Pergamon

Tetrahedron, Vol. 53, No. 26, pp. 8751-8778, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00567-X

Design, Synthesis and Biological Evaluation of Carbohydrate-Based Mimetics of cRGD*F*V

K. C. Nicolaou*, John I. Trujillo and Kelly Chibale

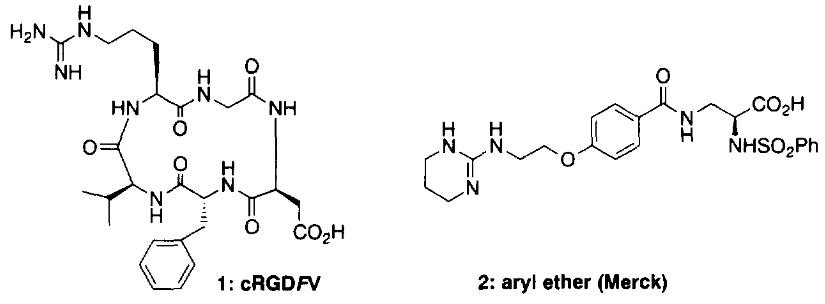
Department of Chemistry and The Skaggs Institute of Chemical Biology, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037
and
Department of Chemistry and Biochemistry, University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093

Abstract: The design, synthesis and preliminary biological evaluation of carbohydrate-based non-peptide mimetics of the potent peptidic antagonist of $\alpha_v\beta_3$ and $\alpha_v\beta_5$, pentapeptide cRGD*F*V (1) is presented. The design was based on the NMR-determined structure of 1. © 1997 Elsevier Science Ltd.

INTRODUCTION

Angiogenesis, the growth of new blood vessels from preexisting blood vessels, plays an important role in the proliferation of tumor cells. In addition, there are at least twenty other angiogenesis-dependent diseases identified so far, including arthritis, atherosclerosis, delayed wound healing and retinopathy.[1] Given the fact that angiogenesis is a rare phenomenon in normal healthy adults, its inhibition has been suggested as a viable approach to cancer therapy.[2] This strategy for the treatment of disease has been substantiated not only for cancer, but also for ocular neovascular disorders.[3]

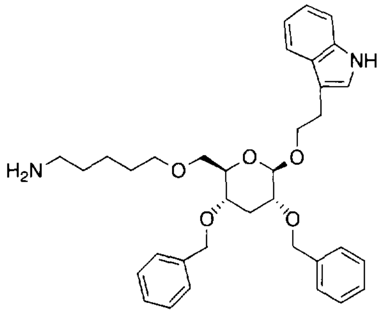
The integrins are a class of extracellular proteins that facilitate cell-cell recognition and cell adhesion.[4] Of the members of this family of receptors, $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are the most studied. A number of known natural ligands to these integrins, such as fibronectin ($\alpha_5\beta_1$), fibrinogen ($\alpha_{IIb}\beta_3$) and vitronectin ($\alpha_v\beta_3$), contain the key peptide sequence Arg-Gly-Asp (RGD) within their native sequence, which is recognized by most integrins. Within the context of angiogenesis, the functions of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ have been shown to be vital.[5] Consequently, *in vivo* inhibition of binding of these integrins to their RGD ligands by antibodies or cyclic peptides has been shown to inhibit angiogenesis and induce tumor regression.[6] Amongst the known antagonists of $\alpha_v\beta_3$ are a number of cyclic peptides such as cRGD*F*V[7] (1, *F* designates unnatural configuration), antibodies LM609 and p1F6, and a class of small molecules represented by aryl system 2 (Figure 1).[8]



1: cRGDFV **2: aryl ether (Merck)**

Fig. 1. Structures of $\alpha_v\beta_3$ antagonists *c*RGD*F*V (**1**) and aryl ether sulfonamide **2**.

Since its original utilization as a template for the synthesis of peptide mimetics, the pyranose carbohydrate ring system has gained popularity as a viable scaffold for the design of various bioactive compounds.[9,10] A recent example is the somatostatin mimic **3**[10] (Figure 2). Carbohydrate-based compounds offer several advantages : (a) rich and well studied chemistry for creating diverse structures; (b) high degree of oxygenation that often assures water solubility; and (c) enough rigidity for precise positioning of important functional groups and side chains. With these advantages in mind, we proceeded to attempt to mimic the structure and biological activity of the cyclopeptide **1** using carbohydrate-based structures. In this article we describe our initial results of molecular design, chemical synthesis and biological evaluation.



3

Fig. 2. Structure of carbohydrate-based somatostatin peptidomimetic **3**.

MOLECULAR DESIGN

Since the design of carbohydrate mimics was to be patterned after the NMR solution structure of cRDG*F*V (**1**)[7], we carried out comparisons of the NMR-determined structure of **1** and minimized (Insight-Discover, CV-Force Field) structures of several carbohydrate-based mimetics. It was known at the outset that the guanidine and carboxylate functionalities and the distance between them were important for binding.[7] The optimum distance between C_β(Arg)-C_β(Asp) for the peptides of Kessler and coworkers was determined to be 5-7 Å. In order to probe this structural space, we chose to introduce a carboxylic acid group at either C-1 or C-2 while maintaining a guanidine side chain of varying lengths at C-6 of the carbohydrate framework. Capping the C-3 hydroxyl group as a benzyl ether was expected to mimic the phenyl group of the phenylalanine residue (*F*), while methylating the C-4 hydroxyl group was expected to result in a hydrophobic moiety similar to that of the isopropyl group of the valine (V) residue in **1**. Figure 3 exhibits, side by side, the NMR-determined structure of cyclopeptide **1** and a minimized representative carbohydrate design (**7**), demonstrating the similarities between the two structures. An initial library of nine compounds **4-12** (Figure 4) was thus designed and each member targeted for synthesis.

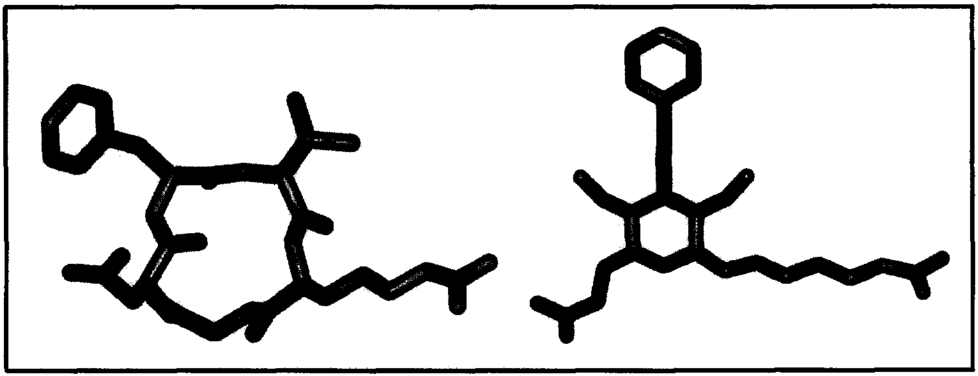
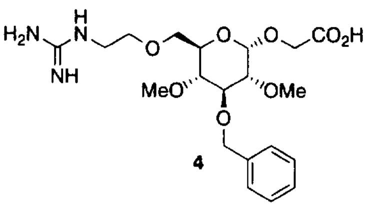


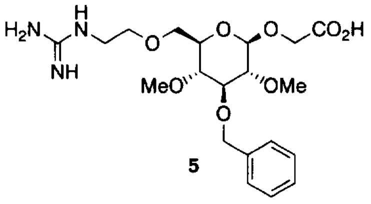
Fig. 3. Computer generated models of cRGD*F*V (**1**) (left) and carbohydrate-based mimetic **7** (right).

CHEMICAL SYNTHESIS

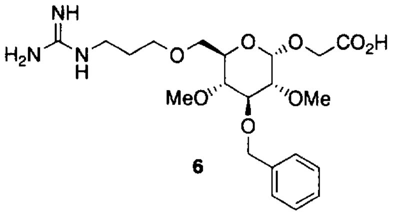
Compounds 4-7. These compounds were synthesized as shown in Scheme 1. Compounds **6** and **7** were prepared similarly according to Scheme 1, utilizing 3-azido-1-propyl triflate instead of its ethyl counterpart. Thus, starting with α-methyl-D-mannopyranoside (**13**), the mono-silyl derivative **14** was prepared by treatment with *t*-butyldiphenylsilyl (TPS) chloride in the presence of excess imidazole in CH_2Cl_2 in 98% yield. Exposure of **14** to excess 2,2-dimethoxypropane in acetone in the presence of an acid catalyst (TsOH) gave hydroxy acetonide **15** (99% yield). The acetonide **15** was then methylated under standard conditions to give the methyl ether **16** (69% yield), which was desilylated under the influence of tetra-*n*-butylammonium fluoride to give the alcohol **17** (92% yield). The alcohol was then *O*-alkylated with 2-azido-1-ethyl triflate in the presence of NaH to afford compound **18** (60% yield). Treatment of **18** with HCl/AcOH/THF resulted in the removal of the acetonide group leading to diol **19** (85% yield), which was selectively benzylated at C-3 by sequential exposure to di-*n*-butyltin oxide (MeOH, Δ) and benzyl bromide (CsF, DMF, 25 °C) to give the benzyl ether **20** (93% yield).[11] Treatment of **20** with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at 40 °C resulted in migration of the C-1-methoxy group to the C-2 position with concomitant fluoride formation at C-1 and inversion of configuration at C-2, furnishing a mixture of α/β (*ca.* 3:2, β:α) fluorides **21ab** (63% yield).[12] Reaction of **21ab** with excess $HOCH_2COOEt$ in the presence of Cp_2ZrCl_2 and $AgClO_4$ (4 Å mol. sieves, benzene, 25 °C) led to a mixture of α/β (*ca.* 2:3, α:β) glycoside **22ab** (55% yield).[13]



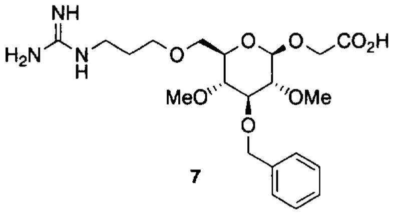
4



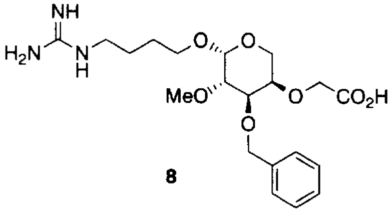
5



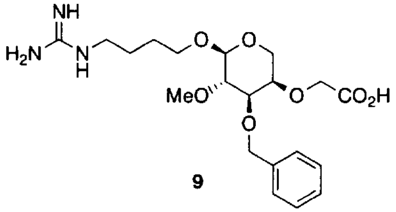
6



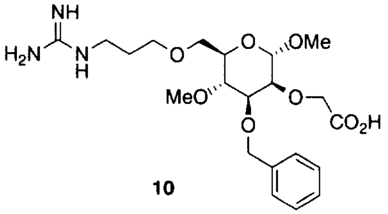
7



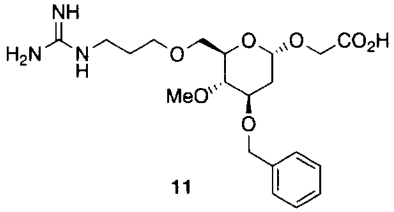
8



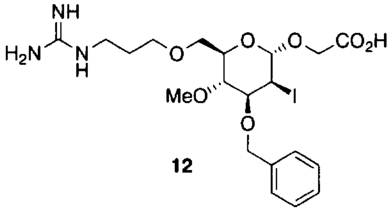
9



10

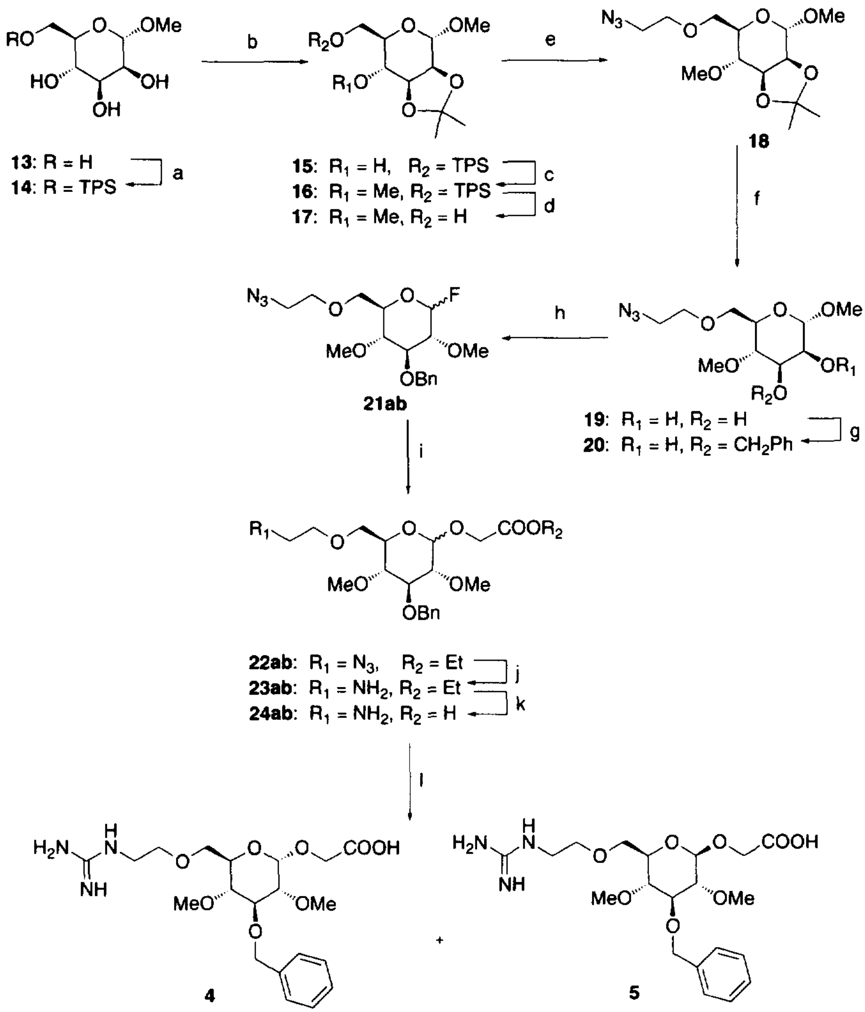


11



12

Fig. 4. Designed carbohydrate-based mimetics **4-12** of cRGD*F*V (**1**).



