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Synthesis of analogues of calicheamicin and neocarzinostatin chromophore

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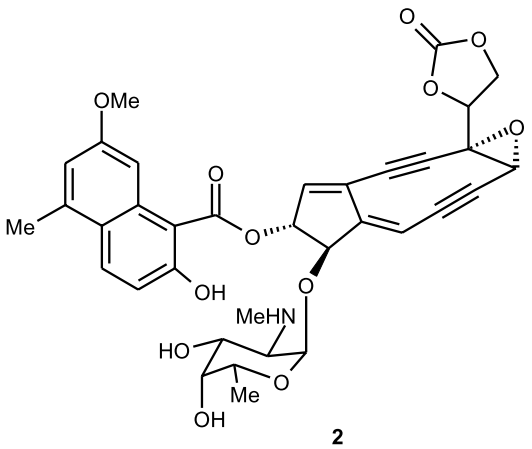
Abstract—The work presents a synthetic route to the CD ring of calicheamicin and in the case of neocarzinostatin an approach to a functionalised cyclopentane-1,3-diol containing the naturally occurring naphthoate and a glucosamine motif. In the case of the NCS derivative some biological activity (cytotoxicity) was observed.

1. Introduction

Calicheamicin γ_1^I **1** from the soil microorganism *Micromonospora echinospora* has been the subject of numerous synthetic and biological studies.[1] Much of its biological activity can be ascribed to the way in which it binds specifically to 5′-TCCT and 5′-ACCT sequences in the minor groove of DNA,[2] and a limited number of analogues have also been prepared with a view to establish structure activity relationships. In particular, both Nicolaou[3] and Danishefsky[4] have prepared glycones with modifications to the A, B and E rings. Moutel and Prandi have prepared AB rings with acyclic E ring analogues, and a DCB analogue where an ester oxygen replaces the thioester linkage.[5] But there has been no investigation of the effects of changing the D-ring. We have devised some novel and flexible chemistry for the production of a range of CD-analogues.

Neocarzinostatin **2** from *Streptomyces carzinostaticus* was in fact the first member of the family of enediynes to be isolated,[6] and also has a range of biological activities including anti-proliferative activity.[7] Its central naphthoate is known to bind duplex DNA intercalatively,[8] but the role of the glycosyl unit has not been established. This natural product has also been the target of numerous synthetic studies[9] and one successful synthesis by Myers.[10] We have prepared a core structure that includes a homochiral polysubstituted cyclopentane with sugar and naphthoate units attached, in order to explore the essential features required for selective DNA duplex binding.



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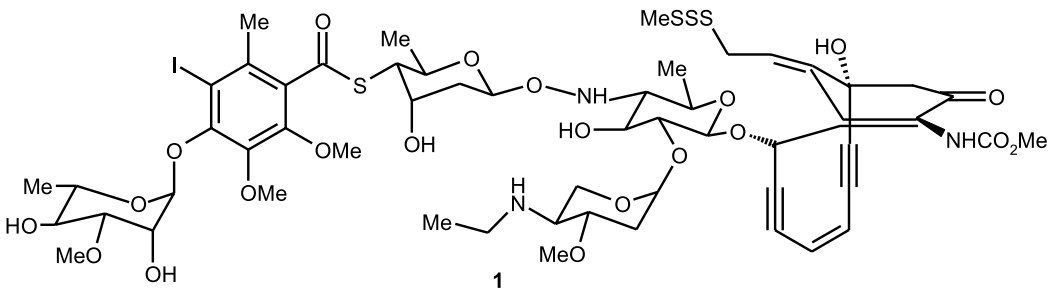

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Keywords: Neocarzinostatin; Calicheamicin; Cyclopentane-1,3-diol.
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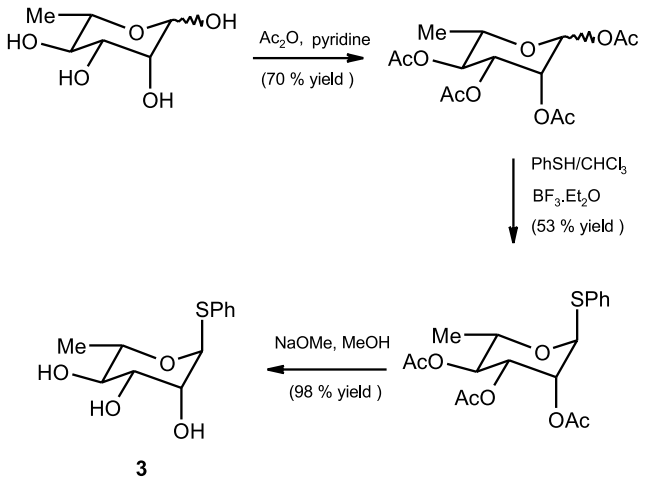
2. Results and discussion

Our key intermediate for the production of the CD ring system of calicheamicin was 1-thiophenyl-α-L-rhamnopyranoside **3** prepared from L-rhamnose via the sequence shown in Scheme 1 (overall yield for the three steps 35%).



