 (dd, *J* = 2.4, 13.2 Hz, 1H), 4.07 (d, *J* = 13.4 Hz, 1H), 3.94 (d, *J* = 9.4 Hz, 1H), 3.77 (d, *J* = 9.4 Hz, 1H), 3.11 (m, 2H), 1.55 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.1, 137.5, 137.1, 129.8, 128.5, 128.1, 127.9, 126.9, 112.3, 109.9, 103.7, 79.2, 74.8, 73.9, 72.5, 72.2, 71.3, 60.9, 39.5, 28.0, 26.6, 26.4. IR: ν 2990, 2931, 1747, 1649, 1455, 1449, 1384, 1372, 1337, 1237, 1220, 1190, 1161, 1114, 1084, 973, 914, 864, 817 cm^{-1}. CIMS: 497 (M-H$^+$). Anal. Calcd for $C_{28}H_{34}O_8$: C, 67.45; H, 6.87. Found: C, 67.38; H, 6.89.

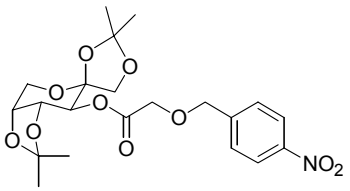


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)butanoate (4d).* The product was obtained in 74% yield using alkylation Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (d, *J* = 7.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.29 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.23 (dd, *J* = 1.6, 5.2 Hz, 1H), 4.15 (dd, *J* = 2.4, 13.2 Hz, 1H), 4.10 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 9.2 Hz, 1H), 3.94 (dd, *J* = 5.6, 6.8 Hz, 1H), 3.88 (d, *J* = 9.2 Hz, 1H), 1.85 (m. 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.01 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.7, 137.6, 128.5, 128.2, 128.1, 127.9, 127.8, 112.2, 109.7, 103.7, 79.2, 74.8, 73.8, 72.2, 72.0, 71.0, 70.9, 60.7, 27.9, 26.5, 26.4, 26.3, 26.3, 26.2, 9.7. IR: ν 2990, 2931, 2884, 1754, 1649, 1455, 1372, 1337, 1296,

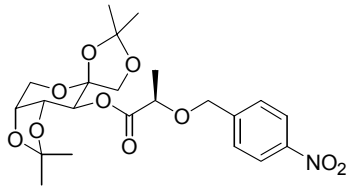
1220, 1190, 1114, 1085, 1026, 976, 908, 888, 852, 817, 738, 668 cm^{-1}. FABMS: 443 $(M+Li)^+$.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)-4-phenyl-butanoate (4e).* The product was obtained in 52% yield using alkylation Method B. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.15 (m, 5H), 5.22 (d, *J* = 8 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.30 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.23 (dd, *J* = 1.6, 5.2 Hz, 1H), 4.15 (dd, *J* = 2.8, 13.6 Hz, 1H), 4.10 (d, *J* = 13.6 Hz, 1H), 3.99 (d, *J* = 9.6 Hz, 1H), 3.98 (d, *J* = 6.8 Hz, 1H), 3.87 (d, *J* = 9.6 Hz, 1H), 2.82-2.69 (m, 2H), 2.12 (m, 2H), 1.55 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.8, 141.4, 137.6, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 126.2, 112.4, 112.2, 110.0, 109.9, 103.8, 103.8, 74.9, 74.0, 72.5, 72.4, 72.3, 72.3, 72.1, 71.2, 71.1, 71.0, 60.9, 60.9, 35.0, 34.8, 32.9, 32.8, 31.5, 31.4, 29.9, 28.1, 27.5, 27.4, 26.7, 26.5, 26.4, 26.3, 26.2, 25.6, 14.1. IR: ν 2987, 2933, 2873, 1754, 1604, 1496, 1454, 1383, 1372, 1296, 1220, 1191, 1168, 1113, 1086, 1066, 1028, 976, 912, 888, 850, 837, 810, 739, 699 cm^{-1}. FABMS: 519.2 $(M+Li)^+$.

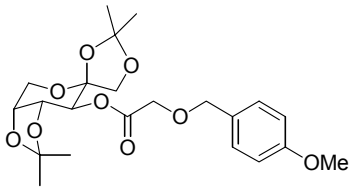


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-nitrobenzyloxy) acetate (3b). This was prepared by the general esterification procedure using the alcohol **1** and *p*-nitrobenzyloxyacetic acid[159] **2b** to give **3b** as a greenish white solid (39%) and recovered alcohol **1** (33% recovery). mp 84-86 ºC (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 5.22 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 2H), 4.31 (d, *J* = 16.4 Hz, 1H), 4.29 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.23 (d, *J* = 16.4 Hz, 1H), 4.15 (dd, *J* = 13.2, 2.4 Hz, 1H), 4.11 (d, *J* = 13.2 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 3.88 (d, *J* = 9.6 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.37 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.7, 147.5, 144.8, 128.0, 123.6, 112.1, 109.7, 103.4, 74.6, 73.6, 72.0, 71.8, 71.2, 67.6, 60.5, 27.8, 26.3, 26.1, 26.0. IR: ν 2987, 2931, 1761, 1607, 1523, 1384, 1347, 1243, 1220, 1196, 1135, 1085, 1026, 976, 914, 885, 851, 818, 805, 740 cm^{-1}. FABMS *m/z* (% of base peak): 454.1 ($M+H^+$, 28), 438.0, ($M+H-O^+$, 88), 396.0 ($M+H-CH_3COCH_3^+$, 82), 243.1 ($M-OCOCH_2OR^+$, 48), 136.0 (CH_2Ar^+, 100). Anal. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09. Found: C, 55.80; H, 6.04; N, 3.09.



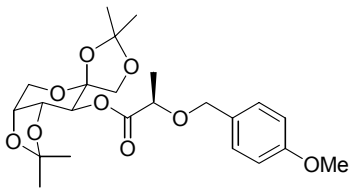
1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-nitrobenzyloxy) propionate (5a). The product was obtained as an oil in 19% yield using alkylation Method C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, *J* = 8.8, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 5.22/5.19 (d, *J* = 8.0 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.57/4.56 (d, *J* = 12.4 Hz, 1H), 4.34-4.07 (m, 5H), 3.99/3.97(d, *J* = 9.6 Hz, 1H), 3.87 / 3.84 (d, *J* = 9.2 Hz, 1H), 1.55 (s, 3H), 1.54 (d, *J* =

6.8 Hz, 3H), 1.49 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.9, 147.7, 145.3, 128.3, 123.8, 112.3, 110.0, 103.8, 75.2, 74.9, 73.9, 72.2, 71.6, 70.9, 60.9, 28.0, 26.6, 26.5, 26.3, 18.9. IR: ν 2987, 2935, 2884, 1753, 1606, 1523, 1454, 1373, 1348, 1296, 1240, 1220, 1196, 1140, 1112, 1085, 1067, 1030, 976, 912, 888, 858, 821, 806, 739 cm^{-1}. FABMS *m/z* (% of base peak): 474.2 (M+Li$^+$, 53), 452.2 (M-Me$^+$, 15), 410.2 (M+H-$CH_3COCH_3^+$, 68), 243.2 (M-OCOCH(Me)OR$^+$, 36), 136.0 (CH_2Ar^+, 100). Anal. Calcd for $C_{22}H_{29}NO_{10}$: C, 56.53; H, 6.25; N, 3.00. Found: C, 56.81; H, 6.32; N, 3.02.

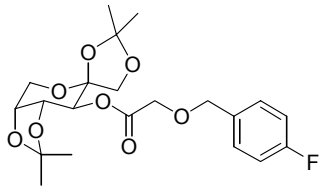


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-methoxybenzyloxy) acetate (3c). This was prepared by the general esterification procedure using the alcohol **1** and *p*-methoxybenzyloxyacetic acid[159] **2c** to give **3c** as a greenish white solid (92%). mp 86 ºC (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 7.6 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.28 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.23 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.19 (d, *J* = 16.8 Hz, 1H), 4.14 (dd, *J* = 13.2, 2.4 Hz, 1H), 4.10 (d, *J* = 16.4 Hz, 1H), 4.09 (d, *J* = 13.2 Hz, 1H), 3.97 (d, *J* = 9.2 Hz, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.3, 159.6, 129.9, 129.1, 113.9, 112.2, 109.8, 103.6, 74.7, 73.7, 73.0, 71.9, 70.8, 66.6, 60.6, 55.3, 27.9, 26.4, 26.3, 26.2. IR: ν 2988, 1931, 1761, 1613, 1514, 1455, 1384, 1302, 1250, 1221, 1195, 1114, 1085, 1032, 976, 914, 886, 851, 818, 805, 714 cm^{-1}. FABMS *m/z* (% of base peak): 437.2 (M-H$^+$, 64), 438 (M$^+$, 20), 423.0 (M-Me+, 46),

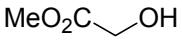
381.0 (M+H-$CH_3COCH_3^+$, 19), 244.0 (M+H-$OCOCH_2OR^+$, 80), 121.0 (CH_2Ar^+, 100). Anal. Calcd for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.15; H, 6.82.



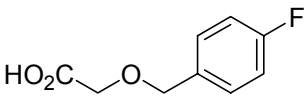
1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-methoxybenzyloxy) propionate (6a). The product was obtained as white crystals in 66% yield using alkylation Method C. mp 121.5-123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 1H), 5.22/5.19 (d, J = 7.6 Hz, 1H), 4.70/4.65 (d, J = 11.2 Hz, 1H), 4.39/4.38 (d, J = 11.2 Hz, 1H), 4.31 (dd, J = 7.8, 5.4 Hz, 1H), 4.23 (dd, J = 5.2, 2.0 Hz, 1H), 4.15 (dd, J = 13.4, 2.2 Hz, 1H), 4.11 (q, J = 6.8 Hz, 1H), 4.10 (dd, J = 13.2, 2.4 Hz, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.86 (d, J = 9.2 Hz, 1H), 3.79 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.46 (d, J = 7.2 Hz, 3H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.3, 159.5, 129.9, 129.7, 113.9, 112.2, 109.8, 103.7, 74.8, 73.8, 73.7, 73.4, 72.0, 71.7, 71.0, 70.9, 60.7, 55.3, 27.9, 26.5, 26.4, 18.9. IR: ν 2987, 2937, 2825 (sh), 2050, 2003, 1901, 1748, 1612, 1587, 1514, 1489, 1467, 1449, 1375, 1344, 1316, 1300, 1251, 1221, 1179, 1137, 1112, 1085, 1063, 1028, 978, 914, 887, 865, 846, 824, 804, 767, 733, 686, 577 cm^{-1}. FABMS *m/z* (% of base peak): 459.3 (M+Li^+, 36), 437.2 (M-Me^+, 10), 243.2 (M-OCOCH(Me)OR^+, 36), 121.0 (CH_2Ar^+, 100). Anal. Calcd for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13. Found: C, 60.96; H, 6.94.



1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-fluorobenzyloxy) acetate (3d).



Methyl glycolate. (This compound is also available from Aldrich Chemical Company.) Glycolic acid (12.35 g, 163 mmol) and *p*-toluenesulfonic acid monohydrate (102 mg, 0.537 mmol) were dissolved in 100 mL dry MeOH. The mixture was heated to reflux in a heating mantle. After 2.5 h, the mixture was rotary evaporated to give a colorless liquid. The liquid was dissolved in Et_2O (85 mL), washed with saturated sodium bicarbonate (5 mL), dried (magnesium sulfate), filtered, rotary evaporated, and dried under vacuum to give a pale green liquid (8.55 g, 59%). The material was pure by ^1H NMR and was used in subsequent reactions. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.18 (d, J = 5.4 Hz, 2H), 3.81 (s, 3H), 2.34 (t, J = 5.5 Hz, 1H, exchanged with D_2O).

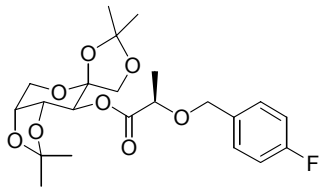


p-Fluorobenzyloxyacetic acid (**2d**). In a two-neck flask a suspension of sodium hydride (60% in mineral oil, 590. mg, 14.8 mmol) was washed with hexanes (3 x 10 mL) and then dried under oil pump vacuum for 10 min. A solution of methyl glycolate (1.04 g, 11.6 mmol) in dry THF (10 mL) was added to the suspension of sodium hydride in dry THF (50

mL) over about 3 min. After 5 min *p*-fluorobenzyl bromide (2.17 mL, 17.3 mmol) was added dropwise over about 3 min. Tetrabutylammonium iodide (110 mg, 0.30 mmol) and DMPU (0.30 mL, 2.5 mmol) were added. The flask was insulated from light with aluminum foil and the mixture was stirred overnight. The reaction was followed by ^{1}H NMR. After stirring at rt for 14 h, the reaction mixture was heated in an oil bath to about 70 ºC. After stirring at this temperature for an additional 6 h, the reaction mixture was allowed to cool to rt. After 30 min the reaction was quenched by slow addition of saturated ammonium chloride (10 mL). The layers were separated, and the solvent was removed from the organic layer. To the residue was added 1 M NaOH (50 mL) and the aqueous quench. After stirring at rt for 1 h, the aqueous layer was washed with Et_2O (3 x 20 mL) and then cooled with crushed ice. Concentrated HCl was added until the pH was 1-2. The aqueous layer was extracted with DCM (3 x 20 mL). These combined organic extracts were dried (magnesium sulfate), filtered, and rotary evaporated to give a yellow liquid (1.0 g). ^{1}H NMR indicated that the liquid still contained some ester. To the liquid was added 4 M NaOH (40 mL). This suspension was heated to 60-70 ºC for 1h, during which time it became a solution. After cooling at rt for 20 min, the aqueous layer was washed with DCM (3 x 20 mL) and then cooled with crushed ice. Concentrated HCl (16 mL) was added until the pH was 1-2. The aqueous layer was extracted with DCM (3 x 20 mL). These combined organic extracts were dried (magnesium sulfate), filtered, rotary evaporated, and dried under vacuum to give **2d** as a yellow liquid which froze into white needles in the freezer (379 mg, 18%). mp 44-45 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.32 (m, 2H), 7.09-7.03 (m, 2H), 4.62 (s, 2H), 4.14 (s, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 175.3, 162.7 ($^{1}J_{C\text{-}F}$ = 246 Hz), 132.7, 130.0 ($^{3}J_{C\text{-}F}$ = 8 Hz), 115.5 ($^{2}J_{C\text{-}F}$ = 21 Hz), 72.7, 66.7. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -114.7. IR: ν 3472-

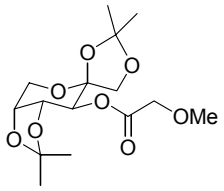
2919, 1731, 1604, 1511, 1433, 1223, 1155, 1116, 1016, 854, 821, 772, 660 cm^{-1}. FABMS *m/z* (% of base peak): 183.1 ($M\text{-}H^+$, 28).