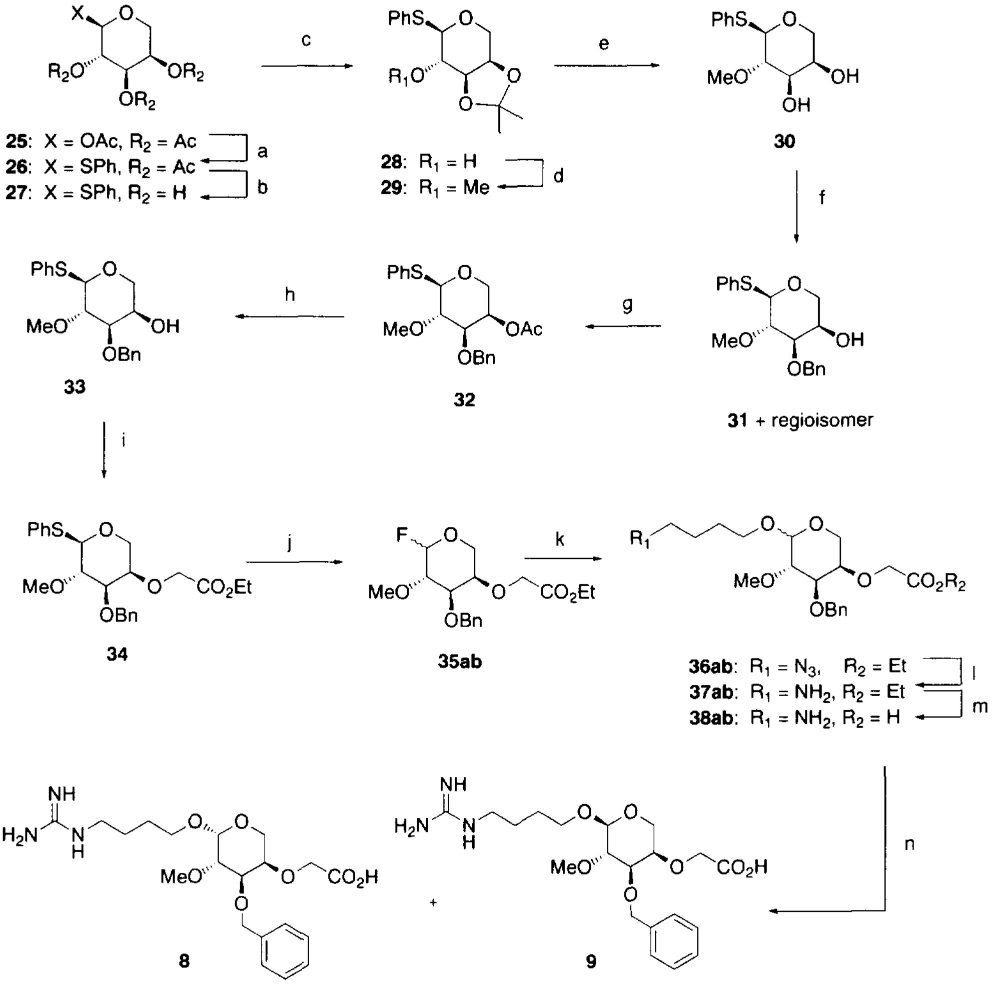
Scheme 1. Synthesis of compounds **4** and **5**. *Reagents and conditions:* (a) 1.05 equiv of TPSCl, 2.0 equiv of imidazole, CH_2Cl_2, 0 °C, 4 h, 98%; (b) 3.0 equiv of $Me_2C(OMe)_2$, *cat.* TsOH , acetone, 25 °C, 4 h, 99%; (c) 1.2 equiv of NaH, 1.2 equiv of MeI, 0.5 equiv of imidazole, THF, 25 °C, 24 h, 69%; d) 2.0 equiv of 1.0 M TBAF, THF, 25 °C, 4 h, 92%; (e) 1.2 equiv of NaH, 5.0 equiv of $TfO(CH_2)_2N_3$, 25 °C, 24 h, 60%; (f) 2.0 M HCl:AcOH:THF (4:3:1), 25 °C, 24 h, 85%; (g) *i)* 1.1 equiv of *n*-Bu_2SnO, MeOH, Δ; *ii)* 1.2 equiv of BnBr, 1.05 equiv of CsF, DMF, 25 °C, 14 h, 93%; (h) 3.0 equiv of DAST, CH_2Cl_2, 40 °C , 4 h, 63% (*ca.* 3:2 ratio of β/α isomers); (i) 5.0 equiv of Cp_2ZrCl_2, 5.0 equiv of $AgClO_4$, 2.0 equiv of $HOCH_2CO_2Et$, 4 Å mol. sieves, PhH, 4 h, 25 °C , 55% (*ca.* 2:3 ratio of α/β isomers); (j) 2.0 equiv of Ph_3P, THF, 24.0 equiv of H_2O, 65 °C, 4 h, 85%; (k) 2.0 equiv of $LiOH{\bullet}H_2O$, THF:H_2O (8:1), 25 °C, 4 h; (l) 1.0 equiv of 1*H*-pyrazole-1-carboxamidine•HCl, *i*-Pr_2NEt, DMF, 25 °C, 16 h, 80% (total yield for 2 steps), isomers **4** and **5** were separated by RP-HPLC. TPSCl = *t*-butyldiphenylsilyl chloride; DAST = diethylaminosulfur trifluoride; Tf = SO_2CF_3.

Reaction of **22ab** with Ph_3P in the presence of H_2O at 65 °C led to the amino compound **23ab** (85% yield). Finally, ester hydrolysis of **23ab** with LiOH in THF:H_2O (8:1) furnished amino acid **24ab** which was guanylated (1*H*-pyrazole-1-carboxamidine hydrochloride, *i*-Pr_2NEt, DMF, 25 °C)[14] to afford compounds **4** and **5** (80% yield for 2 steps) after RP-HPLC separation.

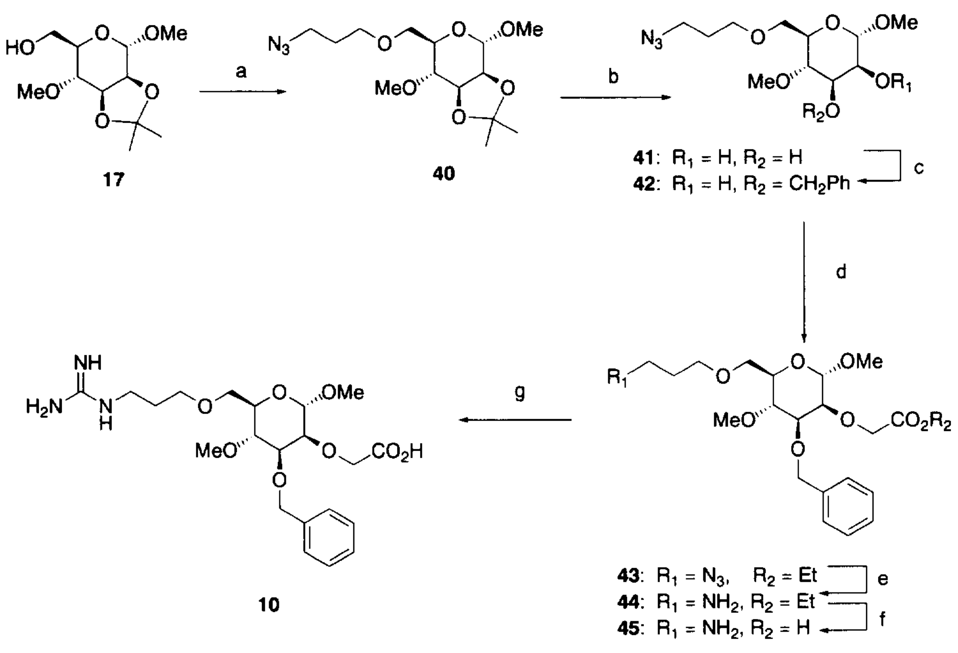
Compounds 8 and 9. These compounds were synthesized as summarized in Scheme 2. Arabinose tetraacetate (**25**) was treated with PhSH in the presence of $SnCl_4$ to give **26** (75% yield), which was then fully deacetylated to afford thioglycoside triol **27** (80% yield). Acetonide formation proceeded smoothly to afford compound **28** (84% yield) as did methylation of the remaining hydroxyl group (97% yield) leading to compound **29** via **28**. Removal of the acetonide group (HCl/AcOH/THF) led to diol **30** (94% yield). An attempt to form the desired C-3 benzyl ether **31** in a selective manner with *n*-Bu_2SnO-BnBr-*n*-Bu_4NBr[11], however, resulted in a mixture of **31**, and its 4-regioisomer in 90% total yield and *ca.* 1:1 ratio. This may be due to subtle steric differences inherent in the substrate. An alternative explanation for the poor regioselectivity may be due to a lack of a strong conformational preference for one particular chair form of the arabinose derivative, resulting in two different reactive conformations of the corresponding stannylene acetal thus leading to different products. A lack of generality for the regioselective functionaliztion of *cis*-diols has previously been noted.[11,15] The regioisomeric mixture was acetylated (Ac_2O, Et_3N, 4-DMAP) and the two resulting acetates were separated by column chromatography (40% yield each). The desired regioisomer (**32**), whose structure was determined by NMR spectroscopy, was then deacetylated with K_2CO_3 in MeOH (95% yield) and the resulting hydroxy compound **33** was alkylated with ethyl bromoacetate in the presence of NaH to afford ester **34** (61% yield). Thioglycoside **34** was then transformed to the corresponding glycosyl fluoride (**35ab**, mixture of anomers, *ca.* 5:1, β:α)[16b], which was reacted with $HO(CH_2)_4N_3$ in the presence of $AgClO_4$ and $SnCl_2$ to furnish the two anomeric glycosides **36ab** in 83% total yield (*ca.* 2:1, β:α).[16] This anomeric mixture was then treated with Ph_3P-H_2O to effect the reduction of the azide to the amine (**36ab**→**37ab**, 81% yield), followed by exposure to LiOH in THF/MeOH/H_2O (**37ab**→**38ab**) and reaction with 1*H*-pyrazole-1-carboxamidine hydrochloride, *i*-Pr_2NEt, (**38ab**→**8** and **9**, 83% overall yield from **38ab**)[14] to give, after separation by RP-HPLC, compounds **8** and **9**.

Compound 10. The sequence for the chemical synthesis of **10** is shown in Scheme 3. Thus *O*-alkylation of alcohol **17** with $TfO(CH_2)_3N_3$ in the presence of NaH led to azide **40** in 60% yield. Acetonide removal from **40** (HCl/AcOH/THF, 85% yield) followed by *n*-Bu_2SnO-mediated selective benzylation at C-3 gave the 2-hydroxy compound **42** (92% yield)[11] via diol **41**. Attachment of the two carbon carboxylate side chain at C-2 was carried out with ethyl bromoacetate in the presence of NaH, furnishing **43** in 65% yield. Finally, reduction of the azide **43** to the amino group (83% yield), followed by ester hydrolysis and guanylation as described above for compounds **4** and **5** (Scheme 2) gave the desired product **10** in 80% overall yield.

Compounds 11 and 12. The synthesis of compounds **11** and **12** begun with the D-glucal derivative **46**. Selective benzylation at C-3 by the standard *n*-Bu_2SnO-BnBr method[11] as summarized in Scheme 4 gave **47** in 74% yield. Methylation of the C-4 hydroxyl group resulted in the formation of compound **48** (88% yield). Compound **48** served as a common intermediate for both **11** and **12**. Thus addition of $HOCH_2CO_2Me$ to glycal

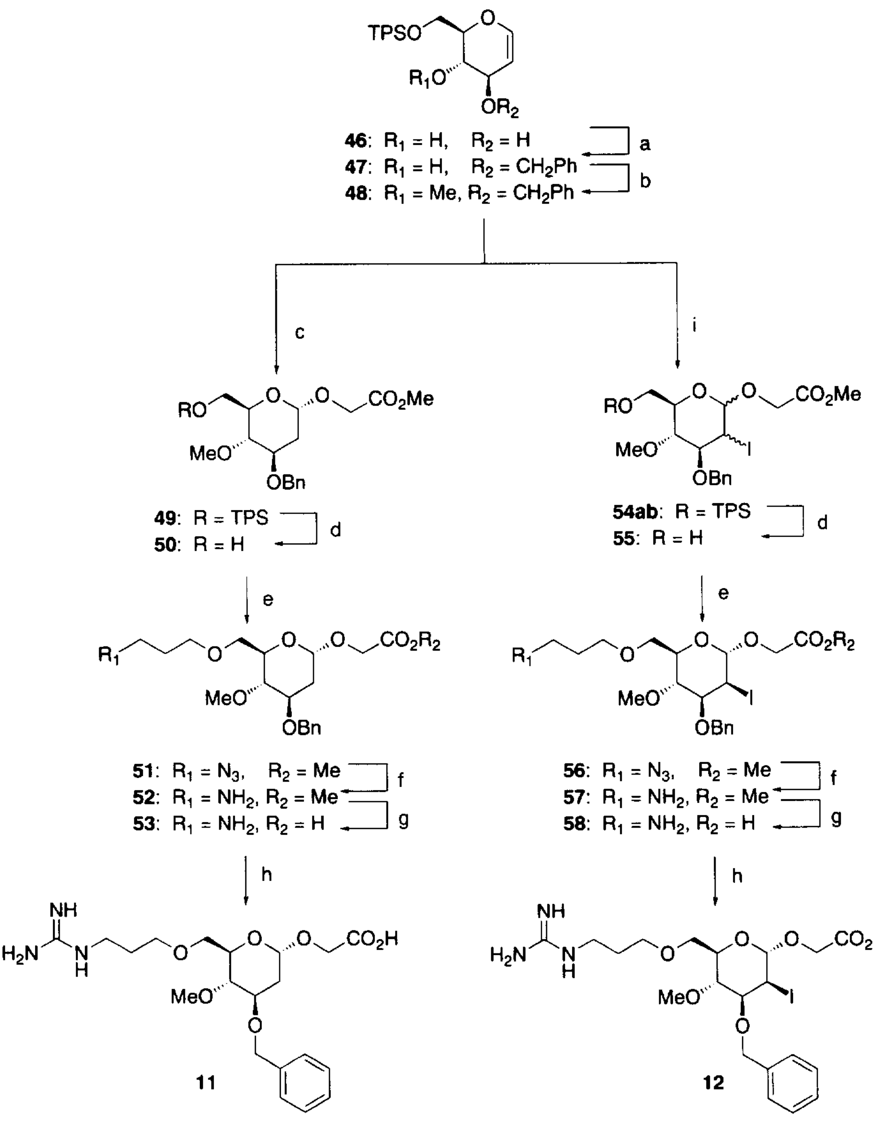


Scheme 2. Synthesis of compounds **8** and **9**. *Reagents and conditions:* (a) 1.1 equiv of PhSH, 0.7 equiv of $SnCl_4$, CH_2Cl_2, 0 °C, 4 h, 75%; (b) 0.5 equiv of K_2CO_3, MeOH, 25 °C, 4 h, 80%; (c) 3.0 equiv of $Me_2C(OMe)_2$, *cat.* TsOH, acetone, 25 °C, 2 h, 84%; (d) 1.3 equiv of NaH, 1.5 equiv of MeI, 0.2 equiv *n*-Bu_4NI, *cat.* imidazole, THF, 25 °C, 20 h, 97%; (e) 3.0 M HCl:AcOH:THF (4:3:1), 25 °C, 3 h, 94%; (f) *i)* 1.5 equiv of *n*-Bu_2SnO, PhMe, Δ; *ii)* 1.0 equiv of BnBr, 1.0 equiv of *n*-Bu_4NBr, PhMe, 80 °C, 20 h, 90% total yield; (g) 6.0 equiv of Ac_2O, 8.0 equiv of Et_3N, 0.1 equiv 4-DMAP, CH_2Cl_2, 0 -25 °C , 12 h, 40% of **32** plus 40% of C-4 regioisomer; (h) 0.5 equiv of K_2CO_3, THF:MeOH (1:1), 25 °C, 4 h, 95%; (i) 1.05 equiv of NaH, 1.5 equiv of $BrCH_2CO_2Et$, THF, 40 °C, 12 h, 61%; (j) 1.3 equiv of NBS, 1.5 equiv of DAST, CH_2Cl_2, -15 °C, 20 min, 63% (*ca.* 5:1 ratio of β/α); (k) 2.0 equiv of $AgClO_4$, 2.0 equiv of $SnCl_2$, 1.5 equiv of $HO(CH_2)_4N_3$, THF, 25 °C, 2 h, 83% (*ca.* 2:1 ratio of β/α); (l) 2.6 equiv of Ph_3P, 16.0 equiv of H_2O, THF, 65 °C, 5 h, 81%; (m) 10% aqueous LiOH, THF: H_2O (8:1), MeOH, 25 °C, 4 h; (n) 1.0 equiv of 1*H*-pyrazole-1-carboxamidine•HCl, 1.0 equiv of *i*-Pr_2NEt, DMF, 25 °C, 16 h, (83% for 2 steps), isomers **8** and **9** were separated by RP-HPLC. NBS = *N*-bromosuccinimide; DAST = diethylaminosulfur trifluoride; 4-DMAP = 4-dimethylaminopyridine.