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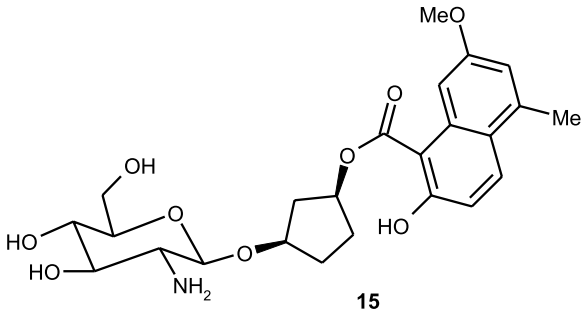
Scheme 1.

Compound **3** was then converted into the bis-acetal **4** using Ley's technology[11] (butan-2,3-dione in MeOH containing camphor sulphonic acid, 58%), and thence into the 2-methyl derivative **5** (MeI/NaH, 67%), and the 2-acetate **6** (acetic anhydride/pyridine, 76%). The thiophenyl group was now removed using aqueous NBS to provide an inseparable mixture of α:β anomers of the 2-methyl-derivative **7** (Scheme 2) (ratio around 1:1, anomeric ^{1}H singlet and doublet J=1.2 Hz); and a 6:1 ratio of anomers (major anomer ^{1}H singlet and minor anomer ^{1}H doublet J=1.2 Hz) of the 2-acetate **11** (again inseparable by flash chromatography), in yields of around 60–80% in each case. Presumably formation of an intermediate acetoxonium species improves the stereoselectivity for the formation of the α-anomer of **11**.

A Mitsunobu reaction with the phenol **8** which had been previously[12] synthesised by us was carried out on the free anomeric alcohols **7** (DEAD, Ph_3P, THF), and a 3:1 ratio of anomers of the protected CD-ring analogue **9** was obtained (in 83% yield). Removal of the bis-acetal using brief exposure to aqueous TFA provided a 3:1 anomeric mixture of the desired CD-ring analogue **10** (63%). These anomers were separated and NMR analysis suggested that the minor product was the desired α-anomer, since the relative δ-values for H-5 were 4.2 ppm (minor compound) and 3.1 ppm (major compound) reflecting the anisotropic effect of the aryl group upon H-5. In contrast, a Mitsunobu reaction on anomeric alcohols **11** provided none of the desired product, but reaction of the trichloroimidates **12** with the phenol **8** produced the protected CD-ring analogue **13**. Removal of the bis-acetal (as before) provided the other CD-ring analogue **14** as one pure anomer in an overall yield of 19% for the three steps. Since H-5 resonated at 4.2 ppm, we believe this to be the α-anomer, and this would be consistent with participation of an acetoxonium intermediate. While the yields of these reactions clearly require optimisation, this approach allows access to novel CD-ring analogues of calicheamicin which possess (in principle) a range of substituents at C-2, 3 and 4 of the rhamnose ring. Despite the efforts of Nicolaou,[3] Danishefski,[4] and Prandi,[5] this possibility has not been available before our work.

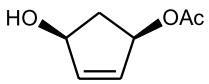
Our initial target in the neocarzinostatin series was the aminoglucoside of hydroxycyclopentyl naphthoate **15** in order to assess its biological activity.



15

The ultimate intention was the preparation of a library of core structures which carry conventional cytotoxic drugs and various carbohydrate moieties, and an investigation of the effects of these substituents on the intercalative binding of the naphthoate unit to duplex DNA. The naphthoic acid component **16** was prepared essentially according to the route described by Myers[13] (Scheme 3), though the initial Heck reaction was improved markedly through the use of DMF as co-solvent (time of reaction reduced from 12 to 2 h).

The homochiral hydroxycyclopent-2-enylacetate derivative **17** was prepared according to our optimisation[14] of an earlier preparation.[15]