The chiral glycolate was prepared by the general esterification procedure using the alcohol **1** and *p*-fluorobenzyloxyacetic acid **2d** to give **3d** as a greenish white solid (84%). mp 105 ºC. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.32 (m, 2H), 7.06-7.00 (m, 2H), 5.22 (d, *J* = 7.8 Hz, 1H), 4.60 (s, 2H), 4.29 (dd, *J* = 7.8, 5.3 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.22 (ddd, *J* = 11.1, 4.5, 1.2 Hz, 1H), 4.15 (d, *J* = 12.8 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 4.07 (d, *J* = 5.1 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 3.87 (d, *J* = 9.3 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.1, 162.6 ($^1J_{C\text{-}F}$ = 246 Hz), 133.0, 129.9 ($^3J_{C\text{-}F}$ = 8 Hz), 115.4 ($^2J_{C\text{-}F}$ = 22 Hz), 112.2, 109.8, 103.6, 74.7, 73.8, 72.6, 72.0, 71.1, 67.1, 60.7, 27.8, 26.4, 26.2. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -115.1. IR: ν 2990, 2931, 2884, 1759, 1602, 1509, 1455, 1373, 1222, 1196, 1127, 1084, 1026, 976, 914, 886, 855, 824, 818, 773, 738, 720, 668 cm^{-1}. FABMS *m/z* (% of base peak): 433.2 ($M+Li^+$, 44), 369.1 ($M+H\text{-}CH_3COCH_3^+$, 62), 243.1 ($M\text{-}OCOCH_2OR^+$, 20). Anal. Calcd for $C_{21}H_{27}FO_8$: C, 59.15; H, 6.38. Found: C, 59.44; H, 6.44.



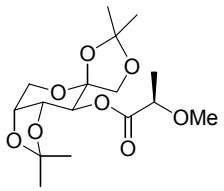
1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-fluorobenzyloxy) propionate (7a). The product was obtained as a colorless oil in 75% yield using alkylation Method C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.34 (m, 2H), 7.05-7.00 (m, 2H), 5.22/5.19 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.30 (dd, *J* = 8.0,

5.2 Hz, 1H), 4.23 (dd, J = 5.4, 1.8 Hz, 1H), 4.16 (dd, J = 13.6, 2.4 Hz, 1H), 4.11 (dd, J = 13.2, 1.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.87 (d, J = 9.2 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.48 (d, J = 6.4 Hz, 3H), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.2, 162.8 ($^1J_{C\text{-}F}$ = 247 Hz), 133.6, 130.1 ($^3J_{C\text{-}F}$ = 8 Hz), 115.5 ($^2J_{C\text{-}F}$ = 22 Hz), 112.4, 110.0, 103.8, 75.0, 74.4, 74.0, 72.2, 71.5, 71.3, 60.9, 28.0, 26.6, 26.4, 19.0. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -115.4. IR: ν 3424, 2987, 2931, 1754, 1602, 1510, 1454, 1372, 1326, 1296, 1221, 1190, 1138, 1112, 1084, 1067, 1032, 975, 908, 885, 820 cm^{-1}. FABMS *m/z* (% of base peak): 447.2 (M+Li$^+$, 27), 425.2 (M-Me$^+$, 15), 383.2 (M+H-$CH_3COCH_3^+$, 84), 243.1 (M-OCOCH(Me)OR$^+$, 24). Anal. Calcd for $C_{22}H_{29}FO_8$: C, 59.99; H, 6.64. Found: C, 59.95; H, 6.61.

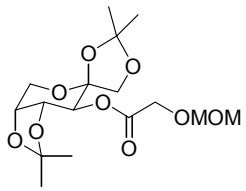


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl methoxyacetate (3e).* This was prepared by the general esterification procedure using the alcohol **1** and methoxyacetic acid (Acros) to give **3e** as a yellowish green oil (74%) and recovered alcohol **1** (25% recovery). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.21 (d, J = 8.0 Hz, 1H), 4.29 (dd, J = 7.8, 5.4 Hz, 1H), 4.24 (ddd, J = 5.4, 2.4, 1.2 Hz, 1H), 4.16 (d, J = 16.4 Hz, 1H), 4.15 (dd, J = 13.4, 2.6 Hz, 1H), 4.09 (d, J = 13.2 Hz, 1H), 4.08 (d, J = 16.8 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 3.86 (d, J = 9.6 Hz, 1H), 3.47 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.1, 112.2, 109.8, 103.6, 74.5, 73.8, 72.0, 71.0, 69.7, 60.7, 59.5, 27.9, 26.5, 26.3, 26.2. IR: ν 2988, 2936, 2825, 1764, 1454, 1373, 1221, 1192, 1129,

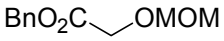
1085, 976, 913, 885, 850, 839, 804, 714, 668 cm^{-1}. FABMS *m/z* (% of base peak): 331.2 ($M-H^+$, 68), 317.2 ($M-Me^+$, 54), 275.2 ($M+H-CH_3COCH_3^+$, 100), 243.2 ($M-OCOCH_2OR^+$, 27). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.14; H, 7.11.



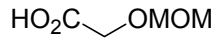
1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-methoxypropionate (8a). The product was obtained as white crystals in 75% yield using alkylation Method C. mp 81-85 ºC. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.20 / 5.17 (d, *J* = 7.8 Hz, 1H), 4.31 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.23 (dd, *J* = 5.2, 1.6 Hz, 1H), 4.15 (dd, *J* = 13.6, 2.4 Hz, 1H), 4.10 (d, *J* = 13.6 Hz, 1H), 4.0-3.9 (m, 1H), 3.95 (dd, *J* = 6.6 Hz, 1H), 3.85 / 3.82 (d, *J* = 9.2 Hz, 1H), 3.41 (s, 3H), 1.60-1.34 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.1, 112.3, 109.9, 103.8, 74.9, 73.9, 72.1, 71.1, 60.8, 57.9, 28.0, 26.6, 26.5, 26.4, 18.7. IR: ν 2988, 2939, 2889, 2825, 1755, 1737, 1454, 1451, 1373, 1264, 1237, 1220, 1189, 1127, 1113, 1084, 1066, 1041, 976, 914, 886, 854, 845, 820, 806, 800 cm^{-1}. FABMS *m/z* (% of base peak): 353.2 ($M+Li^+$, 62), 331.2 ($M-Me^+$, 72), 289.1 ($M+H-CH_3COCH_3^+$, 100), 243.2 ($M-OCOCH(Me)OR^+$, 33). Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.73; H, 7.66.



4.1.17. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (methoxy methoxy)acetate (3f).



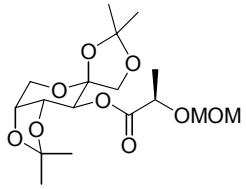
Benzyl (methoxymethoxy)acetate. Benzyl glycolate[160] (2.77 g, 16.7 mmol) was dissolved in 20 mL dry THF at rt. DIEA (4.7 mL, 27 mmol) and iodomethyl methyl ether (2.1 mL, 25 mmol) were added. The mixture fumed and formed white precipitate upon the addition of the iodide. After stirring at rt for 3.5 h, the mixture was heated to reflux. After 22 h, 25 mL ice-cold saturated potassium carbonate was added to the reaction mixture. The mixture was extracted with EtOAc (3 x 25 mL). The combined DCM extracts were washed with saturated sodium chloride (10 mL), dried (magnesium sulfate), and rotary evaporated to give a brown semi-solid. The liquid was separated on a flash silica column (1:10 EtOAc: hexanes to 1:8 EtOAc: hexanes). Fractions were combined, rotary evaporated, and dried under vacuum to give the product as a yellow liquid (2.97 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (s, 5H), 5.21 (s, 2H), 4.72 (s, 2H), 4.21 (s, 2H), 3.39 (s, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.8, 135.4, 128.4, 128.3, 96.2, 66.3, 64.1, 55.5. IR: ν 3033, 2952, 2896, 2825, 1758, 1498, 1456, 1404, 1364, 1279, 1194, 1152, 1121, 1062, 1015, 920, 841, 818, 804, 753, 698 cm^{-1}. FABMS *m/z* (% of base peak): 211.1 ($M+H^+$, 100).



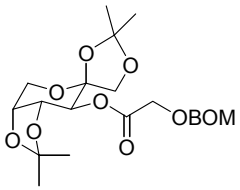
(Methoxymethoxy)acetic acid (**2f**).[161] The ester (204 mg, 0.971 mmol) from above was dissolved in EtOAc (5 mL). The flask was evacuated and flushed with N_2 three times. $Pd(OH)_2$ (23 mg) was added to the solution. The flask was evacuated and flushed with H_2

(balloon pressure) three times. The mixture was stirred at rt for 2 h. The mixture was filtered through a pad of packed filter aid. The filter aid was washed with EtOAc (40 mL). The filtrate was rotary evaporated and dried under vacuum to give **2f** as a yellow liquid (96 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.52 (s, 1H), 4.74 (s, 2H), 4.24 (s, 2H), 3.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 175.7, 96.5, 64.0, 56.0. IR: ν 3449, 1734, 1605, 1428, 1215, 1151, 1114, 1055 cm^{-1}. FABMS *m/z* (% of base peak): 120.0 (M^+, 13). Anal. Calcd for $C_4H_8O_4$: C, 40.00; H, 6.71. Found: C, 39.86; H, 6.85.

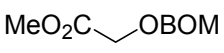
The glycolate was prepared by the general esterification procedure using the alcohol **1** and methoxymethoxyacetic acid **2f** to give **3f** as a yellow oil (771 mg, 31%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.20 (d, *J* = 7.6 Hz, 1H), 4.72 (s, 2H), 4.30 (d, *J* = 16.8 Hz, 1H), 4.29 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.24 (ddd, *J* = 6.8, 1.2, 1 Hz, 1H), 4.20 (d, *J* = 16.8 Hz, 1H), 4.14 (dd, *J* = 13.4, 2.2 Hz, 1H), 4.09 (d, *J* = 13.6 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 3.85 (d, *J* = 9.3 Hz, 1H), 3.40 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.0, 112.3, 109.9, 103.6, 96.6, 74.8, 73.8, 71.9, 71.0, 64.3, 60.7, 55.9, 27.9, 26.5, 26.4, 26.2. IR: ν 3624, 3530, 2990, 2931, 2884, 2825, 1764, 1737, 1455, 1384, 1373, 1243, 1220, 1196, 1149, 1120, 1085, 1061, 979, 920, 885, 850, 808, 720 cm^{-1}. FABMS *m/z* (% of base peak): 369.3 ($M+Li^+$, 44), 347.2 ($M-Me^+$, 43), 305.2 ($M+H-CH_3COCH_3^+$, 100), 243.2 ($M-OCOCH_2OR^+$, 52). Anal. Calcd for $C_{16}H_{26}O_9$: C, 53.03; H, 7.23. Found: C, 53.25; H, 7.32.



1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(methoxymethoxy) propionate (9a). The product was obtained in 65% yield using alkylation Method C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.18/5.14 (d, J = 8.4 Hz, 1H), 4.70 (q, J = 7.1 Hz, 2H), 4.29 (dd, J = 7.8, 5.0 Hz, 1H), 4.23 (dd, J = 5.6, 1.8 Hz, 1H), 4.14 (dd, J = 13.6, 2.4 Hz, 1H), 4.09 (d, J = 13.6 Hz, 1H), 3.96 (d, J = 9.2 Hz, 1H), 3.85 (d, J = 9.2 Hz, 1H), 3.39 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.0, 112.3, 109.8, 103.8, 96.3, 75.0, 74.0, 71.9, 71.8, 70.9, 60.7, 56.0, 27.9, 26.6, 26.2, 18.7. IR: ν 2987, 2937, 2891, 2826, 1758, 1454, 1373, 1326, 1296, 1221, 1190, 1156, 1126, 1085, 1026, 976, 915, 886, 852, 810, 765, 750, 654, 626 cm^{-1}. FABMS *m/z* (% of base peak): 383.2 ($M+Li^+$, 72), 361.2 ($M-Me^+$, 20), 319.2 ($M+H-CH_3COCH_3^+$, 69), 243.2 ($M-OCOCH(Me)OR^+$, 34). Anal. Calcd for $C_{17}H_{28}O_9$: C, 54.25; H, 7.50. Found: C, 54.38; H, 7.51.

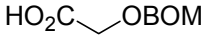


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (benzyloxymethoxy) acetate (3g).



Methyl (benzyloxymethoxy)acetate. Sodium iodide (84 mg, 0.56 mmol) was dissolved in 25 mL dry THF at 0 °C. Methyl glycolate (2.50 g, 27.8 mmol), DIEA (10.0 mL, 57.5 mmol), and benzyl chloromethyl ether[162] (8.65 g, 55.3 mmol) were added. The mixture

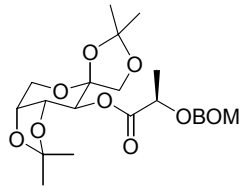
was left to stir, with warming to rt. After 45 h, the reaction mixture was poured into 30 mL ice-cold saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with 4 x 25 mL EtOAc. The combined organic layers were washed with 10 mL saturated sodium chloride, dried (magnesium sulfate), and rotary evaporated to give a yellow liquid. It was separated on a flash silica column (1:10 EtOAc: hexanes to 1:4 EtOAc: hexanes). Fractions were combined, rotary evaporated, and dried under vacuum to give the ester as a pale yellow liquid (4.524 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 5H), 4.85 (s, 2H), 4.65 (s, 2H), 4.23 (s, 2H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.3, 137.4, 128.2, 127.7, 127.6, 94.4, 69.6, 64.2, 51.6. IR: ν 3037, 2953, 2896, 1758, 1737, 1498, 1454, 1437, 1383, 1285, 1215, 1170, 1122, 1063, 1028, 931, 844, 824, 814, 742, 699 cm^{-1}. FABMS *m/z* (% of base peak): 211.0 ($M+H^+$, 60). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.57; H, 6.69.



(Benzyloxymethoxy)acetic acid (**2g**). The ester (1.01 g, 4.80 mmol) from above was dissolved in THF (5 mL), deionized H_2O (5 mL), and 4 M NaOH (3 mL). After stirring vigorously at rt for 30 min, the mixture was extracted with Et_2O (2 x 15 mL). The aqueous layer was cooled with ice and then acidified with 10% citric acid and concentrated HCl (0.5 mL) (pH < 2 by pH paper). The aqueous layer was extracted with Et_2O (4 x 25 mL). These combined Et_2O layers were washed with 10 mL saturated sodium chloride, dried (magnesium sulfate), filtered, rotary evaporated, and dried under vacuum to give **2g** as a colorless oil (914 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (s, 5H), 4.87 (s, 2H), 4.67 (s, 2H), 4.27 (s, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 175.8, 137.3, 128.6, 128.0, 94.6,

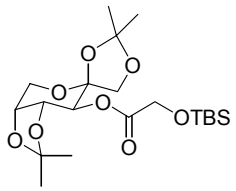
70.1, 64.1. IR: ν 3436, 3032, 2897, 1760, 1732, 1497, 1454, 1433, 1384, 1249, 1209, 1170, 1120, 1062, 1028, 938, 908, 824, 742, 698 cm^{-1}. FABMS *m/z* (% of base peak): 197.0 ($M+H^+$, 56). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.93; H, 5.99.