Scheme 3. Synthesis of compound **10**. *Reagents and conditions:* (a) 1.2 equiv of NaH, 5.0 equiv of $TfO(CH_2)_3N_3$, 25 °C, 24 h, 60%; (b) 2.0 M HCl:AcOH:THF (4:3:1), 25 °C, 24 h, 85%; (c) *i)* 1.1 equiv of *n*-Bu_2SnO, MeOH, Δ; *ii)* 1.2 equiv of BnBr, 1.05 equiv of CsF, DMF, 25 °C, 14 h, 92%; (d) 1.2 equiv of NaH, 1.2 equiv of $BrCH_2CO_2Et$, THF, 25 °C, 14 h, 65%; (e) 2.0 equiv of Ph_3P, THF, 24.0 equiv of H_2O, 65 °C, 4 h, 83%; (f) 2.0 equiv of LiOH•H_2O, THF: H_2O (8:1), 25 °C, 4 h; (g) 1.0 equiv of 1*H*-pyrazole-1-carboxamidine•HCl, 1.0 equiv of *i*-Pr_2NEt, DMF, 25 °C, 16 h, 80% (total yield over 2 steps). Tf = SO_2CF_3.

48 under acid catalysis (Ph_3P•HBr)[17] conditions led to the formation of the α-glycoside **49** in 75% yield as expected. Removal of the silyl group from **49** was accomplished with TBAF to afford compound **50** (79% yield), which, after *O*-alkylation with NaH-$TfO(CH_2)_3N_3$, furnished azide **51** in 66% yield. The azide **51** was then reduced under standard conditions to give the amine **52** (77% yield), which was hydrolyzed and guanylated to give compound **11** (95% overall yield). For the synthesis of compound **12**, glucal **48** was subjected to iodoglycosidation (*N*-iodosuccinimide, CH_2Cl_2) with $HOCH_2CO_2Me$ to afford a mixture of diastereoisomers, **54ab** in 75% yield.[18, 19] Removal of the silyl ether from **54ab** with *n*-Bu_4NF gave a mixture of alcohols which were separated by column chromatography (silica gel, 60% ether in hexane, R_f = 0.1 and 0.17). The desired α-anomer **50** (R_f = 0.17) was carried forward to compound **12** by the same sequence as described for **12** and via intermediates **56-58** (Scheme 4).



Scheme 4. Synthesis of compounds **11** and **12**. *Reagents and conditions:* (a) *i)* 1.5 equiv of *n*-Bu_2SnO, PhMe, Δ; *ii)* 1.0 equiv of BnBr, 1.0 equiv of *n*-Bu_4NBr, PhMe, 80 °C, 18 h, 74%; (b) 2.2 equiv of NaH, 10.0 equiv of MeI, PhH, Δ, 14 h, 88%; (c) *i)* 2.0 equiv of $HOCH_2CO_2Me$, CH_2Cl_2, 25 °C, 3 h; *ii)* 0.05 equiv of $Ph_3P{\bullet}HBr$, 75%; (d) 1.2 equiv of *n*-Bu_4NF, THF, 25 °C, 10 h, 79% (for **50** and **55**); (e) 1.05 equiv of NaH, 7.0 equiv of $TfO(CH_2)_3N_3$, 25 °C, 14 h, 66% (for **51**), 50% (for **56**); (f) 2.6 equiv of Ph_3P, 16.0 equiv of H_2O, THF, 65°C, 5 h, 77% (for **52**), 91% (for **57**); (g) 10% aqueous LiOH, THF, MeOH, 25 °C, 4 h; (h) 1.0 equiv of 1 *H*-pyrazole-1-carboxamidine•HCl, 1.0 equiv of *i*-Pr_2NEt, DMF, 25 °C, 16 h, 95% (for **11** over 2 steps), 93% (for **12** over 2 steps); (i) *i)* 1.5 equiv of $HOCH_2CO_2Me$, CH_2Cl_2, 25 °C; *ii)* 1.2 equiv of NIS, CH_2Cl_2, 25 °C, 3 h, 75% (*ca.* 3:1 mixture of diastereisomers). Bn = CH_2Ph; Tf = SO_2CF_3; NIS = *N*-iodosuccinimide.

CONCLUSION

A number of novel carbohydrate-based structures have been designed and synthesized as potential mimics of RGD*F*V (**1**). Preliminary biological data indicate that, unlike **1**, these compounds do not bind to $\alpha_V\beta_3$.[20] The compounds have also been tested in other cell adhesion assays against the integrin $\alpha_{IIb}\beta_3$ and have also been shown to be inactive.[21] However, compound **12** did show small inhibition of cell adhesion mediated by $\alpha_{IIb}\beta_3$ with an IC_{50} of 85 µM. These results suggest that subtle requirements may exist for the active conformation of the cyclopeptide antagonist **1**, which are not fulfilled by the synthesized carbohydrate structures. A possible explanation for the lack of activity seen for the carbohydrate designs may be due to the inadequate rigidity of the carbohydrate mimetics as compared to other mimetics which have shown activity.[8] Further studies involving modification of our designs to improve upon the biological activity are ongoing in these laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Techniques

All reactions were carried out under a dry argon atmosphere using freshly distilled solvents unless otherwise noted. All solvents were dried utilizing an activated alumina column. Amine bases were dried and stored over potassium hydroxide. Glassware was either oven dried (120 °C) or flame dried (0.5 torr) prior to use. When necessary, compounds were dried by azeotropic removal of water with benzene or toluene under reduced pressure. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using UV light (254 nm) and/or heating with *p*-anisaldehyde solution (340 mL ethanol, 9.2 mL *p*-anisaldehyde, 12.5 mL sulfuric acid and 3.75 mL acetic acid). Reaction temperatures were measured externally unless otherwise noted. Solvents used for work-up, chromatography, and recrystallizations were reagent grade from either Fisher Scientific or E. Merck. Reactions were worked-up by washing with saturated aqueous solutions of the salts indicated. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040-0.063 mm). Reverse Phase Preparative HPLC was performed on a Waters Model 600E HPLC instrument utilizing a Vydac 218TP1022 or a Vydac 201HS1022 column with detection at 254 nm. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials.

NMR spectra were recorded on a Bruker AMX 400 MHz or 500 MHz spectrometer at ambient temperature. Chemical shifts are reported relative to the residual solvent peak. Multiplicities are designated as: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad singlet (bs). IR samples were prepared by evaporation of a solution of the compound in $CHCl_3$ or $CDCl_3$ onto a NaCl plate under a stream of argon. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrophotometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under Fast Atom Bombardment (FAB) conditions unless otherwise stated. Electrospray mass spectra were recorded on a Perkin Elmer Science API III mass spectrometer.

Synthesis of Compounds 4 and 5

Silyl ether 14. To a solution of α-methyl-D-mannopyranoside (**13**) (7.70 g, 0.04 mol) in DMF (75 mL) was added imidazole (5.44 g, 0.08 mol) and *tert*-butyldiphenylsilyl chloride (10.8 mL, 0.04 mol) at 0 °C. After 1 h, the cooling bath was removed and the mixture was allowed to stir at room temperature for 12 h. Water (200 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which after flash chromatography (silica, 40 → 70% ethyl acetate in hexane) gave **14** as a colorless oil (17.0 g, 98%). **14**: R_f = 0.12 (silica, 70% ethyl acetate in hexane); IR (thin film) ν_{max} 3416, 2930, 1652, 1471, 1427, 1111, 962 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 7.64-7.60 (m, 4 H, Ar), 7.30-7.24 (m, 6 H, Ar), 4.60 (d, *J* = 1.5 Hz, 1 H, H-1), 3.92-3.88 (m, 1 H), 3.73-3.68 (m, 2 H), 3.56-3.51 (m, 2 H), 3.46-3.42 (m, 1 H), 3.29 (s, 3 H, OCH_3), 0.93 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, CD_3OD): δ 136.8, 135.2, 130.8, 130.7, 128.7, 128.7, 102.6, 75.1, 72.8, 72.0, 68.8, 65.3, 55.0, 27.3; FAB-HRMS calcd (M+Cs$^+$) 455.1866, found 455.1851.

Acetonide 15. To a solution of **14** (8.48 g, 0.02 mol) in acetone (200 mL) was added 2,2-dimethoxypropane (7.22 mL, 0.06 mol) and TsOH•H_2O (0.74 g, 0.004 mol) at 0 °C. After 4 h, triethylamine (1 mL) was added, the solvent was removed *in vacuo* and the residue was diluted with water (250 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **15** as a colorless oil (9.1 g, 99%). **15**: R_f = 0.6 (silica, 50% ethyl acetate in hexane); IR (thin film) ν_{max} 3454, 2931, 2856, 1472, 1427, 1220, 1142, 1090, 972 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.69 (m, 4 H, Ar), 7.44-7.38 (m, 6 H, Ar), 4.88 (s, 1 H, H-1), 4.15-4.11 (m, 2 H, H-2, H-3), 3.92 (dd, *J* = 11.0, 5.5 Hz, 1 H, H-6), 3.83 (dd, *J* = 11.0, 5.0 Hz, 1 H, H-6′), 3.80 (ddd, *J* = 9.5, 6.5, 3.5 Hz, 1 H, H-4), 3.62 (ddd, *J* = 9.5, 5.5, 5.0 Hz, 1 H, H-5), 3.34 (s, 3 H, OCH_3), 2.74 (d, *J* = 3.5 Hz, 1 H, OH), 1.51 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 135.6, 132.8, 133.0, 129.8, 127.8, 127.7, 109.5, 98.2, 78.1, 75.3, 70.7, 69.3, 64.6, 54.9, 27.8, 26.8, 26.1, 19.2; FAB-HRMS calcd (M+Na$^+$) 495.2179, found 495.2162.

Methyl ether 16. To a solution of **15** (11.8 g, 0.025 mol) in dry THF (100 mL) was added NaH (60 % dispersion in mineral oil, 1.3 g, 0.03 mol), imidazole (0.34 g, 0.005 mol) and methyl iodide (3.11 mL, 0.05 mol) at 0 °C. After 24 h, the reaction was quenched with saturated aqueous solution of ammonium chloride (20 mL). The reaction mixture was allowed to stir at room temperature for 30 min and then was diluted further with water (200 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which after flash chromatography (silica, 30% ether in hexane) gave **16** as a colorless oil (8.40 g, 69%). **16**: R_f = 0.48 (silica, 20 % ether in hexane); IR (thin film) ν_{max} 2931, 2857, 1587, 1472, 1428, 1371, 1221, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75-7.73 (m, 4 H, Ar), 7.44-7.36 (m, 6 H, Ar), 4.94 (s, 1 H, H-1), 4.21 (t, *J* = 6.0 Hz, 1 H, H-2), 4.12 (dd, *J* = 10.0, 6.0 Hz, 1 H, H-3), 3.90-3.88 (m, 2 H, H-6 and H-6′), 3.57 (ddd, *J* =10.0, 7.0, 3.5 Hz, 1 H, H-5), 3.49 (s, 3 H, OCH_3), 3.44 (dd, 1 H, *J* = 10.0, 7.0 Hz, H-4), 3.37 (s, 3 H, OCH_3), 1.55 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.06 (s, 9 H, t-Bu) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 135.6, 133.7, 133.4, 129.5, 127.6, 127.5, 109.2, 98.1, 78.7, 77.4, 75.8, 69.5, 63.2, 59.1, 54.7, 27.9, 26.7, 26.3, 19.3; FAB-HRMS calcd (M+Na$^+$) 509.2335, found 509.2353.

Alcohol 17. To a solution of **16** (7.20 g, 0.015 mol) in dry THF (200 mL) was added TBAF (1 M solution in THF, 19.1 mL, 0.013 mol) at 0 °C. After 14 h, the reaction mixture was diluted with water (200 mL) and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The organic fractions were washed with brine (150 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a crude oil, which after flash chromatography (silica, 30 → 50% ethyl acetate in hexane) gave **17** as a colorless oil (3.37 g, 92%). **17**: R_f = 0.16 (silica, 30% ethyl acetate in hexane); IR (thin film) ν_{max} 3481, 2935, 1452, 1382, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.91 (d, J = 0.5 Hz, 1 H, H-1), 4.19 (dd, J = 7.0, 5.5 Hz, 1 H, H-3), 4.11 (dd, J = 5.5, 0.5 Hz, 1 H, H-2), 3.85 (ddd, J = 12.0, 5.0, 3.5 Hz, 1 H, H-6), 3.75 (ddd, J = 12.0, 8.0, 4.5 Hz, 1 H, H-6′), 3.55-3.52 (m, 1 H, H-5), 3.53 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.31 (dd, J = 10.0, 7.0 Hz, 1 H, H-4), 2.04 (dd, J = 8.0, 5.0 Hz, 1 H, OH), 1.55 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 109.3, 98.2, 78.3, 78.2, 75.6, 68.3, 62.6, 59.2, 55.0, 28.0, 26.3; FAB-HRMS calcd ($M+Na^+$) 271.1158, found 271.1150.

Azide 18. To a solution of **17** (0.70 g, 2.8 mmol) in dry THF (10 mL) was added NaH (60% dispersion in mineral oil, 0.195 g, 3.64 mmol) at 0 °C. After 30 min at 0 °C, a solution of $TfO(CH_2)_2N_3$ (2.85 g, 0.013 mol) in dry THF (5 mL) was added via canula. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was diluted with aqueous saturated solution of ammonium chloride (20 mL) and allowed to stir for 15 min. Water (30 mL) was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (3 x 25 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which after flash chromatography (silica, 40% ethyl acetate in hexane) gave **18** as a colorless oil (0.53 g, 60%). **18**: R_f = 0.40 (silica, 40% ethyl acetate in hexane); IR (thin film) ν_{max} 2986, 2935, 2834, 2105, 1953, 1220, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.92 (s, 1 H, H-1), 4.17 (t, J = 6.0 Hz, 1 H, H-2), 4.10 (d, J = 6.0 Hz, 1 H, H-3), 3.77-3.65 (m, 3 H), 3.61 (dd, J = 7.0, 5.0 Hz, 1 H, H-6), 3.53 (s, 3 H, OCH_3), 3.47-3.42 (dd, J = 10.0, 7.0, 3.5 Hz, 1 H, H-5), 3.38 (s, 3 H, OCH_3), 3.36 (t, J = 3.0 Hz, 2 H, CH_2), 3.33 (dd, J = 10.0, 7.0 Hz, 1 H, H-4), 1.54 (s, 3 H, OCH_3), 1.35 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 109.3, 98.2, 78.5, 77.4, 75.7, 70.6, 70.4, 68.1, 59.1, 54.9, 50.9, 27.9, 26.3; FAB-HRMS calcd ($M+Cs^+$) 450.0641, found 450.0628.

Diol 19. To a solution of **18** (0.34 g, 1.1 mmol) in dry THF (4.7 mL) at room temperature was added acetic acid (0.6 mL) and 2 M aqueous HCl (1.8 mL). After stirring for 24 h, the reaction mixture was poured into an aqueous saturated solution of potassium carbonate (15 mL) and ethyl acetate (60 mL). The mixture was stirred for 30 min and then the two layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The organic fractions were combined and washed with brine (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give **19** as a colorless oil (0.25 g, 85%). **19**: R_f = 0.12 (silica, ethyl acetate in hexane); IR (thin film) ν_{max} 3416, 2923, 2105, 1118, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.73 (d, J = 2.0 Hz, 1 H, H-1), 3.91 (dd, J = 3.5, 2.0 Hz, 1 H, H-2), 3.87-3.84 (m, 1 H, H-3), 3.80-3.68 (m, 4 H), 3.60-3.58 (m, 1 H), 3.58 (s, 3 H, OCH_3), 3.45 (t, J = 9.0 Hz, 2 H, CH_2), 3.38 (dd, J = 6.0, 3.5 Hz, 1 H, H-4), 3.36 (s, 3 H, OCH_3), 1.80 (bs, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 100.6, 77.1, 71.7, 70.9, 70.6, 70.5, 69.9, 60.7, 55.0, 50.9; FAB-HRMS calcd ($M+Na^+$) 300.1172, found 300.1186.