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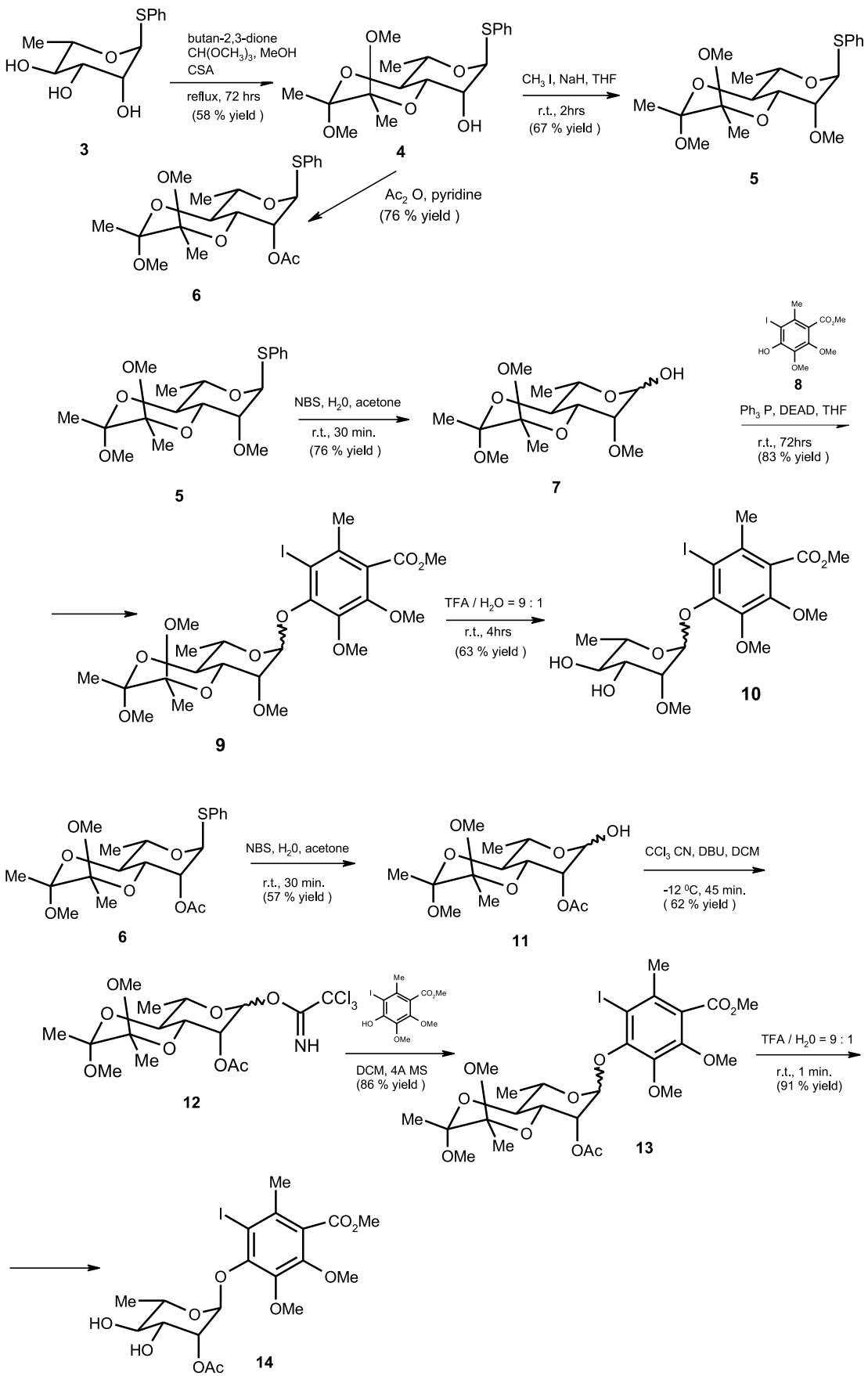
With these key substrates in hand, we employed the fully protected thioacetal of *N*-phthalimidoglucosamine **18** (prepared according to Scheme 4) as a model carbohydrate for investigation of the coupling methodology.

Reaction of this thioacetal with (1*R*,3*S*)-(+)-1-acetoxycyclopent-2-en-3-ol **17** in the presence of *N*-iodosuccinimide and catalytic BF_3 etherate[16] yielded the desired glycoside **19** (R=triethylsilyl) exclusively as the β-anomer. Unfortunately, during the work-up, one or more of the triethylsilyl protecting groups were lost and a complex mixture of products was obtained. In consequence, the fully benzylated thioglycoside **20** (R=benzyl) was prepared and this could be converted into the glycoside **21** (R=benzyl) (60%). Removal of the acetate with methanolic potassium carbonate to yield **22** was followed by coupling with **16** using DCC and DMAP in dichloromethane and thence conversion into the desired naphthoate ester **23** (60%) (Scheme 5). This was treated with Pearlman's catalyst