The chiral glycolate was obtained by the general esterification procedure using the alcohol **1** and benzyloxymethoxyacetic acid **2g** to give **3g** as a green oil (85%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35 (s, 5H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.86 (s, 2H), 4.66 (s, 2H), 4.35 (d, *J*= 16.8 Hz, 1H), 4.28 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.25 (d, *J* = 16.4 Hz, 1H), 4.23 (dd, *J* = 2.8, 1.2 Hz, 1H), 4.14 (dd, *J* = 13.6, 2.4 Hz, 1H), 4.09 (d, *J* = 13.2 Hz, 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 3.83 (d, *J* = 9.6 Hz, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.1, 137.6, 128.6, 128.1, 128.0, 112.3, 109.9, 103.7, 94.8, 74.7, 73.9, 72.0, 71.1, 70.2, 64.5, 60.7, 27.9, 26.5, 26.5, 26.3. IR: ν 2986, 2934, 2889, 1763, 1496, 1455, 1373, 1220, 1198, 1167, 1114, 1085, 1063, 1028, 976, 913, 884, 849, 805, 739, 699 cm^{-1}. FABMS *m/z* (% of base peak): 445.3 ($M+Li^+$, 52), 423.3 ($M-Me^+$, 26), 381.3 ($M+H-CH_3COCH_3^+$, 72), 351.2 ($M+H-CH_3COCH_3-CH_2O^+$, 47), 243.2 ($M-OCOCH_2OR^+$, 100). Anal. Calcd for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.53; H, 6.91.

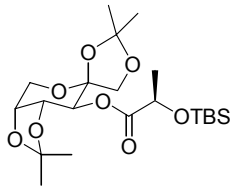


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxymethoxy) propionate (10a). The product was obtained in 68% yield using alkylation Method C. mp 82-83.5 ºC. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.35 (m, 5H), 5.19/5.13 (d, *J* = 8.0 Hz, 1H), 4.85-4.81 (m, 2H), 4.68-4.61 (m, 2H), 4.34 (q, *J* = 6.8 Hz, 1H), 4.27 (dd, *J* = 7.8, 5.4 Hz,

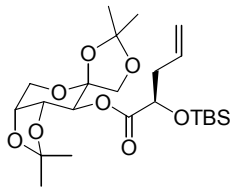
1H), 4.22-4.20 (m, 1H), 4.13 (dd, J = 13.2, 2.6 Hz, 1H), 4.07 (d, J = 13.6 Hz, 1H), 3.84 (d, J = 9.6 Hz, 1H), 3.77 (d, J = 9.6 Hz, 1H), 1.54 (s, 3H), 1.48 (d, J = 7.6 Hz, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.0, 137.8, 128.6, 128.2, 128.0, 112.3, 109.9, 130.8, 96.4, 94.4, 75.0, 74.0, 72.0, 71.8, 70.9, 70.2, 60.7, 28.0, 26.6, 26.2, 18.8. IR: ν 2987, 2937, 2890, 1760, 1454, 1373, 1221, 1167, 1123, 1114, 1084, 1026, 976, 912, 886, 852, 805, 738, 699 cm^{-1}. FABMS *m/z* (% of base peak): 459.3 (M+Li$^+$, 53), 437.2 (M-Me$^+$, 38), 395.2 (M+H-$CH_3COCH_3^+$, 48), 365.2 (M+H-CH_3COCH_3-CH_2O^+, 24), 243.2 (M-OCOCH(Me)OR$^+$, 100). Anal. Calcd for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13. Found: C, 61.30; H, 7.00.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl (*t*-butyldimethylsilyloxy) acetate (3h).* The glycolate was obtained by the general esterification procedure using alcohol **1** and (*t*-butyldimethylsilyloxy)acetic acid[163] **2h** to give **3h** (49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (d, J = 7.5 Hz, 1H), 4.39-4.21 (m, 4H), 4.14 (dd, J = 2.4, 13.8 Hz, 1H), 4.08 (d, J = 13.2 Hz, 1H), 3.96 (d, J = 9.6 Hz, 1H), 3.85 (d, J = 8.7 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.7, 112.3, 109.9, 103.8, 74.9, 74.0, 72.0, 70.9, 61.8, 60.7, 28.0, 26.6, 26.5, 26.4, 26.0, 25.9, -5.3. IR: ν 2990, 2931, 2860, 1768, 1461, 1378, 1369, 1255, 1220, 1142, 1086, 973, 914, 885, 853, 836, 779 cm^{-1}. FABMS: 439.1 (M+Li$^+$). Anal. Calcd for $C_{20}H_{36}O_8Si$: C, 55.53; H, 8.39. Found: C, 55.35; H, 8.39.

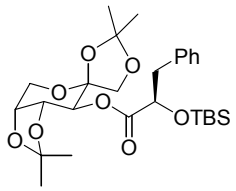


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyl-oxy)propionate (11a).* The product was obtained in 76% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13 (d, *J* = 7.2 Hz, 1H), 4.39 (dd, *J* = 7.5, 14.1 Hz, 1H), 4.28 (m, 1H), 4.21 (m, 1H), 4.14 (dd, *J* = 2.1, 13.2 Hz, 1H), 4.08 (d, *J* = 14.1 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.83 (d, *J* = 9.6 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.3, 112.3, 109.8, 103.9, 74.9, 73.9, 72.1, 70.9, 68.6, 60.8, 28.0, 26.7, 26.6, 26.4, 26.0, 21.9, 18.5, -4.7, -5.2. IR: ν 2987, 2933, 2888, 2857, 1768, 1740, 1472, 1383, 1372, 1254, 1220, 1143, 1086, 1068, 1030, 976, 914, 887, 837, 810, 780, 668 cm^{-1}. FABMS: 445.1 (M-H$^+$). Anal. Calcd for $C_{21}H_{38}O_8Si$: C, 56.48; H, 8.58. Found: C, 56.61; H, 8.63.

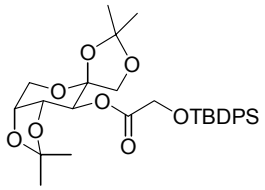


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyl-oxy)-4-pentenoate (11b).* The product was obtained in 78% yield using alkylation Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.80 (m, 1H), 5.17-5.08 (m, 3H), 4.33-4.26 (m, 2H), 4.21 (dd, *J* = 1.6, 5.2 Hz, 1H), 4.13 (dd, *J* = 2.4, 13.2 Hz, 1H), 4.08 (d, *J* = 9.9 Hz, 1H), 3.95 (d, *J* = 9.2 Hz, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 2.51 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.40 (s,

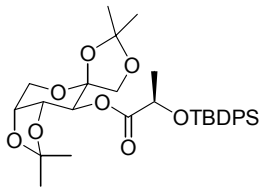
3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.2, 133.5, 118.5, 112.3, 109.8, 103.9, 74.8, 73.9, 72.3, 72.0, 71.0, 60.8, 40.2, 28.0, 26.7, 26.5, 26.4, 25.9, 18.5, -4.7, -5.2. IR: ν 3080, 3987, 2932, 2887, 2838, 1765, 1738, 1643, 1472, 1462, 1434, 1384, 1372, 1296, 1220, 1140, 1086, 1044, 976, 913, 888, 836, 810, 779, 737, 668, 626 cm^{-1}. FABMS: 471.0 (M-H$^+$). Anal. Calcd for $C_{23}H_{40}O_8Si$ (472.64); C, 58.45; H, 8.57. Found: C, 58.47; H, 8.57.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyl-oxy)-3-phenylpropionate (11c).* The product was obtained in 89% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 5.16 (d, *J* = 8.1 Hz, 1H), 4.41 (dd, *J* = 3.6, 8.7 Hz, 1H), 4.28 (dd, *J* = 5.1, 7.2 Hz, 1H), 4.21 (dd, *J* = 1.5, 5.1 Hz, 1H), 4.15 (dd, *J* = 2.1, 13.8 Hz, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 3.12 (dd, *J* = 3.6, 13.8 Hz, 1H), 2.93 (dd, *J* = 8.7, 14.1 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.80 (s, 6H), -0.09 (s, 3H), -0.23 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.2, 137.5, 130.2, 128.3, 126.8, 112.2, 109.8, 103.8, 74.8, 73.9, 73.8, 72.0, 71.1, 60.8, 42.0, 28.0, 26.6, 26.5, 26.4, 25.8, 18.4, -5.2, -5.6. IR: ν 2990, 2931, 2860, 1764, 1736, 1490, 1456, 1372, 1251, 1220, 1128, 1086, 976, 938, 903, 888, 845, 810, 779, 699 cm^{-1}. FABMS: 529.1 (M+Li$^+$).

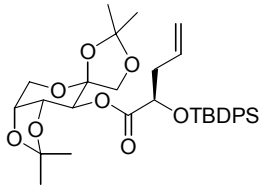


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl(*t*-butyldiphenylsilyl-oxy)acetate (3i). The glycolate was obtained by the general esterification procedure using the alcohol **1** and (*t*-butyldiphenylsilyloxy)acetic acid[164] to give **3i** (79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.67 (m, 4H), 7.44-7.37 (m, 6H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 16.8 Hz, 1H), 4.24 (d, *J* = 16.8 Hz, 1H), 4.24-4.18 (m, 2H), 4.10 (dd, *J* = 1.5, 13.8 Hz, 1H), 4.05 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 9.6 Hz, 1H), 3.68 (d, *J* = 9 Hz, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.0, 135.8, 135.7, 133.0, 132.8, 130.1, 130.1, 128.0, 112.2, 109.8, 103.7, 74.9, 73.9, 71.9, 70.7, 62.2, 60.6, 28.0, 26.9, 26.7, 26.6, 26.2, 19.5. IR: ν 3071, 2987, 2932, 2857, 1770, 1740, 1472, 1428, 1383, 1372, 1297, 1221, 1197, 1140, 1113, 1085, 1067, 1028, 976, 914, 881, 849, 822, 800, 741, 702, 609 cm^{-1}. FABMS: 563.4 (M+Li$^+$).

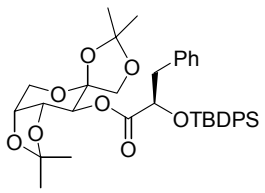


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyl-oxy)propionate (12a). The product was obtained in 83% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.47-7.33 (m, 6H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.33 (dd, *J* = 6.6, 13.8 Hz, 1H), 4.24-4.18 (m, 2H), 4.11 (dd, *J* = 2.1, 13.8 Hz, 1H), 4.05 (d, *J* = 14.1 Hz, 1H), 3.85 (d, *J* = 9.6 Hz, 1H), 3.49 (d, *J* = 9.6 Hz, 1H), 1.54 (s, 3H), 1.45 (s,

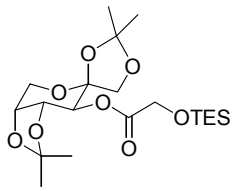
3H), 1.43 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.7, 136.1, 135.9, 133.8, 133.1, 130.0, 127.9, 112.2, 109.8, 103.7, 74.9, 73.9, 71.7, 70.6, 69.0, 60.6, 28.0, 27.0, 26.8, 26.7, 26.2, 21.9, 19.4. IR: ν 3071, 2987, 2932, 2857, 1764, 1740, 1472, 1428, 1372, 1221, 1189, 1135, 1112, 1085, 1066, 1026, 975, 911, 887, 866, 823, 785, 740, 702, 608 cm^{-1}. FABMS: 577.5 (M+Li$^+$).



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyl-oxy)-4-pentenoate (12b).* The product was obtained in 88% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 4H), 7.45-7.33 (m, 6H), 5.90-5.77 (m, 1H), 5.18-5.03 (m, 3H), 4.38 (t, J = 5.1 Hz, 1H), 4.27 (dd, J = 2.1, 13.8 Hz, 1H), 4.22-4.16 (m, 2H), 4.04 (d, J = 13.8 Hz, 1H), 3.82 (d, J = 9.3 Hz, 1H), 3.49 (d, J = 9.3 Hz, 1H), 2.46 (t, J = 6.6, 5.8 Hz, 2H), 1.52 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.4, 136.2, 136.1, 133.6, 133.1, 132.8, 130.0, 127.9, 118.7, 112.2, 109.7, 103.7, 74.9, 74.0, 72.4, 71.7, 70.7, 60.6, 40.0, 28.1, 27.1, 26.9, 26.8, 26.7, 19.6. IR: ν 3072, 2990, 2931, 2861, 1766, 1738, 1472, 1372, 1243, 1220, 1136, 1113, 1086, 1030, 996, 976, 912, 887, 862, 824, 740, 702 cm^{-1}. FABMS: 603.5 (M+Li$^+$).

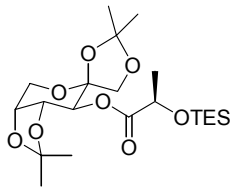


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyl-oxy)-3-phenylpropionate (12c).* The product was obtained in 88% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.53 (m, 2H), 7.43-7.17 (m, 13H), 5.00 (d, *J* = 7.2 Hz, 1H), 4.54 (t, *J* = 5.9 Hz, 1H), 4.14-4.03 (m, 3H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.66 (d, *J* = 9.3 Hz, 1H), 3.07 (d, *J* = 9.6 Hz, 1H), 3.02 (s, 1H), 3.00 (d, *J* = 1.5 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.2, 136.8, 136.3, 136.0, 133.4, 133.0, 130.3, 130.0, 129.9, 128.3, 127.8, 126.8, 112.1, 109.7, 103.5, 74.7, 73.9, 73.7, 71.5, 70.5, 60.6, 41.8, 27.9, 27.0, 26.9, 26.6, 26.2. IR: ν 2990, 2931, 2860, 1766, 1731, 1455, 1384, 1372, 1214, 1113, 1085, 1032, 973, 886, 853, 818, 773, 738, 701, 668 cm^{-1}. FABMS: 653.3 ($M+Li^+$).

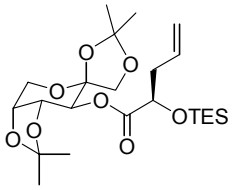


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl (triethylsilyloxy)acetate (3j).* A solution of **3a** in EtOAc was stirred in the presence of H_2 (balloon pressure) and 20% $Pd(OH)_2$/C overnight. $Pd(OH)_2$ was removed by filtration through filter aid. The crude product (1.52 g, 5.84 mmol) was dissolved in anhydrous pyridine (15 mL), and triethylsilyl chloride (1.1 mL, 6.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at rt overnight. Pyridine was removed on the rotary evaporator. The residue was dissolved in EtOAc and washed with saturated sodium bicarbonate and saturated sodium chloride and dried over magnesium sulfate. Upon removing solvent, the residue was purified by flash chromatography on a silica gel column (hexanes:EtOAc) to afford **3j** as an oil (2.08 g, 82%).

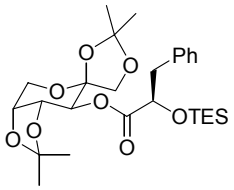
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18 (d, J = 7.7 Hz, 1H), 4.35 (d, J = 16.8 Hz, 1H), 4.30-4.22 (m, 3H), 4.14 (dd, J = 2.1, 13.6 Hz, 1H), 4.08 (d, J = 13.2 Hz, 1H), 3.96 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 9.5 Hz, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 0.98 (t, J = 7.8 Hz, 9H), 0.65 (dd, J = 7.6, 15.6 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.6, 112.3, 109.9, 103.8, 74.9, 74.0, 72.0, 70.8, 61.4, 60.7, 28.0, 26.6, 26.3, 6.8, 4.5. IR: ν 2990, 2954, 2884, 1768, 1737, 1455, 1384, 1372, 1221, 1196, 1142, 1086, 1067, 976, 887, 852, 816, 794, 745 cm^{-1}. FABMS: 439.1 (M+Li$^+$). Anal. Calcd for $C_{20}H_{36}O_8Si$: C, 55.53; H, 8.39. Found: C, 55.69; H, 8.39.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(triethylsilyloxy) propionate (13a).* The product was obtained in 77% yield using alkylation Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (d, J = 5.7 Hz, 1H), 4.39 (dd, J = 4.8, 9.9 Hz, 1H), 4.27 (dd, J = 3.9, 6.0 Hz, 1H), 4.22 (dd, J = 1.5, 3.9 Hz, 1H), 4.14 (dd, J = 1.8, 10.2 Hz, 1H), 4.08 (d, J = 10.2 Hz, 1H), 3.97 (d, J = 6.9 Hz, 1H), 3.83 (d, J = 6.9 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H), 1.46 (d, J = 5.4 Hz, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.97 (t, J = 6.6 Hz, 9H), 0.63 (dd, J = 5.7, 11.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 112.2, 109.8, 103.8, 74.8, 73.9,71.9, 70.8, 68.0, 60.7, 27.9, 26.6, 26.5, 26.3, 21.9, 6.8, 4.7. IR: ν 2990, 2943, 2884, 2731, 1764, 1624, 1459, 1414, 1372, 1325, 1296, 1221, 1190, 1140, 1086, 1018, 977, 912, 889, 865, 850, 836, 812, 786, 746, 674, 626, 514 cm^{-1}. FABMS: 453.1 (M+Li$^+$). Anal. Calcd for $C_{21}H_{38}O_8Si$ (446.61); C, 56.48; H, 8.58. Found: C, 56.24; H, 8.50.