Benzyl ether 20. To a solution of **19** (0.25 g, 0.9 mmol) in dry MeOH (10 mL) was added di-*n*-butyl tin oxide (0.25 g, 0.99 mmol) at room temperature. The reaction mixture was heated at 50 °C for 4 h and then allowed to cool to room temperature. The solvent was removed *in vacuo* to give an oil which was azeotroped with benzene (2 x 10 mL) and dried over P_2O_5 for 5 h. To the tin acetal in dry DMF (15 mL) was added benzyl bromide (0.12 mL, 0.99 mmol) and CsF (0.15 g, 0.99 mmol) at room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 40% ethyl acetate in hexane) to give **20** as a colorless oil (0.30 g, 93%). **20**: R_f = 0.4 (silica, 60% ethyl acetate in hexane); IR (thin film) ν_{max} 3448, 2914, 2104, 1453, 1366, 1302,1196, 1124, 1063 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.31 (m, 5 H, Ar), 4.75 (d, J = 2.0 Hz, 1 H, H-1), 4.69 (s, 2 H, $PhCH_2$), 3.98 (dd, J = 3.5, 2.0 Hz, 1 H, H-2), 3.80-3.67 (m, 5 H), 3.65-3.61 (m, 1 H), 3.56 (s, 3 H, OCH_3), 3.53 (t, J = 9.5 Hz, 1 H), 3.47-3.42 (m, 1 H), 3.38 (dd, J = 6.0, 3.5 Hz, 1 H, H-4), 3.36 (s, 3 H, OCH_3), 1.58 (bs, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0, 128.5, 127.9, 127.7, 100.2, 79.8, 75.7, 72.0, 71.0, 70.6, 70.3, 68.3, 60.8, 54.9, 50.9; FAB-HRMS calcd (M+Cs$^+$) 500.0798, found 500.0783.

Fluoride 21ab. To a solution of **20** (0.27 g, 0.7 mmol) in dry CH_2Cl_2 (8 mL) was added diethylaminosulfur trifluoride (0.29 mL, 2.1 mmol) at room temperature. After heating at 50 °C for 4 h the reaction mixture was allowed to cool to room temperature and then was poured into ice water (20 mL) and dichloromethane (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic fractions were combined and washed with an aqueous saturated solution of sodium bicarbonate (20 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 30% ethyl acetate in hexane) to give **21** as a colorless oil (0.16 g, 63%, mixture of anomers *ca.* 3:2, β:α). **21ab**: R_f = 0.45 (silica, 40% ethyl acetate in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5 H, Ar), 5.69 (dd, J = 53.0, 2.5 Hz, 0.4 x 1 H, H-1, α-anomer), 5.12 (dd, J = 53.0, 6.5 Hz, 0.6 x 1 H, H-1, β-anomer), 4.78 (d, J = 11.5 Hz, 0.4 x 1 H, PhC*H*H, α-anomer), 4.88 (d, J = 11.0 Hz, 0.6 x 1 H, PhCH*H*, β-anomer), 4.82 (d, J = 11.5 Hz, 0.4 x 1 H, PhC*H*H, α-anomer), 4.85 (d, J = 11.0 Hz, 0.6 x 1 H, PhC*H*H, β-anomer), 3.80-3.30 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 138.3, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 110.4, 108.7, 105.9, 104.1, 83.2, 83.2, 83.1, 83.1, 81.6, 81.4, 81.1, 78.1, 77.9, 75.4, 75.1, 74.7, 74.7, 72.7, 72.6, 70.6, 70.4, 69.6, 69.1, 60.7, 60.6, 60.1, 59.3, 50.7; FAB-HRMS calcd (M+Na$^+$) 392.1598, found 392.1609.

Ester 22ab. A mixture of silver perchlorate (0.15 g, 0.75 mmol) and zirconocene dichloride (0.01 g, 0.75 mmol) was azeotroped with benzene (2 x 15 mL) and dried under high vacuum. To the silver perchlorate/zirconocene dichloride mixture was added benzene (10 mL) and heat-activated 4 Å molecular sieves (0.05 g). After 10 min, a solution of **21** (0.05 g, 0.15 mmol) and ethyl glycolate (0.03 mL, 0.3 mmol) in benzene (5 mL) was added via canula. The reaction mixture was stirred at room temperature for 4 h. The solution was then filtered through a pad of celite and the solid was rinsed with dichloromethane (2 x 10 mL). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 40% ethyl acetate in hexane) to give **22ab** as a colorless oil (0.036 g, 55%, *ca.* 3:2, α:β). **22ab**: R_f = 0.40 (silica, 50% ethyl acetate in hexane); IR (thin film) ν_{max} 2920, 2104, 1753, 1451, 1381, 1285, 1207, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5 H, Ar), 5.20 (d, J = 3.5 Hz, 1 H), 4.92 (d, J = 11.0 Hz, 0.4 x 1 H, PhC*H*H, β-anomer), 4.88 (d, *J* = 11.5 Hz, 0.6 × 1 H, PhC*H*H, α-anomer), 4.77 (d, *J* = 11.5 Hz, 0.6 × 1 H, PhCH*H*, α-anomer), 4.76 (d, *J* = 11.0 Hz, 0.4 × 1H, PhCH*H* , β-anomer), 4.37 (d, *J* = 5.5 Hz, 1 H), 4.40-4.15 (m, 4 H), 3.85 (t, *J* = 9.5 Hz, 2 H, CH_2), 3.75-3.61 (m, 5 H), 3.64 (s, 0.4 × 3 H, OCH_3), 3.59 (s, 0.6 × 3 H, OCH_3), 3.55 (s, 0.6 × 3 H, OCH_3), 3.54 (s, 0.4 × 3 H, OCH_3), 3.50-3.15 (m, 3 H), 1.29-1.26 (m, 3 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 169.5, 138.9, 138.6, 128.3, 128.2, 127.9, 127.9, 127.6, 127.5, 103.0, 95.5, 84.3, 83.6, 81.9, 81.3, 78.9, 78.8, 75.4, 75.4, 75.3, 74.9, 70.7, 70.6, 70.4, 70.0, 69.8, 60.9, 60.9, 60.7, 60.6, 60.4, 58.6, 50.7, 14.1, 14.1; FAB-HRMS calcd (M+Cs$^+$) 580.1165, found 586.1150.

Amine 23ab. To a solution of **22** (0.057 g, 0.13 mmol) in THF:H_2O (10 mL:0.05 mL) was added Ph_3P (0.066 g, 0.26 mmol) at room temperature. The reaction mixture was heated at 65 °C for 4 h. The solvent was removed *in vacuo* to give a white solid, which after preparative thin layer chromatography (silica, dichloromethane:methanol:acetic acid, 10:1:0.5) gave **23ab** as a yellowish oil (0.046 g, 85%, *ca.* 3:2, α:β). **23ab**: R_f = 0.31 (silica,CH_2Cl_2:MeOH: AcOH, 10:1:0.5); IR (thin film) ν_{max} 3380, 2923, 1752, 1678, 1449, 1094 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5 H, Ar), 5.19 (d, *J* = 3.5 Hz, 1 H, H-1), 4.93-4.71 (m, 5 H), 4.37-4.11 (m, 7 H), 3.84 (t, *J* = 9.0 Hz, 2 H), 3.70-3.12 (m, 3 H), 3.64 (s, 0.4 × 3 H, OCH_3), 3.59 (s, 0.6 × 3 H, OCH_3), 3.54 (s, 0.3 × 3 H, OCH_3), 3.53 (s, 0.6 × 3 H, OCH_3), 2.02 (bs, 2 H, NH_2), 1.29-1.26 (m, 3 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 138.9, 138.7, 128.4, 128.3, 127.9, 127.6, 127.5, 103.0, 95.5, 84.6, 84.3, 83.7, 83.5, 81.8, 81.7, 81.4, 79.2, 78.9, 75.5, 75.4, 74.8, 70.7, 69.7, 69.2, 65.9, 62.9, 61.0, 60.9, 60.8, 60.7, 60.5, 58.6, 58.5, 14.2, 14.1; FAB-HRMS calcd (M+Cs$^+$) 560.1260, found 560.1278.

Compounds 4 and 5. To a solution of **23** (0.046 g, 0.11 mmol) in THF:H_2O (4 mL:0.5 mL) was added LiOH•H_2O (0.01g, 0.22 mmol) at room temperature. After stirring for 4 h, the reaction mixture was acidified with acetic acid and the solvent was removed *in vacuo* to afford the crude acid **24**. To a solution of the crude acid **24** in DMF (5 mL) was added *N*,*N*-diisopropylethylamine (0.02 mL, 0.12 mmol) and 1*H*-pyrazole-1-carboxamidine•HCl (0.018 g, 0.12 mmol) at room temperature. After stirring at room temperature for 16 h, the solvent was removed *in vacuo* to give an oil, which after RP-HPLC (C-18) gave **4** (0.023 g, 47%) and **5** (0.016 g, 33%) as foams. **4**: R_t = 18.76 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^{1}H NMR (500 MHz, D_2O): δ 7.40-7.36 (m, 5 H, Ar), 5.13 (d, *J* = 3.5 Hz, 1 H, H-1), 4.23 (s, 2 H), 3.8 (t, *J* = 9.5 Hz, 1 H), 3.75-3.73 (m, 1 H), 3.67-3.58 (m, 5 H), 3.48 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.36-3.30 (m, 4 H), 3.25 (t, *J* = 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O): δ 169.0, 153.0, 133.1, 125.1, 124.7, 124.5, 91.8, 76.6, 76.3, 74.7, 71.7, 66.0, 65.4, 64.7, 56.3, 54.4, 37.1; Electrospray mass spectrum calcd (M+H$^+$) 442, found 442. **5**: R_t = 20.5 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^{1}H NMR (500 MHz, D_2O): δ 7.33-7.26 (m, 5 H, Ar), 4.38 (d, *J* = 8.0 Hz, 1 H, H-1), 4.15 (AB system, *J* = 16.5 Hz, 2 H), 3.65-3.46 (m, 6 H), 3.47 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.39-3.33 (m, 2 H), 3.28-3.22 (m, 2 H), 3.17 (t, *J* = 9.5 Hz, 1 H), 3.01 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O): δ 176.4, 159.1, 133.1, 125.1, 124.7, 124.6, 97.9, 78.9, 78.7, 74.9, 71.6, 69.6, 65.6, 64.6, 56.2, 56.2, 37.2; Electrospray mass spectrum calcd (M+H$^+$) 442, found 442.

*Synthesis of Compounds **6** and **7***

Fluoride. Prepared similarly as fluoride **17** (*ca.* 3:2, β:α): R_f = 0.43 (silica, 20% ethyl acetate in hexane; IR (thin film) ν_{max} 2933, 2097, 1454, 1359, 1300, 1263, 1205, 1161, 1105, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5 H, Ar), 5.69 (dd, *J* = 53.2, 2.5 Hz, 0.4 × 1 H, H-1), 5.12 (dd, *J* = 53.5, 6.5 Hz, 0.6 × 1 H, H-1), 4.88 (d, *J* = 11.0 Hz, 0.6 × 1 H, PhC*H*H), 4.85 (d, *J* = 11.0 Hz, 0.4 × 1 H, PhC*H*H), 4.81 (d, J =11.0 Hz, 0.4 × 1 H, PhCH*H*), 4.77 (d, J = 11.0 Hz, 0.6 × 1 H, PhC*H*H), 4.18-4.13 (m, 2 H), 4.05-4.02 (m, 2 H), 3.80-3.20 (m, 12 H), 1.96-1.92 (m, 0.6 × 2 H, CH_2), 1.89-1.85 (m, 0.4 × 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 138.3, 128.4, 127.9, 127.9, 127.7, 127.7, 110.4, 108.7, 105.9, 104.1, 83.4, 83.3, 83.2, 81.6, 81.5, 81.1, 78.5, 78.2, 75.6, 75.1, 74.6, 74.6, 72.6, 72.6, 70.6, 69.3, 68.9, 68.2, 68.1, 60.8, 60.6, 60.2, 59.4, 59.0, 48.3, 48.3, 47.6, 29.1, 29.0, 28.9; FAB-HRMS calcd ($M+Cs^+$) 516.0911, found 516.0924.

Ester. Prepared similarly as ester **18** (*ca.* 3:2, α:β). R_f = 0.38 (silica, 35% ethyl acetate in hexane); IR (thin film) ν_{max} 2924, 2096, 1754, 1738, 1454, 1360, 1263, 1206, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.27 (m, 5 H, Ar), 5.20 (d, *J* = 3.5 Hz, 0.6 × 1 H, H-1), 4.93 (d, *J* = 11.0 Hz, 0.6 × 1 H, OC*H*HCO$_2$CH$_2$CH$_3$), 4.89 (d, *J* = 11.0 Hz, 0.4 × 1 H, OC*H*HCO$_2$CH$_2$CH$_3$), 4.89-4.87 (m, 1 H), 4.77 (d, *J* = 13.0 Hz, 0.4 × 1 H, OCH*H*CO$_2$CH$_2$CH$_3$), 4.76 (d, *J* = 11.0 Hz, 0.6 × 1 H, OCH*H*CO$_2$CH$_2$CH$_3$), 4.78 (m, 1 H), 4.37 (d, *J* = 8.0 Hz, 0.4 × 1 H, H-1), 4.35 (d, *J* = 16.0 Hz, 0.4 × 1 H, PhC*H*H), 4.3 (d, *J* = 16.5 Hz, 0.4 × 1 H, 1 H, PhCH*H*), 4.26 (d, *J* = 16.0 Hz, 0.4 × 1 H, PhC*H*H), 4.25-4.21 (m, 1 H), 4.17 (d, *J* = 16.5 Hz, 0.6 × 1 H, PhCH*H*), 3.86-3.78 (m, 2 H), 3.66 (s, 0.4 × 3 H, OCH_3), 3.61 (s, 0.6 × 3 H, OCH_3), 3.55 (s, 0.4 × 3 H, OCH_3), 3.53 (s, 0.4 × 3 H, OCH_3), 3.71-3.53 (m, 6 H), 1.93-1.82 (m, 2 H, CH_2), 1.30-1.26 (m, 3 H, CO$_2$CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 169.7, 138.2, 138.1, 128.3, 128.0, 127.6, 127.6, 103.0, 95.5, 84.4, 83.7, 81.8, 81.4, 79.2, 78.9, 75.6, 75.4, 74.8, 70.7, 69.5, 68.1, 65.8, 62.9, 61.0, 60.8, 58.7, 48.4, 29.1; FAB-HRMS calcd ($M+Cs^+$) 600.1322, found 600.1350.

Amine. Prepared similarly as amine **19** (*ca.* 3:2, α:β). R_f = 0.32 (silica, CH_2Cl_2:MeOH:AcOH, 8:1:0.5); IR (thin film) ν_{max} 3382, 2920, 1750, 1652, 1557, 1406, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5 H, Ar), 5.14 (d, *J* = 3.5 Hz, 0.6 × 1 H, H-1), 4.89 (d, *J* = 11.0 Hz, 0.6 × 1 H, OC*H*HCO$_2$CH$_2$CH$_3$), 4.86 (d, *J* = 11.0 Hz, 0.4 × 1 H, OC*H*HCO$_2$CH$_2$CH$_3$), 4.88-4.81 (m, 2 H), 4.75 (d, *J* = 11.0 Hz, 0.4 × 1 H, OCH*H*CO$_2$CH$_2$CH$_3$), 4.73 (d, *J* = 11.0 Hz, 0.6 × 1 H, OCH*H*CO$_2$CH$_2$CH$_3$), 4.35 (d, *J* = 8.0 Hz, 0.4 × 1 H, H-1), 4.28 (d, *J* = 14.0 Hz, 0.4 × 1 H, PhC*H*H), 4.26 (d, *J* = 17.0 Hz, 0.6 × 1 H, PhC*H*H), 4.23-4.17 (m, 1 H), 4.17 (d, *J* = 14.0 Hz, 0.4 × 1 H, PhCH*H*), 4.15 (d, *J* = 17.0 Hz, 0.6 × 1 H, PhCH*H*), 3.83-3.76 (m, 2 H), 3.72-3.10 (m, 6 H), 3.61 (s, 0.4 × 3 H, OCH_3), 3.57 (s, 0.6 × 3 H, OCH_3), 3.50 (s, 0.6 × 3 H, OCH_3), 3.49 (s, 0.4 × 3 H, OCH_3), 1.94-1.92 (m, 2 H, CH_2), 1.28-1.24 (m, 3 H, CO$_2$CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 138.8, 138.5, 128.2, 127.9, 127.6, 127.5, 103.3, 95.8, 84.5, 84.1, 81.8, 81.2, 78.9, 75.4, 75.3, 74.4, 70.4, 69.9, 69.5, 69.4, 66.4, 63.4, 61.1, 60.6, 60.5, 58.7, 38.7, 26.9, 14.1; FAB-HRMS calcd ($M+H^+$) 442.2441, found 442.2455.

*Compound **6**.* Prepared similarly as compound **4**: R_t = 20.4 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^{1}H NMR (500 MHz, D_2O): δ 7.41-7.34 (m, 5 H, Ar), 5.12 (d, *J* =3.5 Hz, 1 H, H-1), 4.23 (s, 2 H, $PhCH_2$), 3.80 (t, *J* =9.5 Hz, 1 H, H-3), 3.74-3.72 (m, 1 H), 3.64-3.62 (m, 2 H), 3.57-3.51 (m, 2 H), 3.47 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.32 (dd, *J* = 9.5, 3.5 Hz, 1 H, H-2), 3.24-3.20 (m, 3 H), 1.82-1.80 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, D_2O): δ 169.5, 159.1, 133.2, 125.0, 124.7, 124.5, 91.8, 76.6, 76.3, 74.9, 71.6, 66.0, 64.6, 63.9, 60.0, 56.2, 54.4, 34.1, 23.8; FAB-HRMS calcd ($M+H^+$) 456.2346, found 456.2360.

Compound 7. Prepared similarly as compound **5**: R_t = 22.1 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^1H NMR (500 MHz, D_2O): δ 7.33-7.26 (m, 5 H, Ar), 4.39 (d, *J* = 8.0 Hz, 1 H, H-1), 4.27 (s, 2 H, OCH_2CO_2H), 3.62-3.60 (m, 1 H), 3.53-3.45 (m, 4 H), 3.47 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.36 (m, 2 H), 3.16-3.11 (m, 3 H), 3.02 (t, *J* = 9.0 Hz, 1 H), 1.74-1.69 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, D_2O): δ 169.4, 152.8, 133.0, 125.1, 124.7, 124.6, 98.0, 78.9, 78.6, 76.7, 75.1, 69.7, 64.6, 64.1, 60.2, 56.3, 34.2, 23.8; FAB-HRMS calcd ($M+H^+$) 456.2346, found 456.2357.

Synthesis of Compounds 8 and 9

Thioglycoside 26. To a solution of **25** (10.4 g, 0.033 mol) in dichloromethane (150 mL) at 0 °C was added thiophenol (3.52 mL, 0.036 mol) and tin(IV) chloride (2.70 mL, 0.0231 mol). The reaction mixture was stirred at 0 °C for 4 h and then diluted with ether (150 mL). The mixture was then poured into a separatory funnel and diluted with 2% aqueous hydrochloric acid (200 mL). The layers were separated and the organic fraction was washed with water (200 mL), aqueous saturated solution of sodium bicarbonate (200 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 80% ether in petroleum ether) gave **26** as a colorless oil (9.10 g, 75%). **26**: R_f = 0.28 (silica, 80% ether in petroleum ether); IR (thin film) ν_{max} 3058, 3020, 2938, 2859, 1754, 1584, 1479, 1439, 1371, 1244, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 2.0 Hz, 1 H, Ar), 7.46 (d, *J* = 2.0 Hz, 1 H, Ar), 7.30-7.26 (m, 3 H, Ar), 5.25 (m, 1 H, H-4), 5.24 (dd, *J* = 8.5, 8.0 Hz, 1 H, H-2), 5.08 (dd, *J* = 8.5, 3.5 Hz, 1 H, H-3), 4.8 (d, *J* = 8.0 Hz, 1 H, H-1), 4.13 (dd, *J* = 13.0, 4.0 Hz, 1 H, H-5), 3.66 (dd, *J* = 13.0, 2.0 Hz, 1 H, H-5′), 2.07 (s, 6 H, $OC(O)CH_3$), 2.02 (s,3 H, $OC(O)CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.7, 169.2, 133.1, 132.0, 128.8, 127.8, 86.5, 70.3, 68.2, 67.4, 65.2, 20.7, 20.7, 20.5; FAB-HRMS calcd ($M+Cs^+$) 500.9984, found 500.9968.

Triol 27. To a solution of **26** (9.10 g, 0.025 mol) in dry MeOH (200 mL) at room temperature was added anhydrous potassium carbonate (1.24 g, 0.0125 mol). The reaction mixture was stirred at room temperature for 4 h and then filtered through a pad of celite. The solvent was removed *in vacuo* to give **27** as a colorless oil (4.52 g, 80%). **27**: R_f = 0.32 (silica, 10% methanol in dichloromethane); IR (thin film) ν_{max} 3415, 3058, 2929, 2834, 1583, 1489, 1479, 1242, 1120, 1081 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.34-7.32 (m, 2 H, Ar), 7.12-7.05 (m, 3 H, Ar), 4.47 (d, *J* = 8.0 Hz, 1 H, H-1), 3.79 (dd, *J* = 8.0, 3.5 Hz, 1 H, H-3), 3.71 (ddd, *J* = 5.0, 3.5, 2.0 Hz, 1 H, H-4), 3.51 (t, *J* = 8.0 Hz, 1 H, H-2), 3.42-3.38 (m, 2 H, H-5, H-5′); ^{13}C NMR (125 MHz, CD_3OD): δ 136.2, 132.3, 129.9, 128.1, 90.4, 75.1, 71.7, 69.6, 69.6; FAB-HRMS calcd ($M+K^+$) 265.0301, found 265.0297.

Acetonide 28. To a solution of **27** (9.11 g, 0.037 mol) in acetone (80 mL) at 0 °C was added 2,2-dimethoxypropane (13.9 mL, 0.11 mol) and $TsOH•H_2O$ (0.72 g, 1.85 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. After 2 h, triethylamine (0.8 mL, 5.55 mmol) was added and the solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 5% methanol in dichloromethane) gave **28** as a colorless oil (8.76, 84%). **28**: R_f = 0.36 (silica, 80% ether in petroleum ether); IR (thin film) ν_{max} 3382, 3059, 2920, 2851, 1737, 1658, 1643, 1583, 1478, 1439, 1271, 1242, 1081 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2 H, Ar), 7.32-7.29 (m, 3 H, Ar), 4.52 (d, *J* = 9.5 Hz, 1 H, H-1), 4.29 (dd, *J* = 13.0, 2.5 Hz, H-5), 4.25 (ddd, *J* = 8.0, 6.5, 2.5 Hz, 1 H, H-4), 4.10 (t, *J* = 6.5 Hz, 1 H, H-3), 3.80 (dd, *J* = 13.0, 3.0 Hz, 1 H, H-5′), 3.64 (dd, *J* = 9.5, 6.5 Hz, 1 H, H-2), 2.76 (bs, 1 H, OH), 1.46 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.6, 132.2, 129.0, 128.0, 88.1, 78.1, 72.9, 71.4, 65.7, 27.9, 26.1; FAB-HRMS calcd ($M+Na^+$) 305.0824, found 305.0812.

Methyl ether ***29***. To a solution of **28** (2.58 g, 9.15 mmol) in dry THF (60 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.48 g, 11.9 mmol). After stirring for 1 h, imidazole (5.0 mg), tetra-*n*-butylammonium iodide (0.68 g, 1.83 mmol) and methyl iodide (0.85 mL, 13.72 mmol) were added and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was then diluted with aqueous saturated solution of ammonium chloride (15 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic fractions were washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which after flash chromatography (silica, 40% ether in petroleum ether) gave **29** as a colorless oil (2.62 g, 97%). **29**: R_f = 0.41 (silica, 60% ether in petroleum ether); IR (thin film) ν_{max} 3058, 2985, 2933, 2383, 1584, 1479, 1455, 1381, 1242, 1219, 1165, 1124, 1084, 1002 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2 H, Ar), 7.31-7.24 (m, 3 H, Ar), 4.79 (d, *J* = 7.5 Hz, 1 H, H-1), 4.28 (dd, *J* =13.0, 4.5 Hz, 1 H, H-5), 4.20-4.16 (m, 2 H, H-3, H-4), 3.76 (dd, *J* = 13.0, 4.0 Hz, 1 H, H-5′), 3.53 (s, 3 H, OCH_3), 3.38 (dd, *J* = 7.5, 6.0 Hz, 1 H, H-2), 1.53 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.0, 131.8, 128.8, 127.4, 85.9, 80.2, 77.5, 72.2, 64.2, 59.3, 27.8, 26.1; FAB-HRMS calcd ($M+Na^+$) 319.0980, found 319.0994.

Diol ***30***. To a solution of **29** (7.9 g, 0.27 mol) in dry tetrahydrofuran (40 mL) at room temperature was added 3 M aqueous hydrochloric acid (6.5 mL) and glacial acetic acid (29 mL). After stirring for 3 h, the reaction mixture was poured into an aqueous saturated solution of potassium carbonate (300 mL) and ethyl acetate (1.5 L). The mixture was stirred for 30 min and then the two layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 500 mL). The organic fractions were combined and washed with brine (500 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **30** as a colorless oil (6.42 g, 94%). **30**: R_f = 0.11 (silica, 80% ether in petroleum ether); IR (thin film) ν_{max} 3342, 3059, 2908, 2870, 1659, 1643, 1583, 1477, 1438, 1371, 1344, 1319, 1242, 1147, 1085, 1025, 992 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 7.39-7.37 (m, 2 H, Ar), 7.19-7.12 (m, 3 H, Ar), 4.61 (d, *J* = 7.5 Hz, 1 H, H-1), 3.86 (dd, *J* = 12.0, 4.5 Hz, 1 H, H-5), 3.74-3.72 (m, 1 H, H-4), 3.56 (dd, *J* = 7.5, 3.0 Hz, 1 H, H-2), 3.42 (s, 3 H, OCH_3), 3.41 (dd, *J* = 12.0, 2.5 Hz, 1 H, H-5′), 3.28 (dd, *J* = 3.0, 3.0 Hz, 1 H, H-3); ^{13}C NMR (125 MHz, CD_3OD): δ 135.2, 132.1, 129.9, 128.1, 88.4, 82.0, 74.0, 69.2, 68.5, 60.5; FAB-HRMS calcd ($M+Na^+$) 279.0667, found 279.0659.

Benzyl ether 31. To a solution of **30** (0.49 g, 1.9 mmol) in dry toluene (10 mL) at room temperature was added di-*n*-butyltin oxide (0.7 g, 2.0 mmol). The reaction flask was equipped with a Dean-Stark apparatus and the reaction mixture was heated to reflux. After 2 h, the Dean-Stark apparatus was removed and the reaction mixture was allowed to cool to room temperature. To the reaction mixture was added tetra-*n*-butylammonium bromide (0.60 g, 1.9 mmol) and benzyl bromide (0.23 mL, 1.9 mmol). The reaction mixture was then heated to 80 °C for 20 h and the solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 80% ether in petroleum ether) gave **31** plus its regioisomer as a colorless oil (0.57 g, 90%, *ca.* 1:1 ratio). **31**: R_f = 0.32 (silica, 80% ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.52 (m, 4 H, Ar), 7.43-7.23 (m, 16 H, Ar), 4.94 (d, *J* = 5.5 Hz, 0.5 × 1 H, H-1), 4.92 (d, *J* = 5.0 Hz, 0.5 × 1 H, H-1), 4.82 (d, *J* = 11.5 Hz, 0.5 × 1 H, PhC*H*H), 4.70 (d, *J* = 11.5 Hz, 0.5 × 1 H, PhC*H*H), 4.65 (d, *J* = 11.0 Hz, 0.5 × 1 H, PhCH*H*), 4.58 (d, *J* = 11.5 Hz, 0.5 × 1 H, PhCH*H*), 4.25 (dd, J = 12.0, 6.0 Hz, 0.5 × 1 H, H-5), 4.11 (dd, *J* = 12.0, 6.5 Hz, 0.5 × 1 H, H-5), 4.00-3.97 (m, 1 H, H-5), 3.92 (dd, *J* = 9.0, 6.0 Hz, 1 H, H-4), 3.84-3.82 (m, 0.5 × 1 H, H-2), 3.67 (dd, *J* = 5.5, 3.5 Hz, 0.5 × 1 H, H-2), 3.61 (dd, *J* = 3.5, 3.5 Hz, 1 H, H-3), 3.56-3.50 (m, 4 H), 3.53 (s, 0.5 × 3 H, OCH_3), 3.52 (s, 0.5 × 3 H, OCH_3), 2.56 (d, *J* = 5.5 Hz, 0.5 × 1 H, OH), 2.37 (d, *J* = 7.0 Hz, 0.5 × 1 H, OH).

Acetate 32. To a solution of **31** plus its regioisomer (0.059 g, 1.7 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (2.4 mL, 17.0 mmol), acetic anhydride (0.96 mL, 10.0 mmol) and 4-dimethylaminopyridine (0.02 g, 0.17 mmol). The reaction mixture was stirred for 12 h at room temperature and the reaction mixture was then diluted with dichloromethane (20 mL) and poured into a separation funnel containing water (20 mL). The layers were separated and the organic fraction was washed with aqueous saturated solution of sodium bicarbonate (20 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 35% ether in hexane) gave **32** as a colorless oil (0.26 g, 40%). **32**: R_f = 0.37 (silica, 40% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.54 (m, 2 H, Ar), 7.36-7.27 (m, 2 H, Ar), 5.28-5.26 (m, 1 H, H-4), 4.70 (d, *J* = 12.0 Hz, 1 H, PhC*H*H), 4.69 (d, *J* = 7.5 Hz, 1 H, H-1), 4.62 (d, *J* = 12.0 Hz, 1 H, PhCH*H*), 4.13 (dd, *J* = 12.5, 4.0 Hz, 1 H, H-5), 3.64-3.62 (m, 1 H), 3.57 (s, 3 H, OCH_3), 3.60-3.55 (m, 1 H), 3.45-3.30 (m, 1 H, H-3), 2.12 (s, 3 H, $OC(O)CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 137.6, 134.1, 131.6, 128.7, 128.3, 127.8, 127.3, 87.4, 78.7, 72.0, 67.6, 65.5, 60.5, 21.0; FAB-HRMS calcd ($M+Na^+$) 411.1242, found 411.1257.