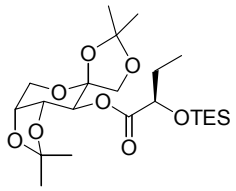


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(triethylsilyloxy)-4-pentenoate (13b).* The product was obtained in 71% yield using alkylation Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91-5.81 (m, 1H), 5.18-5.09 (m, 3H), 4.33 (dd, *J* = 5.2, 6.8 Hz, 1H), 4.28 (dd, *J* = 6.6, 8.4 Hz, 1H), 4.21 (dd, *J* = 2.0, 5.6 Hz, 1H), 4.14 (dd, *J* = 2.8, 13.6 Hz, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 2.52 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.62 (dd, *J* = 7.6, 15.6 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.2, 133.4, 118.4, 112.2, 109.8, 103.9, 74.9, 74.0, 72.0, 72.0, 71.0, 60.8, 40.2, 28.0, 26.7, 26.6, 26.4, 6.9, 4.8. IR: ν 3079, 2987, 2954, 2878, 1763, 1738, 1642, 1457, 1415, 1383, 1372, 1296, 1240, 1220, 1190, 1139, 1114, 1086, 1067, 1043, 1030, 1004, 976, 912, 888, 850, 832, 810, 745, 676, 626, 514 cm^{-1}. FABMS: 471.0 ($M-H^+$). Anal. Calcd for $C_{23}H_{40}O_8Si$ (472.64); C, 58.45; H, 8.53. Found: C, 58.70; H, 8.58.



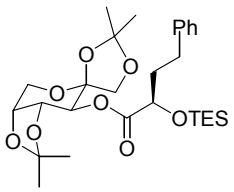
1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 3-phenyl-2-(triethylsilyloxy)propionate (13c).* The product was obtained in 75% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.44 (dd, *J* = 3.9, 8.3

Hz, 1H), 4.27 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.21 (m, 1H), 4.14 (dd, *J* = 2.2, 13.4 Hz, 1H), 4.07 (d, *J* = 13.4 Hz, 1H), 3.92 (d, *J* = 9.4 Hz, 1H), 3.72 (d, *J* = 8.7 Hz, 1H), 3.11 (dd, *J* = 3.7, 13.4 Hz, 1H), 2.95 (dd, *J* = 8.3, 13.5 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.83 (t, *J* = 7.83 Hz, 9H), 0.46 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 137.4, 130.1, 128.3, 126.8, 112.2, 109.8, 103.8, 74.8, 73.9, 73.3, 71.9, 71.0, 60.7, 41.9, 28.0, 26.6, 26.6, 26.3, 6.8, 4.5. IR: ν 3064, 3030, 2987, 2955, 2877, 1764, 1737, 1605, 1496, 1455, 1415, 1383, 1372, 1296, 1240, 1220, 1191, 1128, 1086, 1067, 1043, 1030, 976, 910, 888, 852, 811, 774, 743, 699, 668, 626 cm^{-1}. FABMS: 529.0 (M+Li$^+$). Anal. Calcd for $C_{27}H_{42}O_8Si$: C, 62.04; H, 8.10. Found: C, 62.01; H, 8.05.

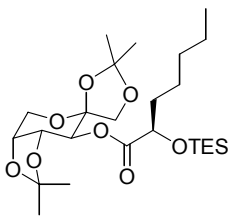


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(triethylsilyloxy) butanoate (13d).* The product was obtained in 83% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, *J* = 7.8 Hz, 1H), 4.29-4.20 (m, 3H), 4.14 (dd, *J* = 1.8, 13.5 Hz, 1H), 4.08 (d, *J* = 13.4 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 3.84 (d, *J* = 9.3 Hz, 1H), 1.79 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.99 (t, *J* = 4.2 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.63 (dd, *J* = 7.8, 15.6 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.8, 112.2, 109.7, 103.9, 74.9, 73.9, 72.9, 72.0, 70.8, 60.7, 28.9, 28.0, 26.6, 26.5, 26.3, 9.4, 6.9, 4.8. IR: ν 2986, 2956, 2878, 1760, 1736, 1460, 1415, 1383, 1372, 1326, 1296, 1240, 1221, 1190, 1140, 1114, 1086, 1069, 1028, 976, 910, 888, 848, 810, 743, 669, 626 cm^{-1}.

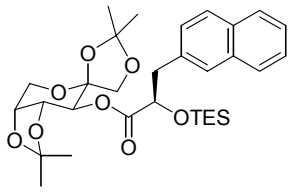
FABMS: 466.9 ($M+Li^+$). Anal. Calcd for $C_{22}H_{40}O_8Si$: C, 57.36; H, 8.75. Found: C, 57.22; H, 8.74.



1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 4-phenyl-2-(triethylsilyl-oxy)butanoate (13e).* The product was obtained in 61% yield using alkylation Method B. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.18 (m, 5H), 5.18 (d, J = 7.6 Hz, 1H), 4.36 (t, J = 5.2 Hz, 1H), 4.29 (dd, J = 5.2, 8.0 Hz, 1H), 4.22 (dd, J = 1.6, 5.2 Hz, 1H), 4.15 (dd, J = 2.0, 13.6 Hz, 1H), 4.09 (d, J = 13.2 Hz, 1H), 3.98 (d, J = 9.2 Hz, 1H), 3.85 (d, J = 9.2 Hz, 1H), 2.74 (m, 2H), 2.07 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.97 (t, J = 8 Hz, 9H), 0.64 (dd, J = 10.4, 18.4 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.6, 141.9, 128.7, 128.5, 126.0, 112.2, 109.8, 103.9, 74.9, 73.9, 72.0, 71.4, 71.1, 60.8, 37.6, 31.0, 28.0, 26.6, 26.5, 26.4, 6.9, 4.8. IR: ν 3063, 3029, 2987, 2955, 2877, 1760, 1737, 1604, 1497, 1455, 1415, 1383, 1372, 1326, 1296, 1240, 1220, 1187, 1155, 1129, 1086, 1066, 1029, 976, 911, 888, 850, 931, 804, 744, 700, 669, 626 cm^{-1}. FABMS: 542.9 ($M+Li^+$). Anal. Calcd for $C_{28}H_{44}O_8Si$: C, 62.66; H, 8.26. Found: C, 62.68; H, 8.12.

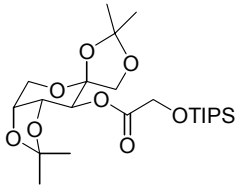


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(triethylsilyloxy) heptanoate (13f).* The product was obtained in 58% yield using alkylation Method B. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, *J* = 7.8 Hz, 1H), 4.29-4.20 (m, 3H), 4.14 (dd, *J* = 2.0, 13.5 Hz, 1H), 4.05 (d, *J* = 13.4 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 1.73 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.43-1.30 (m, 6H), 1.40 (s, 3H), 1.33 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.62 (dd, *J* = 7.6, 15.6 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ174.0, 112.2, 109.8, 103.9, 74.9, 74.0, 72.0, 70.8, 60.8, 35.7, 31.8, 28.0, 26.7, 26.6, 26.4, 24.6, 22.7, 14.2, 6.9, 4.8. IR: ν 2987, 2955, 2876, 1761, 1736, 1458, 1416, 1382, 1372, 1296, 1240, 1220, 1190, 1140, 1114, 1030, 976, 912, 888, 851, 838, 810, 744, 668 cm^{-1}. FABMS: 500.9 ($M-H^+$). Anal. Calcd for $C_{25}H_{46}O_8Si$: C, 59.73; H, 9.22. Found: C, 59.95; H, 9.31.

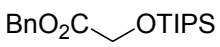


1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 3-naphthalen-2-yl-2-(triethylsilyloxy)propionate (13g).* The product was obtained in 71% yield using alkylation Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.70 (m, 4H), 7.45-7.39 (m, 3H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.54 (dd, *J* = 3.9, 7.8 Hz, 1H), 4.24 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.18 (s, 1H), 4.10 (d, *J* = 1.5 Hz, 1H), 4.06 (d, *J* = 13.2 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.74 (d, *J* = 9.3 Hz, 1H), 3.27 (dd, *J* = 4.1, 13.6 Hz, 1H), 3.13 (dd, *J* = 8.0, 13.4 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 0.80 (t, *J* = 7.8 Hz, 9H), 0.45 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.2, 134.9, 133.6, 132.6, 128.8, 128.3, 127.8, 126.0, 125.5, 112.2,

109.8, 103.8, 74.8, 73.9, 73.3, 72.0, 71.1, 60.8, 42.2, 27.9, 26.6, 26.5, 26.4, 6.8, 4.6. IR: ν 2990, 2954, 2872, 1760, 1731, 1455, 1372, 1220, 1190, 1124, 1085, 973, 888, 853, 817, 740 cm^{-1}. FABMS: 579.0 ($M+Li^+$). Anal. Calcd for $C_{31}H_{44}O_8Si$: C, 65.01; H, 7.74. Found: C, 65.13; H, 7.81.

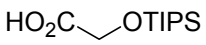


1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (triisopropylsilyloxy) acetate (3k).



Benzyl (triisopropylsilyloxy)acetate. Benzyl glycolate[160] (1.66 g, 10.0 mmol) and TEA (3.0 mL, 21 mmol) were dissolved in dry DCM (15 mL) at rt. After 15 min triisopropyl trifluoromethanesulfonate (3.6 mL, 13 mmol) was added quickly. The mixture bubbled and became warm. The pale green solution was stirred at rt overnight. After 22 h the reaction mixture (red in color) was washed with 10 mL ice-cold saturated sodium bicarbonate and 10 mL saturated sodium chloride, dried (magnesium sulfate), filtered, and rotary evaporated to give a red liquid (4.21 g). The liquid was dissolved in DCM and separated on a flash silica column (1:6 EtOAc:hexanes, ~ 0.5% TEA). Fractions were combined, rotary evaporated, and dried under vacuum to give the ester as a yellow liquid (3.088 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (s, 5H), 5.18 (s, 2H), 4.36 (s, 2H), 1.15-1.03 (m, 21H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.3, 135.7, 128.5, 128.4, 128.3,

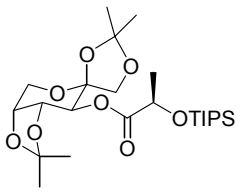
66.4, 62.1, 17.8, 12.0. IR: ν 3034, 2943, 2865, 1765, 1735, 1498, 1464, 1443, 1385, 1366, 1281, 1267, 1208, 1194, 1147, 1071, 1044, 996, 967, 919, 882, 834, 823, 809, 796, 748, 694, 661, 644 cm^{-1}. FABMS *m/z* (% of base peak): 323.1 ($M+H^+$, 13). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.90; H, 9.51.



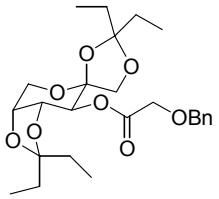
(Triisopropylsilyloxy)acetic acid (**2k**). Hydrogenolysis of the ester above according to the procedure for **2f** gave the acid **2k** in quantitative yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.3 (br s, 1H), 4.28 (s, 2H), 1.19-1.00 (m, 21H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 175.3, 61.6, 17.7, 12.3. FABMS *m/z* (% of base peak): 233.2 ($M+H^+$, 21). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.90; H, 10.57.

The chiral glycolate was prepared by the general esterification procedure using the alcohol **1**and triisopropylsilyloxyacetic acid **2k** to give **3k** as a green oil (87% yield) and recovered alcohol **1** (9% recovery). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.18 (d, J = 7.6 Hz, 1H), 4.43 (d, J = 16.4 Hz, 1H), 4.36 (d, J = 16.8 Hz, 1H), 4.27 (dd, J = 7.8, 5.4 Hz, 1H), 4.22 (dd, J = 5.6, 1.8 Hz, 1H), 4.13 (dd, J = 13.8, 2.2 Hz, 1H), 4.08 (d, J = 13.6 Hz, 1H), 3.96 (d, J = 9.2 Hz, 1H), 3.85 (d, J = 9.6 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.13-1.05 (m, 21H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.4, 112.2, 109.8, 103.8, 74.8, 73.9, 72.0, 70.7, 62.0, 60.7, 28.0, 26.5, 26.3, 18.0, 12.1. IR: ν 2986, 2942, 2892, 2867, 2120, 1770, 1738, 1463, 1383, 1372, 1326, 1297, 1241, 1221, 1198, 1146, 1114, 1086, 1068, 1030, 977, 916, 883, 855, 816, 798, 748, 682, 668 cm^{-1}. FABMS *m/z* (% of base peak): 481.4 ($M+Li^+$, 60), 473.4 ($M-H^+$, 31), 459.4 ($M-Me^+$, 34), 417.3 ($M+H-CH_3COCH_3^+$, 78), 243.2

(M-$OCOCH_2OR^+$, 100). HRFABMS: Calcd for $C_{23}H_{42}O_8SiLi$ $(M+Li)^+$: 481.2809, Found: 481.2810.



1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triisopropylsilyloxy) propionate (14a). The product was obtained as white needles in 70% yield using alkylation Method C. mp 77-79 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.14 (d, *J* = 8.0 Hz, 1H), 4.50 (q, *J* = 6.8 Hz, 1H), 4.27 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.21 (dd, *J* = 5.4, 1.0 Hz, 1H), 4.14 (dd, *J* = 13.4, 2.6 Hz, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.49 (d, *J* = 5.6 Hz, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.18-1.05 (m, 21H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.3, 112.2, 109.8, 103.9, 74.9, 73.9, 72.1, 70.8, 68.7, 60.8, 28.0, 26.6, 26.5, 26.4, 22.4, 18.1, 12.3. IR: ν 2990, 2942, 2867, 1765, 1736, 1455, 1372, 1220, 1190, 1141, 1086, 1067, 976, 885, 820 cm^{-1}. FABMS *m/z* (% of base peak): 495.4 ($M+Li^+$, 34), 487.4 ($M-H^+$, 24), 473.4 ($M-Me^+$, 46), 431.4 (M+H-$CH_3COCH_3^+$, 67), 243.2 (M-$OCOCH(Me)OR^+$, 100). Anal. Calcd for $C_{24}H_{44}O_8Si$: C, 58.99; H, 9.08. Found: C, 58.85; H, 9.10.

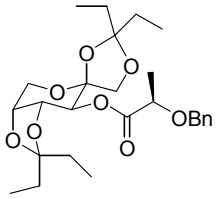


1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranos-3-yl (benzyloxy)acetate (15).

1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranose. This compound was prepared by a procedure modified from the literature.[165] A solution of 3-pentanone (84 mL, 790 mmol), trimethyl orthoformate (42 mL, 330 mmol), and *p*-toluenesulfonic acid monohydrate (280 mg, 1.5 mmol) in 100 mL MeOH was heated in an oil bath to about 76 ºC. After 3 h, the bath temperature was increased to about 95 ºC, and the head temperature rose to 62 ºC. After 2.5 h at this bath temperature, the head temperature started to fall. The mixture was allowed to cool at rt for 20 min. More 3-pentanone (200. mL, 1880 mmol) was added, and the mixture was cooled in an ice bath. After 10 min D-fructose (ground to a powder, 26.9 g, 149 mmol) and $HClO_4$ (70%, 0.1 mL) were added. After stirring in the ice bath for 4.5 h, the reaction was quenched with TEA (5 mL). After 15 min deionized water (25 mL) was added, and the mixture was stirred vigorously. After 10 min stirring at rt, the layers were separated. The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a clear pale green liquid (45.4 g). After overnight storage in the freezer, the crude product was dissolved in EtOAc and rotary evaporated again (42.2 g). The mixture was separated on a flash silica column (1:6 to 1:2 Et_2O:hexanes). Fractions were combined, rotary evaporated, and dried under vacuum to give the product as a light pale yellow oil (25.1 g, 53%). ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra agreed with those in the literature.[165]

The chiral glycolate was prepared by the general esterification procedure using the alcohol above and benzyloxyacetic acid **2a** to give **15** as a pale yellow oil (4.45 g, 70%) ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.30 (m, 5H), 5.23 (d, J = 7.6 Hz, 1H), 4.64 (s, 2H), 4.32 (dd, J = 7.4, 5.4 Hz, 1H), 4.24 (dd, J = 6.4, ~1 Hz, 1H), 4.22 (d, J =16.8 Hz, 1H), 4.11 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 15.4 Hz, 1H), 4.07 (m, 1H), 3.95 (d, J = 9.2 Hz, 1H), 3.84 (d, J = 8.8 Hz, 1H), 1.84-1.59 (m, 8H), 0.98-0.83 (m, 12H). ^{13}C NMR (CD_3OD, 75.5 MHz): δ

171.7, 138.5, 129.4, 129.2, 129.0, 117.5, 114.8, 104.7, 75.8, 74.9, 74.2, 73.1, 72.7, 67.9, 61.9, 31.0, 30.7, 29.7, 8.8, 8.7, 8.1. IR: ν 2966, 2919, 2872, 1760, 1455, 1378, 1349, 1273, 1185, 1128, 1088, 1044, 972, 918, 855, 824, 739, 697 cm^{-1}. FABMS *m/z* (% of base peak): 466.2 ($M+H^+$, 36). Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.64; H, 7.81. Found: C, 64.65; H, 7.78.



1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)propionate (16). The product was obtained as an oil in 71% yield using alkylation Method C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.27 (m, 5H), 5.25/5.20 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.34 (dd, *J* = 7.8, 5.8 Hz, 1H), 4.25 (dd, *J* = 5.6, 1Hz, 1H), 4.16-4.07 (m, 3H), 3.97 (d, *J* = 9.2 Hz, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 1.87-1.58 (m, 8H), 1.48 (d, *J* = 6.4 Hz, 3H), 0.98-0.86 (m, 12H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.3, 137.7, 128.6, 128.2, 128.0, 116.4, 113.9, 103.7, 74.7, 74.2, 73.9, 72.4, 72.1, 71.7, 61.1, 30.4, 29.9, 29.0, 28.9, 19.0, 8.7, 7.9. IR: ν 2978, 2884, 1758, 1462, 1373, 1349, 1260, 1174, 1130, 1114, 1090, 1044, 975, 922, 848, 835, 822, 748, 698 cm^{-1}. FABMS *m/z* (% of base peak): 485.3 ($M+Li^+$, 42), 449.3 ($M-Et^+$, 63), 393.3 ($M-Et_2CO^+$, 100), 299.2 ($M-OCOCH(Me)OR^+$, 58). Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.52; H, 8.15.

General procedure for the removal of the *O*-protecting group and cleavage of the auxiliary. To a solution of ester **13** (PG = TES) in THF/pyridine (1:1) was added several drops of HF-pyridine. This mixture was stirred at room temperature for 10 min. Deionized water then was added. The mixture was extracted with DCM (4 x). The

combined organic layers were washed with saturated sodium chloride and dried (magnesium sulfate). Upon removing solvent, the residue was purified by flash chromatography (elution with hexanes:EtOAc) or used directly for the next step.

The residue obtained above (**17**) was dissolved in THF/MeOH/H_2O (2:2:1, v/v). To this was added LiOH (2 eq.). The reaction was monitored by TLC. When the reaction was complete, THF and methanol were removed on the rotary evaporator. The aqueous solution was extracted with Et_2O (three times) to remove the auxiliary. After the aqueous phase had been acidified with 10% HCl, it was extracted with DCM (three times) and the combined organic layers were dried (magnesium sulfate). Solvent was removed to afford the pure free acid **18**.

Determination of the de's. Representative procedure for preparation of the standards that were racemic at the α-center. All reported yields and de's were based on isolated product. The de's were determined by comparing the HPLC trace or ^{1}H NMR spectrum of the product to a standard that was racemic at the α-position. These pseudo-racemic standards were prepared by a different synthetic route (see below). Pseudo-racemic standards were prepared for alkylated compounds **4a-e, 11b, 12b, 13a,** and **16**; the de's for the remainder of the alkylated compounds were determined by analogies in their ^{1}H NMR spectra to those of the pseudo-racemic standards.

Pseudo-racemic 1,2:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranos-3-yl 2-(benzyloxy)propionate **(4a)**. Racemic (2-benzyloxy)propionic acid was prepared by alkylating benzyloxyacetic acid **2a** with methyl iodide in the presence of LDA according to a literature procedure[166] (11%). The pseudo-racemic standard was prepared by the general

esterification procedure using the alcohol **1** and racemic 2-(benzyloxy)propionic acid to give pseudo-racemic standard **4a** (84%).

The modified Cevalier's method used for checking racemization during hydrolysis of the auxiliary. The method was carried out as described in the literature[80] with the following modifications: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC)/Et_3N were substituted for DCC and the hydrochloride salt of H-Ala-OMe was used directly in the coupling. To verify the identification of diastereomers by ^1H NMR, pseudo-racemic standards of **19a,b** were prepared using the racemic benzyloxy acids,[166] followed by hydrogenolysis with $Pd(OH)_2$.

Part (II) Crystal Structure Data.

Crystal structure of 3a. *Data Collection*. The sample was mounted on the end of a glass fiber using a small amount of silicone grease and transferred to the diffractometer. The sample was maintained at a temperature of -125 ºC using a nitrogen cold stream. All X-ray measurements were made on an Enraf-Nonius CAD4-MACH diffractometer. The unit cell dimensions were determined by a fit of 24 well centered reflections and their Friedel pairs with $33º<2\theta<36º$. A quadrant of unique data and their Bijvoet pairs were collected using the ω scan mode in a non-bisecting geometry. The adoption of a non-bisecting scan mode was accomplished by offsetting ψ by 20º for each data point collected. This was done to minimize the interaction of the goniometer head with the cold stream. The Bijvoet pairs were collected using the negative θ position for the *-h -k -l* reflection. This was done so that the X-ray pathlength through the crystal was identical for each pair. Three standard reflections

were measured every 4800 seconds of X-ray exposure time. Scaling the data was accomplished using a 5 point smoothed curved routine fit to the intensity check reflections. The intensity data was corrected for Lorentz and polarization effects. No absorption correction was applied to the data.

Structure Solution and Refinement. The data were reduced using routines from the NRCVAX[167] set of programs. The structure was solved using SIR92.[168] All of the non-H atom positions were recovered from the initial E-map. All hydrogen atom positions were derived from difference Fourier maps. Hydrogen atom positional and isotropic displacement parameters were allowed to refine in the least squares refinement. The structure was refined using full matrix least-squares based on F. All non-H atoms were allowed to refine with anisotropic displacement parameters (ADP's). The calculated structure factors included corrections for anomalous dispersion from the usual tabulation.[169] A secondary extinction correction was included in the final refinements. The anomalous scattering signal for **3a** was weak which prevented the direct determination of the absolute structure. Therefore, the absolute structure for the sample was set using the absolute configuration around atom C4 which was known to be *S*.

Results. Crystal system: monoclinic. Space group: $P2_1$. Unit cell: a = 12.8625(10) Å, b = 5.5705(3) Å, c = 4.5033(7) Å. Z = 2. A total of 4452 reflections were collected of which 4015 were unique (R_{merge} = 0.010). R = 0.027, R_w = 0.033, GOF = 1.47 for 3791 reflections above 1.0σ(I).

Crystallographic data (excluding structure factors) for this structure will be deposited with the Cambridge Crystallographic Data Centre (CCDC 182697). Copies of the data can be obtained, free of charge, on the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html or

on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Crystal structure of 4c. *Data Collection*. The sample was mounted on the end of a glass fiber using a small amount of silicone grease and transferred to the diffractometer. The sample was maintained at a temperature of -125 ºC using a nitrogen cold stream. All X-ray measurements were made on an Enraf-Nonius CAD4-MACH diffractometer. The unit cell dimensions were determined by a fit of 25 well centered reflections and their Friedel pairs with 31º<2θ<36º. A quadrant of unique data and their Bijvoet pairs were collected using the ω scan mode in a non-bisecting geometry. The adoption of a non-bisecting scan mode was accomplished by offsetting ψ by 20º for each data point collected. This was done to minimize the interaction of the goniometer head with the cold stream. The Bijvoet pairs were collected using the negative θ position for the *-h -k -l* reflection. This was done so that the X-ray pathlength through the crystal was identical for each pair. Three standard reflections were measured every 4800 seconds of X-ray exposure time. Scaling the data was accomplished using a 5 point smoothed curved routine fit to the intensity check reflections. The intensity data was corrected for Lorentz and polarization effects. No absorption correction was applied to the data. During the data collection, the low temperature device developed a problem of excessive ice build up. This may have affected the quality of the data slightly.

Structure Solution and Refinement. The data were reduced using routines from the NRCVAX[167] set of programs. The structure was solved using SIR92.[168] All of the non-H atom positions were recovered from the initial E-map. All hydrogen atom positions were introduced at idealized positions. Hydrogen atom positional parameters were allowed to

refine in the least squares refinement, and the isotropic displacement parameters were allowed to ride on the parent carbon atom. The structure was refined using full matrix least-squares based on F. All non-H atoms were allowed to refine with anisotropic displacement parameters (ADP's). The calculated structure factors included corrections for anomalous dispersion from the usual tabulation.[169] A secondary extinction correction was included in the final refinements. The anomalous scattering signal for **4c** was weak which prevented the direct determination of the absolute structure. Therefore, the absolute structure for the sample was set using the absolute configuration around atom C4 which was known to be *S*.

Results. Crystal system: monoclinic. Space group: $P2_1$. Unit cell: $a = 8.0120(5)$ Å, $b = 14.1477(8)$ Å, $c = 11.7213(8)$ Å. $Z = 2$. A total of 4678 reflections were collected, of which 4479 were unique ($R_{merge} = 0.013$). $R = 0.035$, $R_w = 0.046$, GOF = 1.39 for 3975 reflections greater than $1.0\sigma(I)$.

Crystallographic data (excluding structure factors) for this structure will be deposited with the Cambridge Crystallographic Data Centre (CCDC 182698). Copies of the data can be obtained, free of charge, on the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

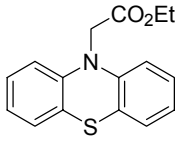
Part (III) Preparation of the Chelator-Transporter Substrate Conjugates.

General procedure for alkylation of phenothiazine. Compounds **49-53** were prepared by this procedure. This procedure was modified from the literature.[135] A representative procedure for the preparation of **51** follows: Phenothiazine (**31**, 509 mg, 2.56

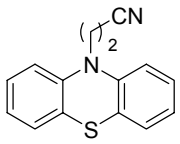
mmol), potassium hydroxide (171 mg, 2.61 mmol, 85%, freshly ground), and sodium iodide (39 mg, 0.26 mmol, oven-dried) were combined under argon in a dry 25 mL round bottom flask equipped with an oven-dried stirbar. The flask was pumped under oil pump vacuum and flushed with argon three times. The flask was covered with aluminum foil. Dry DMF (4.0 mL) was added. After 5 min stirring at rt, neat 5-bromovaleronitrile (0.90 mL, 7.7 mmol) was added dropwise. The reaction mixture was heated in a sand bath (50 ºC) for 42 h. After the reaction mixture (a yellow suspension) had cooled at rt for 30 min, it was diluted with DCM (15 mL). It was washed with deionized water (3 x 10 mL). The organic layer was dried (magnesium sulfate), filtered (coarse frit), and rotary evaporated to give a yellow liquid (1.97 g). It was dry-loaded on a flash silica column and eluted with EtOAc/hexanes (4% to 8% to 15%). Fractions were combined, rotary evaporated, and dried under vacuum to give **51** as a brown liquid (472 mg, 66%). The liquid froze into a solid in the freezer.

All of the electrophiles were commercially available except for benzyl 12-bromododecanoate (**54**).[136] It was prepared by the following procedure modified from the literature.[136] To an ice-cold suspension of 12-bromododecanoic acid (3.15 g, 11.3 mmol) in dry DCM (12 mL) was added DCC (2.36 g, 11.4 mmol). After 10 min benzyl alcohol (1.3 mL, 13 mmol) and DMAP (0.320 g, 2.62 mmol) were added. After 1 h the ice bath was removed. After overnight stirring at rt some solvent had evaporated, so more DCM (10 mL) was added. After an additional 3 h, the mixture was filtered. The filtrate was rotary evaporated and then taken up in EtOAc (30 mL). It was washed with 1 M citric acid (10 mL), saturated sodium bicarbonate (10 mL), 1 M citric acid (10 mL), and saturated sodium chloride (10 mL). Hexanes (40 mL) and magnesium sulfate were added to the organic layer.

After the mixture had set in the freezer for 1 h, it was filtered and rotary evaporated to give a colorless liquid. It was purified on a flash silica column (1:1 DCM:hexanes). Fractions were combined, rotary evaporated, and dried under vacuum to give **54** as a colorless liquid (3.40 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) agreed with that of the literature. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.8, 136.3, 128.7, 128.3, 66.2, 34.4, 34.2, 33.0, 29.6, 29.5, 29.5, 29.4, 29.2, 28.9, 28.3, 25.1.

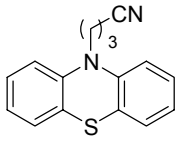


Ethyl 2-(phenothiazin-10-yl)acetate (48).[133] This product was obtained as a white solid in 46% yield following Vos's procedure.[133] The ethyl bromoacetate that was used for the alkylation had been washed with saturated sodium carbonate, dried over calcium chloride, and filtered through cotton immediately before the reaction. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10-7.06 (m, 4H), 6.92-6.88 (m, 2H), 6.60-6.58 (m, 2H), 4.50 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.9, 144.1, 127.3, 127.0, 123.3, 123.0, 114.6, 61.6, 51.0, 14.3.