Alcohol 33 and Ester 34. To a solution of **32** (1.1 g, 2.8 mmol) in dry tetrahydrofuran (20 mL) at room temperature was added dry methanol (20 mL) and anhydrous potassium carbonate (0.08 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through a pad of celite and the solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 60% ether in hexane) gave **33** as a colorless oil (0.92 g, 95%). **33**: R_f = 0.29 (silica, 60% ether in hexane). To a solution of **33** (0.25 g, 0.7 mmol) in dry tetrahydrofuran (10 mL) at 0 °C was addded NaH (60% dispersion in mineral oil, (0.04 g, 1.05 mmol). After stirring at room temperature for 30 min, ethyl bromoacetate (0.1 mL, 0.91 mmol) was added and the reaction mixture was heated to 40 °C for 12 h. The reaction mixture was cooled to room temperature and then water (10 mL) and ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with ether (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a crude oil, which after flash chromatography (silica, 60% ether in hexane) gave **34** as a yellowish oil (0.19 g, 61%). **34**: R_f = 0.32 (silica, 60% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.52 (m, 2 H, Ar), 7.45-7.43 (m, 2 H, Ar), 7.37-7.34 (m, 2 H, Ar), 7.30-7.23 (m, 4 H, Ar), 4.86 (d, *J* = 7.5 Hz, 1 H, H-1), 4.80 (AB-system, *J* = 14 Hz, 2 H, $PhCH_2$), 4.39-4.29 (m, 1 H), 4.25-4.15 (m, 5 H), 3.90-3.86 (m, 1 H), 3.74-3.71 (m, 1 H), 3.67 (t, *J* = 6.0 Hz, 1 H), 3.50 (s, 3 H, OCH_3), 3.52-3.50 (m, 1 H), 1.29 (t, *J* = 6.0 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 138.0, 135.4, 131.1, 128.7, 128.3, 127.9, 127.7, 86.71, 79.4, 78.1, 73.9, 72.5, 68.1, 66.8, 63.1, 61.0, 59.6, 14.0; FAB-HRMS calcd ($M+Cs^+$) 565.0661, found 565.0669.

*Fluoride **35ab**.* To a solution of **34** (0.06 g, 0.14 mmol) in dry dichloromethane (10 mL) at -15 °C was added diethylaminosulfur trifluoride (28 mL, 0.21 mmol) and *N*-bromosuccinimide (0.03 g, 0.18 mmol). After 20 min, the reaction mixture was poured into an aqueous saturated solution of sodium bicarbonate (6 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The organic fractions were combined and washed with brine (15 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 60% ether in hexane) gave **35** as an anomeric mixture (0.03 g, 63%, *ca.* 5:1, β:α). **35ab**: R_f = 0.40 (silica, 50% ethyl acetate in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5 H, Ar), 5.74 (dd, *J* = 56.0, 2.5 Hz, 0.84 x 1 H, H-1), 5.27 (dd, *J* = 51.0, 3.0 Hz, 0.16 x 1 H, H-1), 4.82-4.72 (m, 2 H, OCH_2CO_2Et), 4.36-4.33 (m, 2 H, $PhCH_2$), 4.24-4.16 (m, 4 H), 4.05-4.03 (m, 1 H), 3.89-3.78 (m, 3 H), 3.60 (s, 2 H), 1.30-1.25 (m, 3 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.3, 138.0, 138.0, 128.4, 128.3, 127.7, 127.7, 126.6, 126.6, 107.7, 107.0, 106.0, 105.2, 78.0, 77.8, 77.6, 77.4, 75.5, 74.5, 72.9, 72.8, 68.1, 67.2, 63.2, 63.2, 60.8, 59.2, 14.1, 14.1; FAB-HRMS calcd ($M+Na^+$) 365.1376, found 365.1365.

*Azide **36ab**.* A mixture of silver perchlorate (0.38 g, 1.8 mmol) and tin(II) chloride (0.34 g, 1.8 mmol) was azeotroped with benzene (2 x 10 mL) and dried under high vacuum. To the silver perchlorate/tin(II) chloride solid at -20 °C was added tetrahydrofuran (10 mL) and heat-activated 4 Å molecular sieves (0.39 g). After 10 min, a solution of **35** (0.31 g, 0.9 mmol) and 4-azido-*n*-butanol (0.15 g, 1.3 mmol) in tetrahydrofuran (5 mL) was added via canula. The reaction mixture was stirred at room temperature for 2 h and then diluted with ether and filtered through a pad of celite. The filtrate was washed with aqueous saturated solution of sodium bicarbonate (2 x 80 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 50% ethyl acetate in hexane) to give **36** as an anomeric mixture (0.33 g, 83%, *ca.* 2:1, β:α). **36ab**: R_f = 0.43 (silica, 50% ethyl acetate in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5 H, Ar), 4.96 (d, *J* = 3.0 Hz, 0.33 x 1 H, H-1), 4.81-4.72 (m, 3 H), 4.38-4.26 (m, 5 H), 4.23-4.12 (m, 8 H), 3.92-3.60 (m, 6 H), 3.58 (s, 0.66 x 3 H, OCH_3), 3.54 (s, 0.33 x 3 H, OCH_3), 3.60-3.47 (m, 2 H), 3.35-3.28 (m, 2 H), 1.90-1.67 (m, 4 H, CH_2CH_2), 1.30-1.25 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 138.4, 138.3, 128.3, 127.6, 127.5, 127.5, 103.3, 97.4, 80.4, 79.6, 78.1, 76.1, 74.4, 73.0, 72.6, 68.6, 68.4, 67.3, 63.2, 61.1, 61.0, 60.6, 59.3, 44.8, 44.7, 29.4, 29.3, 26.9, 26.8, 14.1, 14.1; FAB-HRMS calcd ($M+Cs^+$) 570.1216, found 570.1231.

*Amine **37ab**.* To a solution of **36** (0.33 g, 0.75 mmol) in THF:H_2O (20 mL:0.21 mL) was added triphenylphosphine (0.52 g, 1.95 mmol) at room temperature and the reaction mixture was heated at 65 °C for 5 h. The solvent was removed *in vacuo* to give a white solid, which after flash chromatography (silica, 8:1:0.5, CH_2Cl_2:MeOH:AcOH) gave **37ab** as a yellowish oil (0.25 g, 81%, *ca.* 2:1/β:α). **37ab**: R_f = 0.36 (silica, 8:1:0.5 CH_2Cl_2:MeOH:AcOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5 H, Ar), 4.95 (d, *J* = 3.0 Hz, 0.33 × 1 H, 1 H), 4.75 (bs, 2 H, OC*H*$_2$COCH$_2$CH$_3$), 4.30 (bs, 2 H, PhCH$_2$), 4.21-4.09 (m, 4 H), 3.90-3.72 (m, 3 H), 3.59-3.30 (m, 3 H), 3.56 (s, 0.66 × 1 H, 3 H, OCH$_3$), 3.53 (s, 0.33 × 1 H, 3 H, OCH$_3$), 3.01-2.88 (m, 2 H), 1.81-1.62 (m, 4 H, CH$_2$CH$_2$), 1.28-1.22 (m, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 169.5, 138.3, 138.0, 128.3, 127.7, 127.6, 103.0, 97.4, 80.4, 79.3, 77.9, 75.8, 74.5, 72.7, 68.7, 67.4, 63.1, 60.8, 59.5, 39.4, 26.5, 25.2, 14.1; FAB-HRMS calcd (M+Cs$^+$), found 544.1329.

*Compounds **8** and **9**.* To a solution of **37** (0.2 g, 0.48 mmol) in tetrahydrofuran (4.5 mL) at room temperature was added 10% aqueous LiOH solution (2.3 mL) and methanol (7.5 mL). After stirring for 4 h, the reaction mixture was acidified with acetic acid and the solvent was removed *in vacuo* to give the crude acid **38**. To a solution of the crude acid **43** in DMF (10 mL) was added *N,N*-diisopropylethylamine (0.085 mL, 0.48 mmol) and 1*H*-pyrazole-1-carboxamidine•HCl (0.07 g, 0.48 mmol) at room temperature. After stirring for 16 h, the solvent was removed *in vacuo* to give an oil, which after RP-HPLC (C-18) gave **8** (0.06 g, 29%) and **9** (0.11 g, 54%). **8**: R_t = 22 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^{1}H NMR (500 MHz, D_2O): δ 7.31-7.24 (m, 5 H, Ar), 4.98 (d, *J* = 3.5 Hz, 1 H, H-1), 4.58 (d, *J* = 11.5 Hz, 1 H, OC*H*HCO$_2$H), 4.53 (d, *J* =11.5 Hz, 1 H, OCH*H*CO$_2$H), 4.12 (d, *J* = 17.0 Hz, 1 H, PhC*H*H), 4.05 (d, *J* = 17.0 Hz, 1 H, PhCH*H*), 3.80 (bs, 1 H), 3.71-3.67 (m, 2 H), 3.56-3.53 (m, 3 H), 3.41-3.35 (m, 2 H), 3.30 (s, 3 H, OCH$_3$), 3.03-3.01 (m, 1 H), 1.50-1.48 (m, 4 H, CH$_2$CH$_2$); Electrospray mass spectrum calcd (M+H$^+$) 426, found 426. **9**: R_t = 24 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min ; ^{1}H NMR (500 MHz, D_2O): δ 7.30 (m, 5 H, Ar), 4.61 (d, *J* = 11.5 Hz, 1 H, OC*H*HCO$_2$H), 4.52 (d, *J* = 11.5 Hz, 1 H, OCH*H*CO$_2$H), 4.22 (d, *J* = 7.5 Hz, 1 H, H-1), 4.12 (d, *J* = 17.0 Hz, 1 H, PhC*H*H), 4.03 (*J* = 17.0 Hz, 1 H, PhCH*H*), 3.93 (dd, *J* =13.5, 2.5 Hz, 1 H), 3.81 (bs, 1 H), 3.75-3.73 (m, 1 H), 3.54-3.49 (m, 2 H), 3.40 (s, 3 H, OCH$_3$), 3.30 (d, *J* = 13.0 Hz, 1 H), 3.20 (dd, *J* = 9.5, 7.5 Hz, 1 H, H-2), 3.06-3.04 (m, 2 H), 1.54-1.46 (m, 4 H, CH$_2$CH$_2$); ^{13}C NMR (125 MHz, D_2O): δ 170.3, 159.0, 133.2, 124.8, 124.7, 124.5, 98.7, 75.8, 75.4, 70.4, 68.3, 65.9, 62.7, 58.8, 56.3, 36.8, 22.0, 20.8; Electrospray mass spectrum calcd (M+H$^+$) 426, found 426.

*Synthesis of Compound **10***

*Azide **40**.* To a solution of **17** (3.08 g, 0.01 mol) in dry THF (30 mL) was added NaH (60% dispersion in mineral oil, 0.64 g, 0.016 mol) at 0 °C. After 30 min at 0 °C, a solution of $TfO(CH_2)_3N_3$ (14 g, 0.05 mol) in dry THF (20 mL) was added via canula. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was quenched with the addition of saturated aqueous solution of ammonium chloride (100 mL) and stirred for 30 min. Water (60 mL) was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (3 × 75 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which after flash chromatography (silica, 20% ethyl acetate in hexane) gave **40** as a colorless oil (2.30 g, 60%). **40**: R_f = 0.67

(silica, 50 % ethyl acetate in hexane); IR (thin film) ν_{max} 2934, 2097, 1243, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.91 (s, 1 H, H-1), 4.18 (t, *J* = 6.0 Hz, 1 H, H-3), 4.10 (d, *J* = 6.0 Hz, 1 H, H-2), 3.70-3.53 (m, 5 H), 3.51 (s, 3 H, OCH_3), 3.40 (t, *J* = 6.5 Hz, 2 H, OCH_2), 3.38 (s, 3 H, OCH_3), 3.27 (dd, *J* = 6.0, 10.0 Hz, 1 H, H-4), 1.90-1.86 (m, 2 H, CH_2), 1.54 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 109.2, 98.2, 78.5, 77.7, 75.7, 70.0, 68.1, 59.1, 54.8, 48.4, 29.1, 28.3, 26.2; FAB-HRMS calcd ($M+Na^+$) 354.1641, found 354.1625.

Diol 41. To a solution of **40** (0.71 g, 0.002 mol) in THF (9.4 mL) was added acetic acid (1.2 mL) and 2 M aqueous HCl (3.7 mL) at room temperature. After stirring for 24 h, the reaction mixture was poured into a saturated aqueous potassium carbonate solution (30 mL) and ethyl acetate (120 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic fractions were combined and washed with brine (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give **41** as a colorless oil (0.52 g, 85%). **41**: R_f = 0.14 (silica, 50% ethyl acetate in hexane); IR (thin film) ν_{max} 3425, 2930, 2097, 1118, 1063 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.73 (s, 1 H, H-1), 3.91 (bs, 1 H), 3.87-3.83 (m, 1 H), 3.71-3.63 (m, 4 H), 3.60-3.55 (m, 2 H), 3.55 (s, 3 H, OCH_3), 3.42 (t, *J* = 6.5 Hz, 2 H, OCH_2), 3.36 (s, 3 H, OCH_3), 2.51 (bs, 1 H, OH), 2.38 (bs, 1 H, OH), 1.96-1.83 (m, 2 H, CH_2), ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.6, 77.4, 71.7, 70.9, 70.5, 69.7, 68.2, 59.2, 55.0, 48.4, 29.0; FAB-HRMS calcd ($M+Na^+$) 314.1328, found 314.1343.

Benzyl ether 42. To a solution of **41** (0.5 g, 0.002 mol) in dry MeOH (10 mL) was added di-*n*-butyl tin oxide (0.42 g, 0.002 mol) at room temperature. The reaction mixture was heated at 50 °C for 4 h and then allowed to cool to room temperature. The solvent was removed *in vacuo* to give an oil which was azeotroped with benzene (2 × 10 mL) and dried over P_2O_5 for 5 h. To the tin acetal in dry DMF (15 mL) was added benzyl bromide (0.26 mL, 0.003 mol) and CsF (0.3 g, 0.002 mol) at room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 30% ethyl acetate in hexane) to give **42** as a colorless oil (0.61 g, 92%).**42**: R_f = 0.32 (silica, 50% ethyl acetate in hexane); IR (thin film) ν_{max} 3450, 2919, 2096, 1125, 1062 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.36 (m, 5 H, Ar), 4.75 (d, *J* = 1.5 Hz, 1 H, H-1), 4.68 (s, 2 H, $PhCH_2$), 3.99 (ddd, *J* = 3.5, 2.5, 1.5 Hz, 1 H, H-2), 3.75-3.55 (m, 5 H), 3.54 (s, 3 H, OCH_3), 3.49 (t, *J* = 9.5 Hz, 1 H), 3.41 (dd, *J* = 7.0, 1.5 Hz, 2 H), 3.35 (s, 3 H, OCH_3), 2.42 (d, *J* = 2.5 Hz, 1 H, OH), 1.93-1.83 (m, 2 H, CH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 128.5, 127.9, 127.7, 100.2, 79.8, 75.9, 72.0, 70.8, 69.9, 68.3, 68.1, 61.1, 54.9, 48.4, 29.1; FAB-HRMS calcd ($M+Na^+$) 404.1798, found 404.1818.

Ethyl ester 43. To a solution of **42** (0.49 g, 0.0013 mol) in dry THF (20 mL) was added NaH (60% dispersion in mineral oil, 0.07 g, 0.0017 mol) at 0 °C. After 30 min, ethyl bromoacetate (0.16 ml, 0.0014 mol) was added and the solution was allowed to warm to room temperature over 14 h. The reaction mixture was diluted with aqueous saturated solution of ammonium chloride (10 mL) and stirred for 30 min. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The organic fractions were combined and washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a crude oil, which after flash chromatography (silica, 20 → 30% ethyl acetate in hexane) gave **43** as a colorless oil (0.39 g, 65%). **43**: R_f =

0.32 (silica, 30% ethyl acetate in hexane); IR (thin film) ν_{max} 2932, 2096, 1750, 1207, 1113, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5 H, Ar), 4.93 (d, *J* = 1.5 Hz, 1 H, H-1), 4.73 (d, *J* = 12.0 Hz, 1 H,OC*H*HCO$_2$Et), 4.71 (d, *J* = 12.0 Hz, 1 H,OCH*H*CO$_2$Et), 4.3 (s, 2 H, PhCH$_2$), 4.16 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 3.80-3.74 (m, 2 H), 3.70-3.54 (m, 6 H), 3.54 (s, 3 H, OCH$_3$), 3.41 (t, *J* = 6.5 Hz, 2 H), 3.35 (s, 3 H, OCH$_3$), 1.92-1.82 (m, 2 H, CH$_2$), 1.25 (t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 138.2, 128.4, 127.6, 99.5, 80.2, 76.6, 76.56, 76.6, 72.7, 71.6, 70.1, 68.6, 68.1, 60.7, 60.7, 54.8, 48.5, 29.1, 14.2; FAB-HRMS calcd ($M+Cs^+$) 600.1322, found 600.1338.