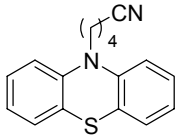


3-(Phenothiazin-10-yl)propionitrile (49).[134] This product was obtained by a literature Michael addition[134] in 59% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22-7.18 (m,

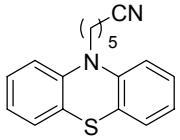
4H), 7.00-6.97 (m, 2H), 6.86-6.84 (m, 2H), 4.25 (t, J = 8.6 Hz, 2H), 2.85 (t, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.0, 128.2, 127.7, 126.5, 123.7, 115.5, 43.7, 16.8.



4-(Phenothiazin-10-yl)butyronitrile (50).[170] This product was obtained as a white solid in 75% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24-7.15 (m, 4H), 7.00-6.86 (m, 4H), 4.06 (t, J = 6.2 Hz, 2H), 2.48 (t, J = 7.2 Hz), 2.15 (p, J = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.9, 127.9, 127.6, 126.3, 123.2, 119.5, 115.8, 45.3, 23.0, 14.5.

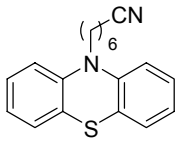


5-(Phenothiazin-10-yl)valeronitrile (51).[170] This product was obtained as a brown liquid in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.15 (m, 4H), 6.97-6.86 (m, 4H), 3.95 (t, J = 6.4 Hz, 2H), 2.33 (t, J = 7.0 Hz, 2H), 1.98-1.94 (m, 2H), 1.82-1.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.2, 127.8, 127.5, 125.8, 122.9, 119.6, 115.7, 46.1, 25.7, 22.8, 16.9.

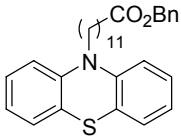


6-(Phenothiazin-10-yl)hexanenitrile (52).[170] The product was obtained as a yellow oil in 58% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19-7.12 (m, 4H), 6.95-6.84 (m, 4H), 3.89

(t, J = 6.9 Hz, 2H), 2.30 (t, J = 6.9 Hz, 2H), 1.88-1.79 (m, 2H), 1.72-1.53 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.2, 127.6, 127.3, 125.3, 122.6, 119.7, 115.5, 46.7, 26.0, 26.0, 25.0, 17.0.



7-(Phenothiazin-10-yl)heptanenitrile (53). The product was obtained as a colorless oil in 33% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.11 (m, 4H), 6.92-6.82 (m, 4H), 3.83 (t, J = 7.4 Hz, 2H), 2.23 (t, J = 7.0 Hz, 2H), 1.81-1.74 (m, 2H), 1.60-1.53 (m, 2H), 1.42-1.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 127.4, 127.2, 125.0, 122.4, 119.8, 115.5, 46.9, 28.1, 26.4, 25.9, 25.1, 16.8. IR: ν 3061, 2634, 2857, 2244, 1729, 1593, 1570, 1485, 1460, 1366, 1333, 1284, 1249, 1160, 1127, 1105, 1038, 929, 899, 860, 842, 822, 804, 750, 728 cm^{-1}. FABMS *m/z* (% of base peak): 308.1 (M^+, 100).

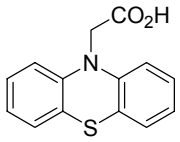


Benzyl 12-(Phenothiazin-10-yl)dodecanoate (55). A suspension of sodium hydride (242 mg, 6.05 mmol, 60% in mineral oil) was placed in a dry 3 neck flask. The suspension was washed with hexanes (3 x 5 mL). Most of the washings were removed by pipet, and the remainder of the solvent was removed under oil pump vacuum. The resulting white solid was suspended in dry DMF (1 mL). While it was stirred, a solution of phenothiazine (**31**, 958 mg, 4.81 mmol) in dry DMF (3 mL) was added dropwise. This addition resulted in a

foamy orange suspension. After it had stirred at rt for 30 min, a solution of benzyl 12-bromododecanoate (**54**, 3.20 g, 8.67 mmol, prepared as above), 15-crown-5 (50. μL, 0.25 mmol), and sodium iodide (75 mg, 0.50 mmol) in dry DMF (4 mL) was added over 2 min. The mixture was heated in a sand bath to 45 ºC. After 13 h the heat was removed. After stirring for another 5 h at rt, the reaction mixture was diluted with DCM (30 mL) and washed with deionized water (3 x 25 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a yellow liquid (3.94 g). It was purified on a flash silica column eluted with 1:3 to 1:2 to 1:1 DCM:hexanes. Fractions were combined, rotary evaporated, and dried under vacuum to give **55** as a yellow liquid (762 mg, 33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.22 (m, 5H), 7.07-7.04 (m, 4H), 6.83-6.75 (m, 4H), 5.06 (s, 2H), 3.72 (t, J = 7.0 Hz, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.71 (p, J = 7.2 Hz, 2H), 1.61-1.55 (m, 2H), 1.34-1.31 (m, 2H), 1.22-1.19 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 145.2, 136.1, 128.4, 128.1, 128.0, 127.3, 127.1, 124.8, 122.2, 115.3, 65.9, 47.2, 34.2, 29.4, 29.4, 29.3, 29.2, 29.1, 29.0, 26.8, 26.8, 24.9. IR: ν 3063, 2925, 2852, 1736, 1593, 1571, 1485, 1460, 1373, 1333, 1284, 1250, 1162, 1106, 1038, 928, 749, 697 cm^{-1}. FABMS *m/z* (% of base peak): 487.2 (M^+, 100). Anal. Calcd for $C_{31}H_{37}NO_2S$: C, 76.34; H, 7.65; N, 2.87. Found: C, 76.08; H, 7.66; N, 2.71.

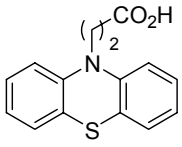
General procedure for the conversion of compounds 48-53 and 55 to the free acids 37-38 and 56-60. Compounds **48-53** were hydrolyzed under basic conditions in a mixture of aqueous sodium hydroxide, methanol, and ethanol according to a literature procedure to give the respective acids, with one modification.[171] The basic reaction mixtures of compounds **48** and **50** were acidified with ice-cold 1 M citric acid instead of ice-cold

concentrated HCl. Compound **55** was prepared by hydrogenolysis of benzyl ester **43** (balloon pressure H_2, 20% $Pd(OH)_2/C$, MeOH).

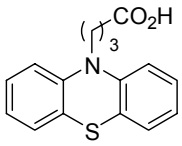


(Phenothiazin-10-yl)acetic acid (37).[172] The product was obtained as a reddish white solid in 89% yield from ethyl ester **37** following the literature procedure.[171]

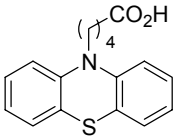
Alternatively, the methyl ester **62** (405 mg, 1.50 mmol) was hydrolyzed in EtOH/MeOH/4M KOH (25:25:8, 116 mL) at 60 °C for 30 min. The reaction mixture was poured into ice water (100 mL) and acidified by slow addition of 10% citric acid until white needles crystallized. The needles were collected filtration and air dried to give **37** as white needles (343 mg, 89%). ^{1}H NMR (CD_3OD, 300 MHz) agreed with the reported values. [172] ^{13}C NMR (CD_3OD, 75.5 MHz): δ 173.7, 145.8, 128.5, 127.8, 124.3, 124.0, 115.6, 51.3.



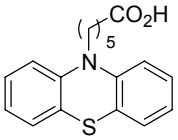
3-(Phenothiazin-10-yl) propionic acid (56).[137] The acid was obtained as a white solid in 75% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.9 (br s, 1H), 7.20-7.15 (m, 4H), 6.97-6.86 (m, 4H), 4.21 (t, J = 7.4 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 177.6, 144.8, 127.9, 127.6, 125.6, 123.1, 115.4, 42.7, 32.6.



4-(Phenothiazin-10-yl)butanoic acid (57).[173] The product was obtained as a reddish solid in 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) agreed with the literature values. [173]

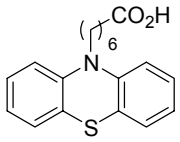


5-(Phenothiazin-10-yl)pentanoic acid (58). The product was obtained as a reddish oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14-7.10 (m, 4H), 6.90-6.86 (m, 2H), 6.82-6.80 (m, 2H), 3.82 (t, *J* = 6.8 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 2H), 1.86-1.67 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.2, 145.3, 127.7, 127.4, 125.4, 122.6, 115.6, 46.9, 33.7, 26.3, 22.1. IR: ν 3061, 2936, 2859, 1705, 1593, 1571, 1485, 1459, 1367, 1333, 1285, 1250, 1162, 1127, 1105, 1038, 928, 822, 750 cm^{-1}. FABMS *m/z* (% of base peak): 299.1 (M^+, 87).

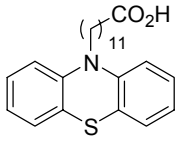


6-(Phenothiazin-10-yl)hexanoic acid (59). The acid was obtained as a yellow oil in 97% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.3 (br s, 1H), 7.15-7.09 (m, 4H), 6.91-6.80 (m, 4H), 3.82 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.79 (p, *J* = 7.2 Hz, 2H), 1.63 (p, *J* = 7.2 Hz, 2H), 1.50-1.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 180.4, 145.4, 127.6, 127.4, 125.3, 122.6, 115.6, 47.2, 34.1, 26.7, 26.5, 24.4. IR: ν 3060, 2931, 2849, 1705, 1593, 1571,

1485, 1459, 1367, 1333, 1284, 1250, 1202, 1159, 1127, 1105, 1038, 928, 842, 822, 750, 728 cm^{-1}. FABMS *m/z* (% of base peak): 313.1 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.21; H, 6.13; N, 4.58.

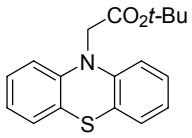


7-(Phenothiazin-10-yl)heptanoic acid (60). The acid was obtained as a brownish yellow oil in quantitative yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 11.4 (br s, 1H), 7.15-7.09 (m, 4H), 6.91-6.81 (m, 4H), 3.82 (t, *J* = 7.1 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.83-1.73 (m, 2H), 1.60 (p, *J* = 7.5 Hz, 2H), 1.47-1.28 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 180.5, 145.4, 127.6, 127.3, 125.2, 122.5, 115.6, 47.3, 34.1, 28.8, 26.8, 26.7, 24.7. IR: ν 3060, 2931, 2849, 1704, 1593, 1572, 1486, 1460, 1414, 1367, 1333, 1285, 1250, 1158, 1127, 1106, 1038, 930, 840, 750, 668 cm^{-1}. FABMS *m/z* (% of base peak): 327.1 (M^+, 100). Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.45; H,6.61; N, 4.36.

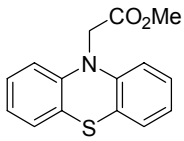


12-(Phenothiazin-10-yl)dodecanoic acid (38). The acid was obtained as a colorless oil in quantitative yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.98 (br s, 1H), 7.15-7.09 (m, 4H), 6.91-6.81 (m, 4H), 3.81 (t, *J* = 7.2 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.77 (p, *J* = 7.2 Hz, 2H), 1.60 (p, *J* = 7.2 Hz, 2H), 1.42-1.23 (m, 14 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 180.6, 145.5, 127.6, 127.3, 125.0, 122.4, 115.5, 47.5, 34.4, 29.6, 29.6, 29.5, 29.4, 29.2, 27.1, 27.0,

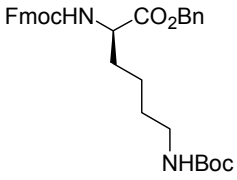
24.9. IR: ν 3060, 2919, 2849, 1705, 1572, 1459, 1367, 1331, 1284, 1250, 1164, 1143, 1126, 1108, 1038, 926, 842, 806, 748, 668 cm^{-1}. FABMS *m/z* (% of base peak): 397.3 (M^+, 100). Anal. Calcd for $C_{24}H_{31}NO_2S$: C, 72.50; H, 7.86; N, 3.52. Found: C, 72.32; H, 7.93; N, 3.56.



***Tert*-butyl 2-(phenothiazin-10-yl)acetate (61)**.[137] This compound was prepared by a procedure modified from the literature.[137] Phenothiazine (**31**, 953 mg, 4.79 mmol), tetrabutylammonium hydrogensulfate (202 mg, 0.594 mmol), and *tert*-butyl bromoacetate (1.77 mL, 12.0 mmol) were dissolved in DCM (20 mL) and methyl ethyl ketone (MEK, 20 mL). Aqueous NaOH (50%, 20 mL) was added to the rapidly stirred mixture. Within 10 min the color of the mixture had changed from pale green to brown. After 2.5 h, the reaction mixture was washed with deionized water (3 x 20 mL) and saturated sodium chloride (20 mL), dried (magnesium sulfate), filtered, and rotvoapped to give a brown liquid (2.63 g). The liquid was separated on a flash silica column eluting with 1:4 DCM:hexanes to 1:3 DCM:hexanes. Fractions were combined, rotary evaporated, and dried under vacuum to give **61** as a white foam (1.18 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) agreed with the literature values recorded in CD_2Cl_2.[137] ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.1, 144.5, 127.4, 127.2, 123.6, 123.0, 114.7, 82.6, 51.9, 28.2.

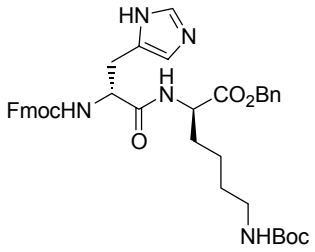


Methyl 2-(phenothiazin-10-yl)acetate (62). MeOH (12 mL) was cooled in an ice bath. After 10 min acetyl chloride (3.4 mL, 48 mmol) was added dropwise. The ice bath was removed. After the solution had stirred at rt for 30 min, solid *tert*-butyl 2-(phenothiazin-10-yl)acetate (**61**, 463 mg, 1.48 mmol) was added. DCM (7 mL) was added to make the mixture homogeneous. After 10 h, the reaction mixture was rotary evaporated. The solid residue was taken up in DCM (20 mL) and washed with deionized water (10 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a brown oil (408 mg). The crude product was separated on a flash silica column eluting with 1:2 DCM:hexanes. Fractions were combined, rotary evaporated, and dried under vacuum to give **62** as a colorless oil (336 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12-7.06 (m, 4H), 6.93-6.88 (m, 2H), 6.59-6.56 (m, 2H), 4.52 (s, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.6, 144.2, 127.5, 127.2, 123.5, 123.2, 114.6, 52.7, 51.0. IR: ν 1748, 1644, 1464, 1444, 1437, 1361, 1264, 1208, 1126, 1114, 1049, 1008, 979, 866, 830, 823, 806, 745 cm^{-1}. FABMS *m/z* (% of base peak): 271.3 (100). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.43; H, 4.96; N, 5.11.



Fmoc-D-Lys(Boc)-OBn (65).[174] This was prepared from Fmoc-D-Lys(Boc)-OH (**64**) by a literature alkylation procedure in 76% yield.[174] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.39-7.23 (m, 9H), 5.60 (d, *J* = 7.8 Hz, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 4.62-4.60 (m, 1H), 4.43-4.31 (m, 3H), 4.18

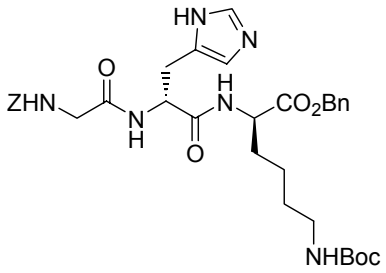
(t, J = 7.1 Hz, 1H), 3.06-3.03 (m, 2H), 1.85-1.80 (m, 1H), 1.69-1.63 (m, 1H), 1.42-1.28 (m, 13H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.4, 156.1, 144.0, 143.8, 141.3, 135.4, 128.7, 128.5, 128.4, 127.8, 127.1, 125.2, 120.0, 79.1, 67.2, 67.1, 53.9, 47.2, 40.1, 32.1, 29.6, 28.5, 22.4.



Fmoc-D-His-D-Lys(Boc)-OBn (66). The amino acid **65** (881 mg, 1.58 mmol) was deprotected by stirring it under argon at rt in 50% DEA/DCM (60 mL) for 2 h in an oven-dried flask equipped with an oven-dried stirbar. The reaction mixture was rotary evaporated, the residue was rotary evaporated with DCM three times, and the residue was dried under vacuum.[139]

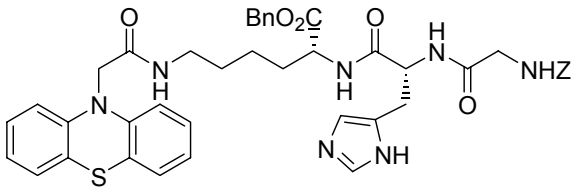
In another flask equipped with an oven-dried stirbar was suspended Fmoc-D-His-OH (659 mg, 1.75 mmol) in dry DMF (45 mL). The resulting mixture was cooled in an ice bath. After 15 min EDC (336 mg, 1.75 mmol) was added. After another 10 min HOBt (262 mg, 1.71 mmol) was added. After another 5 min, DMAP (16.9 mg, 0.139 mmol) was added. After another 20 min DIEA (0.60 mL, 3.5 mmol) and a solution of the free amine prepared above in dry DMF (10 mL, 5 mL rinse) were added over 20 min.[140] After 1 h the ice bath was removed. After 2.5 h the reaction mixture was diluted with EtOAc (400 mL) and washed with 5% sodium carbonate (2 x 125 mL) and saturated sodium chloride (125 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a

pale yellow liquid. Et_2O was added slowly to the liquid to precipitate white solid. The mixture was stored in the freezer for 20 min. The supernatant was removed by pipet and the solid was washed with hexanes and dried under vacuum to give **66** as a cream-colored solid (724 mg, 66%). mp 140-141.5 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.62-7.48 (m, 3H), 7.40-7.26 (m, 9H), 6.86 (s, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.46-4.38 (m, 2H), 4.34-4.23 (m, 2H), 4.17 (t, *J* = 6.8 Hz, 1H), 3.51-3.40 (m, 1H), 3.06-2.84 (m, 3H), 1.87-1.83 (m, 1H), 1.73-1.68 (m, 1H), 1.40-1.06 (m, 13H). ^{13}C NMR (CD_3OD, 100 MHz): δ 174.4, 173.4, 158.4, 145.4, 142.7, 137.4, 136.4, 129.8, 129.5, 129.0, 128.4, 126.4, 121.1, 80.0, 68.2, 68.1, 56.6, 53.9, 49.8, 49.6, 41.3, 34.9, 32.3, 30.9, 30.5, 28.9, 26.9, 26.2, 24.1. IR: ν 3319, 2931, 2860, 1731, 1713, 1683, 1678, 1537, 1514, 1455, 1367, 1252, 1167, 1044, 848, 828, 738, 697 cm^{-1}. HRFABMS Calcd for $C_{39}H_{46}N_5O_7$ ($M+H^+$): Calcd: 696.3397. Found: 696.3391.



Tripeptide Z-Gly-D-His-D-Lys(Boc)-OBn (63). The peptide **66** (681 mg, 0.957 mmol) was deprotected by stirring it under argon at rt in a mixture of DEA:DCM:DMF (15:15:4, 68 mL) for 20 min in an oven-dried flask equipped with an oven-dried stirbar. The reaction mixture was rotary evaporated, the residue was rotary evaporated with DCM three times, and the residue was dried under vacuum to give a yellow liquid.[139]

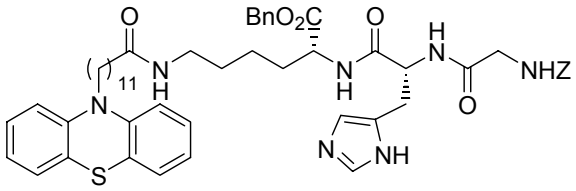
In another oven-dried flask equipped with an oven-dried stirbar was dissolved Z-Gly-OH (252 mg, 1.21 mmol) in dry DMF (5 mL). The resulting solution was cooled in an ice bath. After 5 min 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 262 mg, 1.36 mmol) was added. After another 10 min HOBt (210. mg, 1.37 mmol) was added. After another 10 min, DMAP (23 mg, 0.19 mmol) and DIEA (0.48 mL, 2.8 mmol) were added. After another 10 min a solution of the free amine prepared above in dry DMF (8 mL) was added slowly over 20 min.[140] After 1 h the ice bath was removed. After 4 h the reaction mixture was diluted with EtOAc (150 mL) and washed with 5% sodium carbonate (2 x 75 mL) and saturated sodium chloride (50 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a yellow oil (1.15 g). Et_2O was added and the mixture was set in the freezer. The resulting solid was washed with Et_2O and hexanes, recrystallized from DCM/MeOH, and washed with Et_2O and hexanes again to give **63** as a pale sticky yellow gum (399 mg, 63%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.54 (s, 1H), 7.35-7.28 (m, 10H), 6.84 (s, 1H), 6.53 (br s, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.08 (s, 2H), 4.66-4.63 (m, 1H), 4.42-4.38 (m, 1H), 3.76 (s, 2H), 3.09-2.90 (m, 4H), 1.88-1.76 (m, 1H), 1.76-1.66 (m, 1H), 1.41-1.26 (m, 13H). ^{13}C NMR (CD_3OD, 100 MHz): δ 173.6, 173.3, 172.2, 159.3, 158.7, 138.2, 137.4, 136.4, 130.0, 129.7, 129.6, 129.5, 129.2, 129.0, 128.4, 120.8, 80.0, 68.0, 54.7, 54.0, 45.2, 41.2, 32.1, 30.5, 30.4, 28.9, 24.1. IR: ν 3307, 3060, 2954, 1713, 1694, 1681, 1650, 1566, 1538, 1504, 1454, 1384, 1367, 1254, 1172, 845, 808, 746 cm^{-1}. HRFABMS Calcd for $C_{34}H_{45}N_6O_8$ ($M+H^+$): 665.3299. Found: 665.3328.



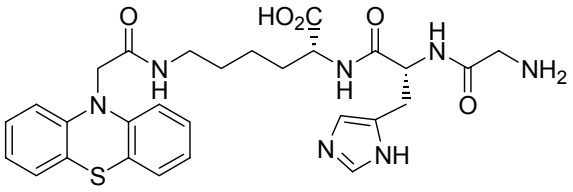
General procedure for the coupling of the tripeptide 63 to the acids 37 and 38. **Z-Gly-D-His-D-Lys[(2-phenothiazin-10-yl)acetyl]-OBn (67)**. The tripeptide **63** (110. mg, 0.166 mmol) was dissolved in dry DCM (20 mL). TFA (7.0 mL) was added. After stirring at rt for 1 h, the reaction mixture was rotary evaporated, rotary evaporated with DCM three times, and dried under vacuum to give a pale yellow solid.

Acid **37** (50.5 mg, 0.196 mmol) was dissolved in dry DMF (1.0 mL) and cooled in an ice bath. After 10 min EDC (41.1 mg, 0.214 mmol) was added. After 10 min, HOBt (31.3 mg, 0.205 mmol) was added. After another 5 min, a solution of the ammonium salt from above in dry DMF (2.0 mL, 1.0 mL rinse), TEA (100 μL, 0.72 mmol), and DMAP (4.9 mg, 0.040 mmol) were added. A check on wet pH paper indicated that the mixture was basic. The mixture was left tot stir in the ice bath but no additional ice was added. After 3 h the reaction mixture was diluted with EtOAc (50 mL). The mixture was washed with 5% sodium carbonate (2 x 25 mL) and saturated sodium chloride (25 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a pale yellow solid (122 mg). Recrystallization from $CHCl_3/Et_2O$ provided **67** as a white solid (59.8 mg, 45%). mp 192-193 °C ^{1}H NMR ($CD_3OD + CDCl_3$, 400 MHz): δ 7.52 (s, 1H), 7.36-7.24 (m, 10H), 7.13-7.07 (m, 4H), 6.90 (dt, J = 7.6, ~1 Hz, 2H), 6.82 (s, 1H), 6.77 (d, J = 8.0 Hz, 2H), 5.16 (d, J = 12.0 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 13.6 Hz, 1H), 4.62 (dd, J = 7.4, 5.0 Hz, 1H), 4.46 (s, 2H), 4.34 (dd, J = 9.2, 4.8 Hz, 1H), 3.74 (s, 2H), 3.21-3.11 (m, 2H), 3.05 (dd, J = 15.2, 4.8 Hz, 1H), 2.95 (dd, J = 14.8, 8.0 Hz, 1H),

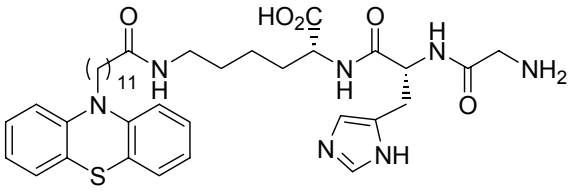
1.78-1.67 (m, 1H), 1.67-1.54 (m, 1H), 1.41-1.27 (m, 2H), 1.19-1.05 (m, 2H). ^{13}C NMR (CD_3OD + $CDCl_3$, 100 MHz): δ 173.2, 173.1, 171.8, 171.1, 158.9, 145.8, 137.8, 136.9, 136.1, 129.6, 129.5, 129.4, 129.3, 129.0, 128.8, 128.6, 128.0, 125.2, 124.3, 116.1, 68.0, 67.9, 54.4, 53.6, 52.9, 45.0, 39.9, 31.8, 30.0, 29.6, 23.7. IR: ν 3213, 3049, 2954, 2919, 1650, 1537, 1514, 1455, 1255, 868 cm^{-1}. HRFABMS Calcd for $C_{43}H_{46}N_7O_7S$ ($M+H^+$): 804.3179. Found: 804.3206.



Z-Gly-D-His-D-Lys[12-(phenothiazin-10-yl)dodecanoyl]-OBn (68). Using a procedure similar to the one above, the amide **68** was obtained as a white solid in 25% yield. mp 150-151 °C. ^{1}H NMR (CD_3OD +$CDCl_3$, 400 MHz): δ 7.53 (s, 1H), 7.40-7.25 (m, 10H), 7.17-7.12 (m, 2H), 7.09 (dd, *J* = 7.4, 1.4 Hz, 2H), 6.94-6.86 (m, 4H), 6.83 (s, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.08 (s, 2H), 4.63 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.55 (s, 1H), 4.42 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 3.12 (d, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 6.4 Hz, 1H), 3.07-2.96 (m, 2H), 2.14 (t, *J* = 7.4 Hz, 2H), 1.89-1.64 (m, 4H), 1.62-1.51 (m, 2H), 1.50-1.36 (m, 4H), 1.36-1.16 (m, 14H). ^{13}C NMR (CD_3OD + $CDCl_3$, 100 MHz): δ 176.2, 173.1, 173.0, 171.7, 158.9, 146.6, 137.7, 136.8, 136.1, 134.7, 132.6, 129.5, 129.4, 129.3, 129.2, 129.0, 128.7, 128.2, 128.2, 126.2, 123.3, 116.6, 67.9, 67.9, 54.4, 53.5, 48.0, 45.0, 40.0, 37.1, 34.9, 31.9, 30.4, 30.4, 30.3, 30.2, 30.1, 30.0, 27.7, 27.6, 23.9. IR: ν 3272, 2919, 2849, 1652, 1539, 1456, 1255, 856 cm^{-1}. HRFABMS Calcd for $C_{53}H_{66}N_7O_7S$ ($M+H^+$): 944.4744. Found: 944.4786.

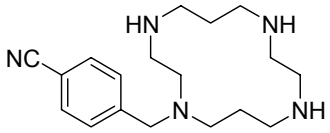


General procedure for the deprotection of the *N*- and *C*- termini of 67 and 68.[146] **H-Gly-D-His-D-Lys[(2-phenothiazin-10-yl)acetyl]-OH (41)**. Compound **67** (23.7 mg, 0.029 mmol) was suspended in stabilizer-free chloroform (3 mL). To the rapidly stirred mixture was added TfOH (20. μL, 0.23 mmol) dropwise. After 1 h the stirbar was rinsed and removed and the solution was basified with aqueous NH_3 (29%, 1 drop). The mixture was shaken; within 30 s the color had faded. The mixture was rotary evaporated; the color had redeveloped. More aqueous NH_3 (29%, 3 drops) was added. The mixture was rotary evaporated with EtOH three times, rotary evaporated with chloroform three times, and dried under vacuum. ^{1}H NMR (CD_3OD) showed the benzylic protons had disappeared. Part of the sample was dissolved in MeOH and purified by reversed-phase HPLC using a Nova-Pak® C_{18} column (4.6 x 150 mm) eluting with solvents A (90%H_2O/MeOH, 0.1% TFA) and B (90%MeOH/ H_2O) at a total flow rate of 1.00 mL/min. The program eluted with 50% B for the first 10 min followed by a linear gradient of 50% B to 100% B over 35 min. Repeated 20 μL injections were made on this column, and the four major fractions were collected, rotary evaporated, and dried under vacuum to give **41** as a white film (3.0 mg, 18%). The product had a retention time of 7.2 min. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.79 (s, 1H), 7.36 (s, 1H), 7.18-7.08 (m, 4H), 6.98-6.93 (m, 2H), 6.79 (d, J = 8.4 Hz, 2H), 4.52/4.51 (s, rotamers, 2H), 4.34-4.29 (m, 1H), 3.66 (s, 2H), 3.20-3.12 (m, 4H), 1.87-1.78 (m, 1H), 1.70-1.61 (m, 1H), 1.50-1.41 (m, 2H), 1.35-1.26 (m, 2H).