Amine ***44***. To a solution of **43** (0.25 g, 0.54 mmol) in THF:H_2O (15 mL:0.23 mL) was added Ph_3P (0.28 g, 1.08 mmol) at room temperature. The reaction mixture was heated to 65 °C for 4 h. The solvent was removed *in vacuo* to give a white solid, which after preparative thin layer chromatography (silica, CH_2Cl_2:MeOH:HOAc, 10:1:0.5) gave **44** as a colorless oil (0.19 g, 83%). **44**: R_f = 0.3 (silica, CH_2Cl_2:MeOH:AcOH, 10:1:0.5); IR (thin film) ν_{max} 2931, 1749, 1574, 1403, 1132, 1066, 783 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5 H, Ar), 5.4 (bs, 2 H, NH$_2$), 4.92 (s, 1 H, H-1), 4.69 (d, *J* = 12.0 Hz, 1 H,OC*H*HCO$_2$Et), 4.66 (d, *J* = 12.0 Hz, 1 H,OCH*H*CO$_2$Et), 4.47 (d, *J* = 15.5 Hz, 1 H,PhC*H*H), 4.37 (d, *J* = 15.5 Hz, 1 H,PhCH*H*), 4.16-4.12 (m, 2 H), 3.93-3.88 (m, 2 H), 3.76-3.70 (m, 3 H), 3.61-3.48 (m, 3 H), 3.53 (s, 3 H, OCH$_3$), 3.34 (s, 3 H, OCH$_3$), 1.75-1.64 (m, 2 H, CH$_2$), 1.24-1.22 (t, *J* = 7.5 Hz, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 137.9, 128.3, 127.6, 99.5, 79.9, 76.3, 75.8, 72.8, 71.3, 70.8, 69.1, 68.9, 61.2, 61.0, 55.1, 39.1, 26.8, 14.0; FAB-HRMS calcd ($M+Cs^+$) 574.1417, found 574.1519.

Compound ***10***. To a solution of **44** (0.19 g, 0.43 mmol) in THF:H_2O (8 mL:1 mL) was added LiOH•H_2O (0.036 g, 0.86 mmol) at room temperature. After stirring for 4 h, the reaction mixture was acidified with acetic acid and the solvent was removed *in vacuo* to afford the crude acid **45**. To a solution of crude acid **45** in DMF (10 mL) was added diisopropylethylamine (0.06 mL, 0.47 mmol) and 1*H*-pyrazole-1-carboxamidine•HCl (0.07 g, 0.47 mmol) at room temperature. After stirring at room temperature for 16 h, the solvent was removed *in vacuo* to give an oil, which after RP-HPLC (C-18) gave **10** as a foam (0.15 g, 80%). **10**: R_t = 22 min [90:10 → 40:60 H_2O:CH_3CN(0.05% TFA)]; ^1H NMR (500 MHz, D_2O): δ 7.30-7.22 (m, 5 H, Ar), 4.75 (d, *J* = 1.5 Hz, 1 H, H-1), 4.58 (d, *J* = 11.5 Hz, 1 H,OC*H*HCO$_2$H), 4.51 (d, *J* = 11.5 Hz, 1 H, OCH*H*CO$_2$H), 4.10 (s, 2 H, PhCH$_2$), 3.75-3.73 (m, 1 H), 3.64 (dd, *J* = 9.5, 3.0 Hz, 1 H, H-3), 3.55 (d, *J* = 3.5 Hz, 2 H), 3.50-3.43 (m, 3 H), 3.38 (t, *J* = 9.5 Hz, 1 H, H-4), 3.19 (s, 3 H, CH$_3$), 3.12 (t, *J* = 6.5 Hz, 2 H, CH$_2$O), 1.74-1.68 (m, 2 H, CH$_2$); ^{13}C NMR (125 MHz, D_2O): δ 170.1, 158.8, 133.1, 124.9, 124.8, 124.5, 94.7, 74.5, 72.5, 71.8, 68.6, 66.3, 64.9, 64.1, 56.3, 50.9, 34.3, 23.8; Electrospray mass spectrum calcd ($M+H^+$) 456, found 456.

Synthesis of Compound 11

Benzyl ether ***47***. To a solution of **46** (0.65 g, 1.64 mmol) in toluene (10 mL) at room temperature was added di-*n*-butyltin oxide (0.63 g, 2.5 mmol). The reaction flask was fitted with a Dean-Stark apparatus and the solution was heated to reflux for 4 h. The Dean-Stark apparatus was then removed and benzyl bromide (0.20 mL, 1.69 mmol) and tetra-*n*-butylammonium bromide (0.54 g, 1.69 mmol) were added. The reaction mixture was heated at 80 °C for 18 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 30% ether in hexane) to give **47** as a colorless oil (0.59 g, 74%). **47**: R_f = 0.13 (silica, 30% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.64 (m, 5 H, Ar), 7.44-7.30 (m, 10 H, Ar), 6.35 (d, *J* = 6.5 Hz, 1 H, H-1), 4.82 (d, *J* = 6.5 Hz, 1 H, H-2), 4.71 (d, *J* = 12.0 Hz, 1 H, PhC*H*H), 4.65 (d, *J* = 12.0 Hz, 1 H, PhCH*H*), 4.12-4.09 (m, 2 H), 4.05-3.82 (m, 3 H), 2.60 (d, *J* = 3.0 Hz, 1 H, OH), 1.07 (s, 9 H, *t*-Bu).

Methyl ether 48. To a solution of **47** (0.31 g, 0.65 mmol) in benzene (10 mL) was added sodium hydride (60% dispersion in mineral oil, 0.067 g, 1.67 mmol) and methyl iodide (0.4 mL, 6.5 mmol) at room temperature. The reaction mixture was heated at reflux with stirring for 14 h and then was allowed to cool to room temperature before dilution with water (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic fractions were combined and washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 30% ether in hexane) gave **48** as an oil (0.28 g, 88%). **48**: R_f = 0.43 (silica, 30% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.70 (m, 5 H, Ar), 7.44-7.26 (m, 10 H, Ar), 6.38 (d, *J* = 5.5 Hz, 1 H, H-1), 4.83 (dd, *J* = 5.5, 3.0 Hz, 1 H, H-2), 4.67 (d, *J* = 11.5 Hz, 1 H, PhC*H*H), 4.61 (d, *J* = 11.5 Hz, 1 H, PhCH*H*), 4.12 (m, 1 H, H-3), 4.02-3.85 (m, 3 H), 3.77 (dd, *J* = 8.0, 6.0 Hz, 1 H, H-4), 3.61 (s, 3 H, OCH_3), 1.07 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 138.3, 135.7, 135.5, 133.5, 133.2, 129.5, 128.3, 127.7, 127.6, 127.5, 99.4, 77.5, 75.7, 75.1, 70.4, 62.0, 59.5, 26.7, 19.2; FAB-HRMS calcd ($M+Cs^+$) 621.1437, found 621.1413.

Methyl ester 49. To a solution of **48** (0.17 g, 0.34 mmol) in dichloromethane (5.0 mL) was added ethyl glycolate (54 mL, 0.68 mmol) and Ph_3P•HBr (6.0 mg, 0.017 mmol) at room temperature. After 3 h, the reaction mixture was diluted with dichloromethane (10 mL) and washed with aqueous saturated solution of sodium bicarbonate (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 30% ether in hexane) gave compound **49** as a colorless oil (0.15 g, 75%). **49**: R_f = 0.16 (silica, 30% ether in hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78-7.76 (m, 5 H, Ar), 7.46-7.31 (m, 10 H, Ar), 5.08 (d, *J* = 2.5 Hz, 1 H, H-1), 4.71 (s, 2 H, $OCH_2CO_2CH_3$), 4.20 (d, *J* =16.5 Hz, 1 H, PhC*H*H), 4.14 (d, *J* = 16.5 Hz, 1 H, PhCH*H*), 4.02-3.87 (m, 3 H), 3.70 (s, 3 H, CO_2CH_3), 3.60 (s, 3 H, OCH_3), 3.41 (t, *J* = 9.0 Hz, 1 H, H-4), 2.47-2.43 (m, 1 H), 1.76-1.72 (m, 1 H), 1.10 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 138.5, 128.3, 127.4, 127.4, 80.0, 76.6, 71.8, 63.5, 62.0, 60.7, 51.8, 35.0; FAB-HRMS calcd ($M+Na^+$) 363.1420, found 363.1434.

Alcohol 50. To a solution of **49** (0.14 g, 0.24 mmol) in THF (2.0 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.29 mL, 0.28 mmol). After 10 h, the reaction mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic fractions were combined and washed with water (30 mL), brine (30 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, ether) gave **50** as a colorless oil (0.64 g, 79%). **50**: R_f = 0.1 (silica, 60% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 5 H, Ar), 5.02 (s, 1 H, H-1), 4.60 (s, 2 H, $OCH_2CO_2CH_3$), 4.18 (d, *J* = 14.0 Hz, 1 H, PhC*H*H), 4.11 (d, *J* = 14.0 Hz, PhCH*H*), 3.99-3.96 (m, 1 H), 3.82-3.79 (m, 2 H), 3.70 (s, 3

H, CO_2CH_3), 3.60 (s, 3 H, OCH_3), 3.61 (m, 1 H), 3.24 (t, J = 9.0 Hz, 1 H), 2.43-2.39 (m, 1 H), 2.03-2.00 (m, 1 H), 1.70-1.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 138.6, 135.7, 135.4, 133.7, 133.4, 129.5, 129.4, 128.3, 127.6, 127.5, 127.4, 127.3, 97.0, 79.8, 76.7, 72.6, 72.1, 63.1, 63.0, 60.6, 51.7, 35.1, 26.7, 19.3; FAB-HRMS calcd ($M+Cs^+$) 711.1754, found 711.1788.

Azide 51. To a solution of compound **50** (0.23 g, 0.67 mmol) in dichloromethane (10 mL) at room temperature was added sodium hydride (60% dispersion in mineral oil, 0.03 g, 0.7 mmol). After stirring at room temperature for 30 min, a solution of $TfO(CH_2)_3N_3$ (1.09 g, 4.69 mmol) in dichloromethane (10 mL) was added via canula. After 14 h, the reaction mixture was diluted with aqueous saturated solution of ammonium choride (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic fractions were combined and washed with brine (40 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 60% ether in hexane) gave pure **51** as a colorless oil (0.18 g, 66%). **51**: R_f = 0.43 (silica, 60% ether in hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H, Ar), 5.03 (d, J = 2.5 Hz, 1 H, H-1), 4.65 (s, 2 H, $OCH_2CO_2CH_3$), 4.18 (d, J = 14.0 Hz, 1 H, PhC*H*H), 4.11 (d, J = 14.0 Hz, PhCH*H*), 3.94-3.84 (m, 1 H), 3.70 (s, 3 H, CO_2CH_3), 3.68-3.51 (m, 5 H), 3.57 (s, 3 H, OCH_3), 3.45-3.38 (m, 2 H), 3.26 (t, J = 9.5 Hz, 1 H), 2.39-2.37 (m, 1 H), 1.91-1.81 (m, 2 H, CH_2), 1.74-1.66 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 138.5, 128.3, 128.2, 127.4, 127.3, 97.2, 79.7, 76.8, 71.8, 71.2, 69.6, 68.0, 63.3, 60.6, 51.8, 47.9, 34.9, 27.9; FAB-HRMS calcd ($M+Cs^+$) 556.1060, found 556.1040.

Amine 52. To a solution of compound **51** (0.19 g, 0.44 mmol) in THF (10 mL) at room temperature was added water (0.13 mL, 7.04 mmol) and Ph_3P (0.30 g, 1.14 mmol). The reaction mixture was heated to 65 °C for 5 h. The solvent was removed *in vacuo* to give a white solid which after preparative thin layer chromatography (silica, CH_2Cl_2:MeOH:Et_3N, 80:19:1) gave **52** as a yellowish oil (0.14 g, 77%). **52**: R_f = 0.18 (silica, CH_2Cl_2:MeOH:AcOH, 8:1:0.5); ^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5 H, Ar), 5.00 (s, 1 H, H-1), 4.63 (AB system, J = 13.2 Hz, 2 H, $OCH_2CO_2CH_3$), 4.16 (d, J = 16.5 Hz, 1 H, PhC*H*H), 4.10 (d, J = 16.5 Hz, 1 H, PhCH*H*), 3.92-3.86 (m, 1 H), 3.73 (s, 3 H, CO_2CH_3), 3.73-3.61 (m, 4 H), 3.55 (s, 3 H, OCH_3), 3.48-3.46 (m, 2 H), 3.21-3.09 (m, 3 H), 2.39-2.36(m, 1 H), 2.05 (bs, 2 H, NH_2), 1.97-1.93 (m, 2 H), 1.69-1.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 145.8, 138.4, 128.2, 127.4, 97.5, 79.8, 76.5, 71.7, 70.6, 70.2, 69.8, 63.9, 60.5, 51.9, 39.3, 34.8, 26.5, 21.2; FAB-HRMS calcd ($M+Cs^+$) 530.1155, found 530.1172.

Compound 11. To a solution of **52** (0.027 g, 0.07 mol) in THF (0.63 mL) at room temperature was added methanol (1.05 mL) and 10% aqueous LiOH solution (0.32 mL). After 4 h, the reaction mixture was acidified with acetic acid and the solvent was removed *in vacuo* to give the crude acid **53**. To a solution of the crude acid **53** in dimethylformamide (0.5 mL) at room temperature was added *N,N*-diisopropylethylamine (12 mL, 0.07 mmol) and 1*H*-pyrazole-1-carboxamidine (0.01 g, 0.07 mmol). After 16 h, the solvent was removed *in vacuo* to give a crude oil, which after RP-HPLC (C-18) gave **11** as a foam (0.03 g, 95%). **11**: R_t = 20.4 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.38 (m, 5 H, Ar), 4.99 (d, J = 2.5 Hz, 1 H, H-1), 4.68 (d, J = 11.0 Hz, 1 H, $OCHHCO_2CH_3$), 4.60 (d, J = 11.0 Hz, 1

H, OCH*H*CO$_2$CH$_3$), 4.14 (s, 2 H, PhCH$_2$), 3.94-3.90 (m, 1 H), 3.70-3.52 (m, 4 H), 3.47 (s, 3 H, OCH$_3$), 3.30-3.10 (m, 4 H), 2.41-2.38 (m, 1 H), 1.84-1.80 (m, 2 H, CH$_2$), 1.67-1.61 (m, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 171.1, 152.0, 133.4, 124.7, 124.7, 124.4, 93.3, 72.04, 67.9, 66.4, 65.1, 63.9, 60.6, 56.0, 34.2, 23.8, 20.3; Electrospray mass spectrum calcd (M-H) 424, found 424.