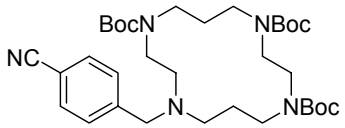
H-Gly-D-His-D-Lys[(12-phenothiazin-10-yl)dodecanoyl]-OH (42). Compound **68** (24.9 mg, 0.0264 mmol) was dissolved in stabilizer-free chloroform (4 mL). TfOH (23 μL, 0.26 mmol) was added dropwise by microsyringe. The reaction mixture changed from a colorless solution to a brown suspension. After it had been stirred at rt for 1 h, the stirbar was rinsed and removed, and the mixture was basified with aqueous NH_3 (29%, 1 drop). The mixture was shaken; within 30 s almost all of the color had faded. The mixture was rotary evaporated, rotary evaporated with EtOH three times, rotary evaporated with chloroform three times, and dried under vacuum to give a white solid (52.7 mg). ^{1}H NMR (CD_3OD) indicated that the deprotection was incomplete. The material was rotary evaporated, rotary evaporated with chloroform three times, and dried under vacuum overnight. The reaction was repeated according to the same procedure using TfOH (20 μL, 0.23 mmol). After 1 h, the reaction mixture was rotary evaporated, rotary evaporated with EtOH three times, rotary evaporated with PhMe three times, and dried under vacuum to give **42** as a brownish white solid (90.2 mg, quantitative yield). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.59/8.59 (s, rotamers, 1H), 7.36 (s, 1H), 7.18-7.07 (m, 4H), 6.95-6.88 (m, 4H), 4.38-4.26 (m, 2H), 3.89 (t, J = 6.6 Hz, 2H), 3.78 (d, J = 16.0 Hz, 1H), 3.73 (d, J = 16.0 Hz, 1H), 3.28-3.24 (m, 2H), 3.19-3.14 (m, 2H), 2.17 (t, J = 7.4 Hz, 2H), 1.93-1.91 (m, 1H), 1.78-1.71 (m, 2H), 1.61-1.47 (m, 2H), 1.47-1.34 (m, 2H), 1.34-1.18 (m, 16 H), 0.92-0.84 (m, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 176.6, 171.7, 167.3, 146.9, 135.4, 130.0, 129.3, 128.5, 128.3,

126.6, 126.5, 123.5, 119.3, 116.9, 55.6, 53.6, 47.9, 41.7, 40.2, 37.3, 32.3, 30.6, 30.5, 30.4, 30.2, 28.9, 27.8, 27.6, 27.2, 24.7, 21.6. IR: ν 3455, 3236, 3072, 2849, 1644, 1454, 1256, 1030, 642 cm^{-1}. HRFABMS Calcd for $C_{38}H_{54}N_7O_5S$ ($M+H^+$): 720.3907. Found: 720.3893.

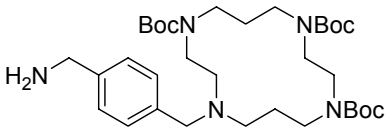


***N*-(*p*-cyanobenzyl)-1,4,8,11-tetraazacyclotetradecane (69)**.[150] This was prepared according to a literature procedure for analogous compounds.[149] 1,4,8,11-Tetraazacylcotetradecane (cyclam **43**, 103 mg, 0.515 mmol) was suspended in dry toluene (10 mL). It was refluxed with a Dean-Stark trap for 1 h and then allowed to cool at rt. After 1 h, tris(dimethylamino)borane (0.09 mL, 0.5 mmol) was added and the mixture was refluxed for 3 h. After cooling at rt for 30 min, the toluene was removed on the rotary evaporator. Dry THF (10 mL) was added to suspend the solid. The mixture was cooled to –30 °C. After 10 min, *n*-BuLi (1.6 M, 0.51 mmol, 0.32 mL) was added dropwise. After 15 min a solution of *p*-cyanobenzyl bromide (103 mg, 0.526 mmol) in dry THF (1 mL) was added dropwise. The cooling bath was removed, and the mixture was stirred at rt for 3 h. Deionized water (5 mL) was added, and the mixture was stirred at rt for 5 min. NaOH (1M) was added to bring the pH > 13, and the organic solvent was removed on the rotary evaporator. The residue was extracted with 5 x 10 mL DCM. The combined organic layers were dried (magnesium sulfate), filtered, and rotary evaporated to give a pale yellow oil (143 mg). The oil was dissolved in DCM and separated on a gravity basic alumina column (1.8 cm x 25 cm) and eluted with 3% MeOH/DCM to 10% MeOH/DCM. Fractions were combined, rotary evaporated, and dried under vacuum to give **69** as a pale yellow oil (83.1

mg, 51%). ^{1}H ($CDCl_3$, 300 MHz) and ^{13}C ($CDCl_3$, 75.5 MHz) NMR agreed with the literature values.[150]

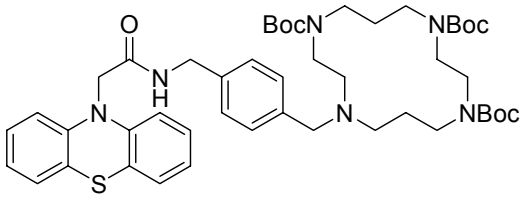


***N*-(*p*-cyanobenzyl)-1,4,8-tri(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclo-tetradecane (70)**. A solution of the macrocycle **69** (53.5 mg, 0.170 mmol) in MeCN (HPLC grade, 2 x 1 mL) was added quickly to a stirred solution of di-*tert*-butyl dicarbonate (167 mg, 0.766 mmol) in MeCN (HPLC grade, 1 mL) at rt. After 90 min, the solvent was removed on the rotary evaporator. The resulting colorless oil was separated on a gravity basic alumina column eluted with 0.75% MeOH/DCM. Fractions, were combined, rotary evaporated, and dried under vacuum to give **70** as a colorless oil (102 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 3.58 (s, 2H), 3.50-3.18 (m, 12H), 2.62 (br s, 2H), 2.39 (br s, 2H), 1.90 (br s, 2H), 1.74-1.64 (m, 4H), 1.47-1.28 (m, 27H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 145.1, 132.1, 129.7, 118.9, 110.8, 79.8, 79.6, 59.5, 53.3, 51.9, 50.5, 47.8, 47.3, 26.2, 29.0, 28.5, 27.0, 26.3. IR: ν 2974, 2931, 2814, 2227, 1692, 1469, 1415, 1366, 1247, 1164, 859, 847, 822, 772, 746 cm^{-1}. Calcd for $C_{33}H_{54}N_5O_6$ ($M+H^+$): 616.4074. Found: 616.4086.



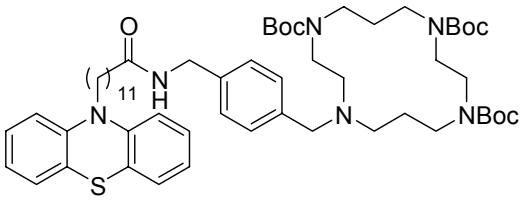
***N*-[(*p*-aminomethyl)benzyl]-1,4,8-tri(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclo-tetradecane (71)**. Macrocycle **70** (336 mg, 0.546 mmol) was dissolved in THF (10 mL).

Aqueous NH_3 (29%, 3 mL) was added. The flask was pumped under aspirator vacuum and flushed with argon three times. Raney® 2800 nickel (50 wt% slurry in water, 3 mL) was added. The flask was pumped under aspirator vacuum and flushed with H_2 (balloon) three times. After stirring at rt for 19 h, the reaction mixture was filtered through a pad of packed filter aid. The filter aid was washed with THF and MeOH. The solvent was removed on the rotary evaporator. The resulting white solid was taken up in DCM (25 mL) and partitioned between an aqueous layer of 29% aqueous NH_3 (10 mL)[175] and 4 M KOH (10 mL). The aqueous layer was extracted with more DCM (3 x 10 mL). The combined organic layers were dried (magnesium sulfate), filtered (coarse frit), rotary evaporated , and dried under vacuum to give **71** as a white foam (277 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.20 (m, 4H), 3.85 (s, 2H), 3.51 (s, 2H), 3.45-3.20 (m, 12H), 2.70-2.50 (br s, 2H, exchanged with CD_3OD), 2.47-2.06 (m, 4H), 1.97-1.80 (m, 2H), 1.77-1.62 (m, 2H), 1.50-1.35 (m, 27H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 141.6, 137.5, 129.6, 127.2, 79.8, 79.6, 59.6, 53.6, 53.1, 51.4, 47.5, 46.2, 28.6, 28.6. IR: ν 3522, 2974, 2931, 1693, 1684, 1470, 1416, 1392, 1366, 1247, 1165, 1058, 864, 852, 824, 800, 773, 733 cm^{-1}. Calcd for $C_{33}H_{58}N_5O_6$ ($M+H^+$): 620.4387. Found: 620.4381.



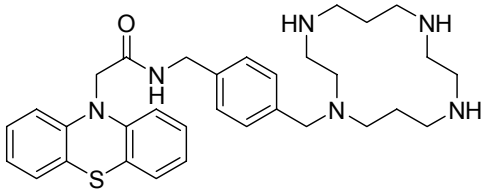
General procedure for the coupling of the protected cyclam 71 to acids 37 and 38. 11-{4-[(2-Phenothiazin-10-yl-acetylamino)methyl]benzyl}-1,4,8-tri(*tert*-butoxy-carbonyl)-1,4,8,11-tetraazacyclotetradecane (72). Acid **37** (82.1 mg, 0.319 mmol) was dissolved in dry DMF (1 mL) and cooled in an ice bath. After 10 min EDC (61.3 mg, 0.319

mmol) was added. After another 10 min a solution of the amine **71** in dry DMF (2 x 0.5 mL), DMAP (2.8 mg, 0.023 mmol), and Et_3N (44 μL, 0.32 mmol) were added sequentially. After 1 h the ice bath was removed. After 7.5 h the reaction mixture was diluted with EtOAc (20 mL) and washed with 5% sodium carbonate (2 x 5 mL) and saturated sodium chloride (5 mL). The organic layer was dried (magnesium sulfate), filtered, and rotary evaporated to give a pale pink liquid (312 mg). Elution on a gravity basic alumina column (DCM and 1% MeOH/DCM) followed by elution on a flash silica column (5% MeOH/DCM) followed by combining fractions, rotary evaporatorping, and drying under vacuum provided the amide **72** as a colorless oil (72.9 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.16 (m, 4H), 7.07-6.98 (m, 4H), 6.88-6.81 (m, 5H), 4.56 (s, 2H), 4.37 (d, J = 5.6 Hz, 2H), 3.47-3.25 (m, 14 H), 2.60 (m, 2H), 2.34 (m, 4H), 1.94-1.90 (m, 2H), 1.67 (m, 2H), 1.47-1.26 (m, 27H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 155.7, 144.6, 137.9, 136.5, 129.5, 127.9, 127.7, 127.2, 125.3, 123.8, 115.4, 79.8, 79.7, 59.5, 53.6, 52.3, 51.6, 47.5, 46.1, 43.0, 28.7, 28.6, 27.1, 26.4 . IR: ν 3425, 2974, 2932, 2245, 1680, 1537, 1465, 1415, 1365, 1284, 1248, 1163, 1039, 909, 860, 849, 732, 645 cm^{-1}. Calcd for $C_{47}H_{67}N_6O_7S$ ($M+H^+$): 859.4792. Found: 859.4847.



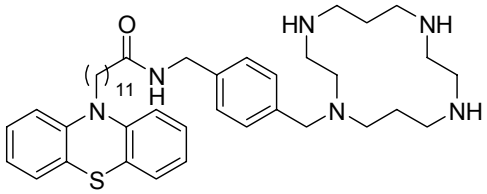
11-{4-[(12-Phenothiazin-10-yl-dodecanoylamino)methyl]benzyl}-1,4,8-tri(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (73). Following the procedure from above, the amide **73** was obtained as a clear colorless oil (44.6 mg, 48%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.11 (m, 8H), 6.92-6.84 (m, 4H), 4.40 (d, J = 3.9 Hz, 2H), 3.83 (t, J = 5.4

Hz, 2H), 3.49 (m, 2H), 3.32 (m, 12H), 2.64-2.58 (m, 4H), 2.36 (m, 2H), 2.22 (t, J = 5.7 Hz, 2H), 1.96-1.73 (m, 5H), 1.72-1.56 (m, 4H), 1.47-1.24 (m, 41H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.3, 155.8, 145.5, 138.3, 137.2, 129.8, 128.2, 127.6, 127.3, 125.0, 122.5, 155.6, 79.7, 59.8, 53.6, 47.6, 43.7, 36.9, 29.7, 29.6, 29.6, 26.4, 28.7, 28.7, 27.1, 27.1, 26.0. IR: ν 3441, 2974, 2927, 2854, 2244, 1681, 1650, 1537, 1462, 1416, 1366, 1285, 1248, 1163, 1108, 908, 859, 850, 795, 731, 645 cm^{-1}. Calcd for $C_{57}H_{87}N_6O_7S$ ($M+H^+$): 999.6357. Found: 999.6327.



General procedure for the deprotection of the cyclam moiety of 72 and 73.[153] 11-{4-[(2-Phenothiazin-10-yl-acetylamino)methyl]benzyl}-1,4,8,11-tetraazacyclotetradecane (46). Amide **72** (137.2 mg, 0.160 mmol) was placed in a flask equipped with an oven-dried stirbar. The vial was pumped under oil pump vacuum and flushed with argon three times. The vial was protected from light by covering it with aluminum foil. Methanolic HCl (12 mL, 0.4 M, freshly prepared by adding acetyl chloride to methanol and stirring at rt for 3 h) was added slowly at rt. After it had stirred at rt for 3 h, the reaction mixture was evaporated. The residue was partitioned between an aqueous layer of 4 M KOH (20 mL) and DCM (30 mL). The aqueous layer was extracted with more DCM (2 x 20 mL). The combined organic layers were dried (magnesium sulfate), filtered, rotary evaporated, and dried under vacuum to give a red oil (83 mg). The crude was dissolved in DCM and loaded on a gravity basic alumina column eluted with 3% MeOH/DCM to 10% MeOH/DCM.

Fractions were combined, rotary evaporated, and dried under vacuum to give **46** as a colorless oil (59.6 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.14 (m, 4H), 7.03-6.86 (m, 8H), 4.56 (s, 2H), 4.38 (d, J = 5.7 Hz, 2H), 3.86 (br s, 4H), 3.54 (s, 2H), 2.91-2.54 (m, 16H), 1.93-1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.4, 144.6, 137.5, 137.0, 129.7, 128.0, 127.7, 127.4, 125.2, 123.9, 115.4, 57.7, 53.7, 53.3, 52.3, 50.5, 49.5, 49.1, 48.8, 47.2, 47.0, 43.1, 26.8, 25.4. IR: ν 3425, 3060, 2931, 2814, 1666, 1572, 1547, 1519, 1464, 1443, 1361, 1284, 1257, 1214, 1132, 1120, 1049, 1020, 1002, 912, 855, 821, 750, 732 cm^{-1}. Calcd for $C_{32}H_{43}N_6OS$ ($M+H^+$): 559.3129. Found: 559.3255.



11-{4-[(12-Phenothiazin-10-yl-dodecanoylamino)methyl]benzyl}-1,4,8,11-tetra-azacyclotetradecane (47). Following the procedure from above, the tetraamine **47** was obtained as a colorless oil in 39% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.24 (m, 4H), 7.16-7.11 (m, 4H), 6.91-6.84 (m, 4H), 5.83 (br s, 1H), 4.41 (d, J = 5.2 Hz, 2H), 3.83 (t, J = 7.2 Hz, 2H), 3.55 (s, 2H), 2.90-2.55 (m, 16H), 2.21 (t, J = 7.6 Hz, 2H), 1.94-1.85 (m, 2H), 1.83-1.74 (m, 4H), 1.68-1.58 (m, 2H), 1.46-1.24 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 145.5, 137.9, 137.7, 129.8, 128.4, 127.6, 127.4, 125.0, 122.5, 115.6, 57.9, 54.1, 53.4, 50.8, 49.5, 49.3, 48.7, 47.6, 47.6, 47.2, 43.7, 36.9, 29.9, 29.7, 29.6, 29.5, 29.4, 27.2, 27.1, 27.1, 26.0, 25.7. IR: ν 3413, 2919, 2849, 1647, 1540, 1458, 1449, 1367, 1331, 1284, 1250, 1126, 1114, 856, 820, 750 cm^{-1}. Calcd for $C_{42}H_{63}N_6OS$ ($M+H^+$): 699.4784. Found: 699.4824.

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