Synthesis of Compound 12

Methyl ester 54ab. To a solution of **48** (1.50 g, 3.7 mmol) in CH$_2$Cl$_2$ (20 mL) at room temperature was added methyl glycolate (0.36 mL, 5.55 mmol) and *N*-iodosuccinimide (0.83 g, 4.44 mmol). After 3 h, the reaction mixture was diluted with ethyl acetate (20 mL) and poured into water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic fractions were combined and washed with 10% aqueous Na$_2$S$_2$O$_3$ solution, dried (MgSO$_4$) and the solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 30% ether in hexanes) gave **54** as a mixture of diastereoisomers (*ca.* 3:1, 1.62 g, 75%). **54ab**: R_f = 0.28 (silica, 60% ether in hexane); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.85-7.74 (m, 4 H), 7.56-7.31 (m, 11 H), 5.01 (d, J = 10.0 Hz, 0.25 × 1 H, OC*H*HCO$_2$CH$_3$), 4.92 (d, J = 10.0 Hz, 0.25 × 1 H, OCH*H*CO$_2$CH$_3$), 4.79 (d, J = 9.0 Hz, 0.25 × 1 H, H-1), 4.74 (d, J = 11.5 Hz, 0.75 × 1 H, OC*H*HCO$_2$CH$_3$), 4.7 (d, J =4.0 Hz, 0.75 × 1 H, H-1), 4.57 (d, J = 11.5 Hz, 0.75 × 1 H, OCH*H*CO$_2$CH$_3$), 4.34 (AB-system, J = 16.0 Hz, 0.25 × 2 H, PhCH$_2$), 4.17 (AB-system, J =16.5 Hz, 0.75 × 2 H, PhCH$_2$), 4.01-3.61 (m, 6 H), 3.81 (s, 0.25 × 3 H, OCH$_3$), 3.75 (s, 0.75 × 3, OCH$_3$), 3.66 (s, 0.25 × 3 H, OCH$_3$), 3.59 (s, 0.75 × 3 H, OCH$_3$), 1.14 (s, 0.75 × 9 H, *t*-Bu), 1.09 (s, 0.25 × 9 H, *t*-Bu); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.0, 169.7, 137.8, 137.6, 135.9, 135.8, 135.4, 133.6, 133.2, 129.7, 129.6, 129.5, 128.3, 127.7, 127.6, 127.5, 127.4, 101.5, 101.2, 85.5, 80.8, 77.3, 76.0, 75.8, 73.7, 70.9, 65.8, 64.7, 63.3, 62.6, 62.1, 60.6, 51.9, 32.4, 26.7; FAB-HRMS calcd (M+Cs$^+$) 837.0721, found 837.0752.

Alcohol 55. To a solution of **54ab** (1.62 g, 2.3 mmol) in THF (10 mL) at room temperature was added TBAF (1 M solution in THF, 2.76 mL, 2.76 mmol). After 10 h, the reaction mixture was diluted with ethyl acetate (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the organic fractions were combined and washed with water (50 mL), brine (50 mL) and dried (MgSO$_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, ether) gave **55** as a colorless oil (0.85 g, 79%). **55**: R_f = 0.17 (silica, 60% ether in hexane); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40-7.26 (m, 5 H, Ar), 4.69 (d, J = 11.0 Hz, OC*H*HCO$_2$CH$_3$), 4.61 (bs, 1 H, H-1), 4.53 (d, J = 11.0 Hz, 1 H, OCH*H*CO$_2$CH$_3$), 4.17 (d, J =12.5 Hz, 1 H, PhC*H*H), 4.15 (d, J =12.5 Hz, 1 H, PhCH*H*), 3.80 (m, 2 H), 3.76 (s, 3 H, CO$_2$CH$_3$), 3.72-3.68 (m, 1 H), 3.57 (s, 3 H, OCH$_3$), 3.62-3.58 (m, 2 H), 3.25-3.23 (m, 1 H), 1.60 (bs, 1 H, OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.8, 137.6, 128.5, 122.7, 127.6, 101.3, 76.7, 76.1, 73.0, 70.7, 63.7, 61.8, 60.4, 52.0, 32.4; FAB-HRMS calcd (M+Cs$^+$) 598.9543, found 598.9559.

Azide 56. To a solution of **55** (0.25 g, 0.54 mmol) in CH$_2$Cl$_2$ (15 mL) was added NaH (60% dispersion in mineral oil , 0.02 g, 0.56 mmol). After stirring at room temperature for 30 min, a solution of TfO(CH$_2$)$_3$N$_3$ (0.87 g, 3.78 mmol) in CH$_2$Cl$_2$ (10 mL) was added via canula. After 14 h, the reaction mixture was diluted with aqueous saturated solution of ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic fractions were combined and washed with brine (40 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after flash chromatography (silica, 60% ether in hexane) gave **56** as an oil (0.15 g, 50%). **56**: R_f = 0.43 (silica, 60% ether in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.27 (m, 5 H, Ar), 4.68 (d, J =11.5 Hz, 1 H, OC*H*HCO_2CH_3), 4.63 (bs, 1 H, H-1), 4.52 (d, J =11.5 Hz, 1 H, OCH*H*CO_2CH_3), 4.20-4.16 (m, 3 H), 3.76 (s, 3 H, CO_2CH_3), 3.55 (s, 3 H, OCH_3), 3.75-3.21 (m, 9 H), 1.88-1.86 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 137.6, 128.5, 128.3, 127.6, 101.1, 76.3, 74.6, 73.7, 72.5, 70.7, 69.5, 58.0, 63.5, 61.0, 52.0, 48.3, 46.6, 32.3, 29.1; FAB-HRMS calcd ($M+Cs^+$) 682.0026, found 682.0010.

Amine 57. To a solution of **56** (0.11 g, 0.21 mmol) in THF (5 mL) at room temperature was added water (59 µL, 3.36 mmol) and Ph_3P (0.19 g, 0.55 mmol). The reaction mixture was heated to 65 °C for 5 h. The solvent was removed *in vacuo* to give a white solid, which after preparative thin layer chromatography (silica, CH_2Cl_2:MeOH:AcOH, 8:1:0.5) gave **57** as a yellowish oil (0.10 g, 91%). **57**: R_f = 0.42 (silica, CH_2Cl_2:MeOH:AcOH, 8:1:0.5); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5 H, Ar), 4.65 (d, J =11.5 Hz, 1 H, OC*H*HCO_2CH_3), 4.57 (d, J = 4.5 Hz, 1 H, H-1), 4.48 (d, J = 11.5 Hz, 1 H, OCH*H*CO_2CH_3), 4.19 (d, J = 16.5 Hz, 1 H, PhC*H*H), 4.13 (d, J = 16.5 Hz, 1 H, PhCH*H*), 3.73 (s, 3 H, CO_2CH_3), 3.76-3.60 (m, 5 H), 3.61-3.57 (m, 1 H), 3.51 (s, 3 H, OCH_3), 3.53-3.50 (m, 1 H), 3.20-3.10 (m, 3 H), 1.96-1.92 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 137.6, 128.3, 128.2, 127.6, 101.4, 76.1, 71.9, 70.6, 70.3, 69.4, 64.0, 60.9, 51.9, 39.0, 32.2, 26.8, 22.3; FAB-HRMS calcd ($M+H^+$) 524.1145, found 524.1130.

Compound 12. To a solution of **57** (0.03 g, 0.06 mmol) in THF (0.55 mL) at room temperature was added methanol (0.92 mL) and 10% aqueous LiOH solution (0.28 mL). After 4 h, the reaction mixture was acidified with acetic acid and the solvent was removed *in vacuo* to give the crude acid **53**. To a solution of the crude acid **58** in DMF (0.5 mL) at room temperature was added diisopropylethylamine (10 µL, 0.06 mmol) and 1*H*-pyrazole-1-carboxamidine (9 mg, 0.06 mmol). After 16 h, the solvent was removed *in vacuo* to give an oil, which after RP-HPLC (C-18) gave **12** as a foam (0.03 g, 93%). **12**: R_t = 21 min [90:10 → 40:60 H_2O/CH_3CN (0.05% TFA)] over 40 min; ^{1}H NMR (500 MHz, CD_3OD): δ 7.40 (d, J = 7.0 Hz, 2 H, Ar), 7.32 (t, J = 7.0 Hz, 2 H, Ar), 7.27-7.21 (m, 1 H), 4.87 (d, J = 4.0 Hz, 1 H, H-1), 4.67 (d, J = 11.5 Hz, 1 H, OC*H*HCO_2H), 4.46 (d, J = 11.5 Hz, 1 H, OCH*H*CO_2H), 3.95 (bs, 2 H, $PhCH_2$), 3.75-3.51 (m, 6 H), 3.50 (s, 3 H, OCH_3), 3.33-3.25 (m, 4 H), 1.90-1.86 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, CD_3OD): δ 177.2, 159.3, 139.6, 129.4, 128.9, 128.7, 102.5, 78.8, 77.8, 73.5, 71.4, 70.8, 68.9, 67.3, 61.3, 39.2, 34.4, 30.5; Electrospray mass spectrum calcd ($M+H^+$) 552, found 552.

ACKNOWLEDGMENTS

We thank Drs. Gary Siuzdak and Dee Huang for their mass spectroscopy and NMR spectroscopy assistance respectively. Financial support provided by E. Merck (Darmstadt), The Skaggs Institute of Chemical Biology, the National Science Foundation (predoctoral fellowship to J.I.T.), The Wellcome Trust, London, UK (International Prize Travelling Research Fellowship to K.C.), the ALSAM Foundation and the National Institutes of Health (USA) is gratefully acknowledged.

REFERENCES

1. Billington, D.C. *Drug Design and Discovery* **1991**, *8*, 3.
2. Folkman, J.; Klagsburn, M. *Science*, **1987** *235*, 442.
3. Friedlander, M.; Theesfled, C.L.; Sugita, M.; Fruttiger, M.; Thomas, M.A.; Chang, S.; Cheresh, D.A. *Proc. Natl. Acad. Sci., USA* **1996**, *93*, 9764.
4. *Integrins: Molecular and Biological Responses to the Extracellular Matrix*; Cheresh, D.A.; Mecham, R.P. Eds.; Academic Press: New York, 1994. For a recent review on the role of integrins in angiogenesis see: Strömblad, S.; Cheresh, D.A. *Chem. Biol.* **1996**, *3*, 881.
5. (a) Brooks, P.C.; Clark, R.A.F.; Cheresh, D.A. *Science* **1994**, *264*, 569. (b) Friedlander, M.; Brooks, P.C.; Shaffer, R.W.; Kincaid, C.M.; Varner, J.A.; Cheresh, D.A. *Science* **1995**, *270*, 1500.
6. Brooks, P.C.; Montgomery, A.M.P.; Rosenfeld, M.; Reisfeld, R.A.; Hu, Tianhua, Klier, G.; Cheresh, D.A. *Cell* **1994**, *79*, 1157.
7. (a) Gurrath, M.; Muller, G.; Kessler, H.; Aumailley, M.; Timpl, R. *Eur. J. Biochem.* **1992**, *210*, 911. (b) Muller, G.; Gurrath, M.; Kessler, H.; Timpl, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 326. (c) Aumailley, M.; Gurrath, M.; Muller, G.; Calvete, J.; Timpl, R.; Kessler, H. *FEBS Lett.* **1991**, *291*, 50. (d) Pfaff, M.; Tangemann, B.; Muller, B.; Gurrath, M.; Muller, G.; Kessler, H.; Timpl, R.; Engel, J. *J. Biol. Chem.* **1994**, *269*, 20233. (e) Haubner, R.; Gurrath, M.; Muller, G.; Aumailley, M.; Kessler, H. *Prospects in Diagnosis and Treatment of Breast Cancer. Proceedings of the Joint International Symposium on Prospects in Diagnosis and Treatment of Breast Cancer*, 10-11 November 1993, Munich; Schmitt, M., Graeff, H., Kindermann, G., Eds.; Elsevier Science Publishers, B.V.: Amsterdam, Netherlands, **1994**. (f) Haubnner, R.; Gratias, R.; Diefenbach, B.; Goodman, S.L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461.
8. Duggan, M.E.; Fisher, J.E.; Gentile, M.A.; Hartman, G.D.; Hoffman, W.F.; Huff, J.R.; Ihle, N.C.; Krause, A.E.; Leu, T.C.; Nagy, R.M.; Perkins, J.J.; Rodan, G.A.; Rodan, S.B.; Wesolowski, G.; Whitman, D.B. *Abstracts of Papers*, 211th ACS National Meeting, New Orleans, LA, March 24-28, 1996; American Chemical Society: Washington, DC, **1996**, MEDI 234. For other reports of $\alpha_v\beta_3$ antagonists see: (a) Gadek, T.R.; McDowell, R.S. *ibid.*, MEDI 235. (b) Keenan, R.; Miller, W.; Ali, F.; Barton, L.; Bondinell, B.; Burgess, J.; Callahan, J.; Calvo, R.; Cousins, R.; Gowen, M.; Huffman, W.; Hwang, S.; Jakas, D.; Ku, T.; Kwon, C.; Lago, A.; Mombouyran, V.; Nguyen,T.; Ross, S.; Samanen, J.; Takata, D.; Uzinskas, I.; Venslavsky, J.; Wong, A.; Yellin, T.; Yuan, C. *ibid.*, MEDI 236.
9. (a) Papageorgiou, C.; Haltiner, R.; Bruns, C.; Petcher, T. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 135. (b) McGee, L.R.; Krawczyk, S.; Harwood, E.; Harada, Y.; Kim, C.U.; Swaminathan, S.; Krishnamurthy, K.; Bischofberger, N.; Mendel, D.; Moon, K.; Smith, J.; Xiong, S.F.; Cherrington, J.M.; Mulato, A.; Flores, C.; Chen, M.S.; Griffin, L.; Oliyai, R.; Cundy, K.C.; Lee, A.; Erickson, J.W. *Abstracts of Papers*, 212th ACS National Meeting, Orlando, Fl, August 25-29, 1996; American Chemical Society: Washington, DC, **1996**, ORGN 124. (c) LeDiguarher, T.; Boudon, A.; Elwell, C.; Paterson, D.E.; Billington, D.C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1983.

10. Hirschmann, R.; Nicolaou, K.C.; Pietranico, S.; Salvino, J.; Leahy, E.M.; Shakespeare, W.C.; Sprengler, P.A.; Hamley, P.; Smith, A.B.; Reisine, T.; Raynor, K.; Donaldson, C.; Vale, W.; Maechler, L.; Freidinger, R.M.; Strader, C.D. *J. Am. Chem. Soc.* **1996**, *115*, 12550.
11. (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643. (b) Grindley, T.B. In *Synthetic Oligosaccharides: Indispensable Probes for the Life Sciences*; Kovac, P. Ed.; American Chemical Society: Washington, **1994**; Ch. 4, pp. 51-76.
12. Nicolaou, K.C.; Ladduwahetty, T.; Randall, J.L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.
13. Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567.
14. Bernatowicz, M.S.; Wu, Y.; Matsueda, G.R. *J. Org. Chem.* **1992**, *57*, 2497.
15. Unpublished results, Helen Mitchell of these laboratories.
16. (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431; **1983**, 935. (b) Nicolaou, K.C.; Dolle, R.E.; Papahatjis, D.P.; Randall, J.L. *J. Am. Chem. Soc.* **1984**, *106*, 4189.
17. Bolitt, V.; Mioskowski, C.; Lee, S.G.; Falck, J.R. *J. Org. Chem.* **1990**, *55*, 5812.
18. (a) Lemieux, R.U.; Morgan, A.R. *Can. J. Chem.* **1965**, 43, 2190. Lemieux, R.U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 532; **1964**, *42*, 539; **1965**, *43*, 1460. (b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis*, **1978**, 696. (c) For a review of the glycosidation of glycals see: Danishefsky, S.J.; Bilodeau, M.T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380.
19. Tatsuta, K.; Fujimoto, M.; Kinoshita, M.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85.
20. We thank David A. Cheresh, Ph.D. and Mauricio Rosenfeld (The Scripps Research Institute, Departments of Immunology and Vascular Biology) for performing the biological assays on the synthesized compounds. These compounds were tested in a cell adhesion assay with β3CS1 cells and measuring their ability to inhibit binding of vitronectin and laminin P1 (0.1 μM -100 μM).
21. We thank Alfred Jonczyk, Ph.D. and Beate Diefenbach (E.Merck, Darmstadt) for performing the biological assays on the synthesized compounds. The compounds were tested in a cell adhesion assay with M21-L-α_{IIb} cells and measuring their ability to inhibit binding of fibrinogen (0.1 μM-100 μM).

(*Received* 6 *January* 1997; *revised* 3 *February* 1997; *accepted* 5 *February* 1997)