butan-2,3-dione
CH(OCH3)3, MeOH
CSA
reflux, 72 hrs
(58 % yield)
CH3 I, NaH, THF
r.t., 2hrs
(67 % yield)
Ac2 O, pyridine
(76 % yield)
NBS, H20, acetone
r.t., 30 min.
(76 % yield)
Ph3 P, DEAD, THF
r.t., 72hrs
(83 % yield)
TFA / H2O = 9 : 1
r.t., 4hrs
(63 % yield)
NBS, H20, acetone
r.t., 30 min.
(57 % yield)
CCl3 CN, DBU, DCM
-12 0C, 45 min.
(62 % yield)
DCM, 4A MS
(86 % yield)
TFA / H20 = 9 : 1
r.t., 1 min.
(91 % yield)
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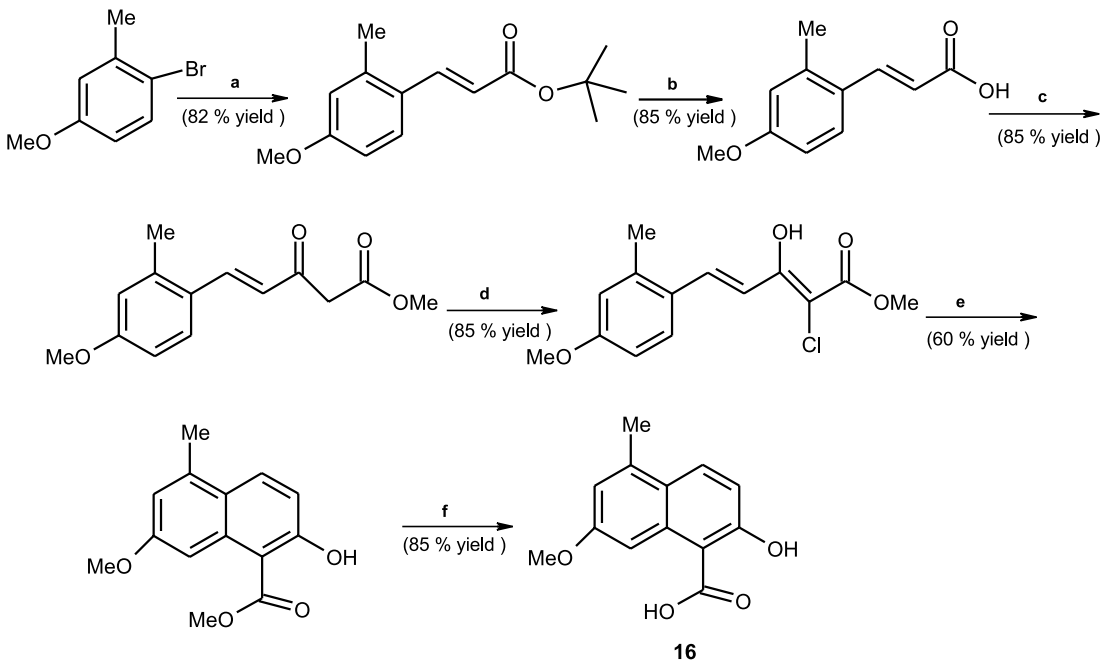
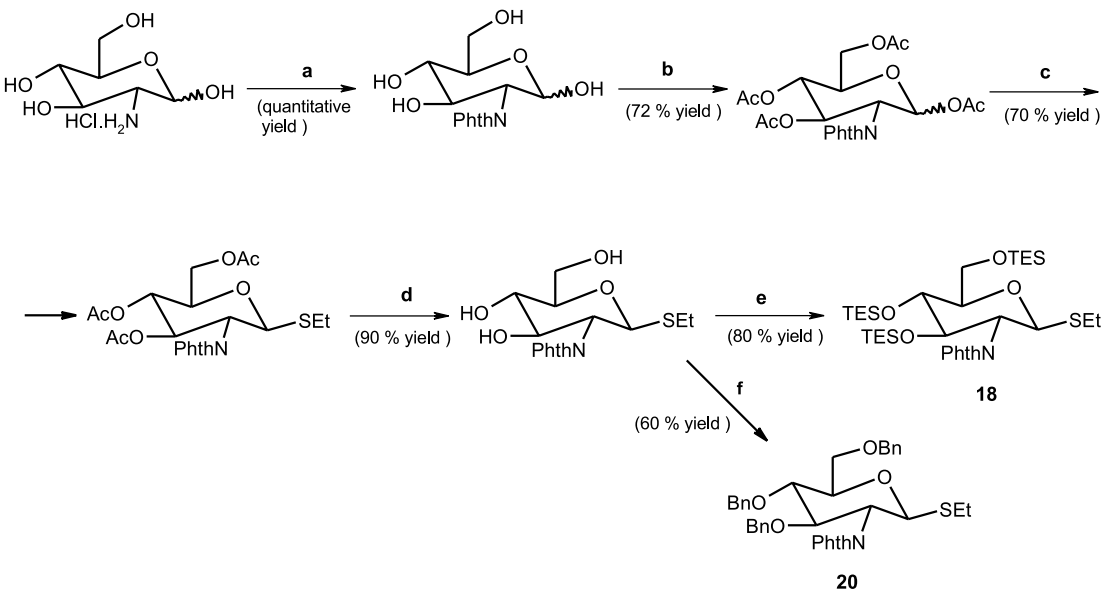
Scheme 2.



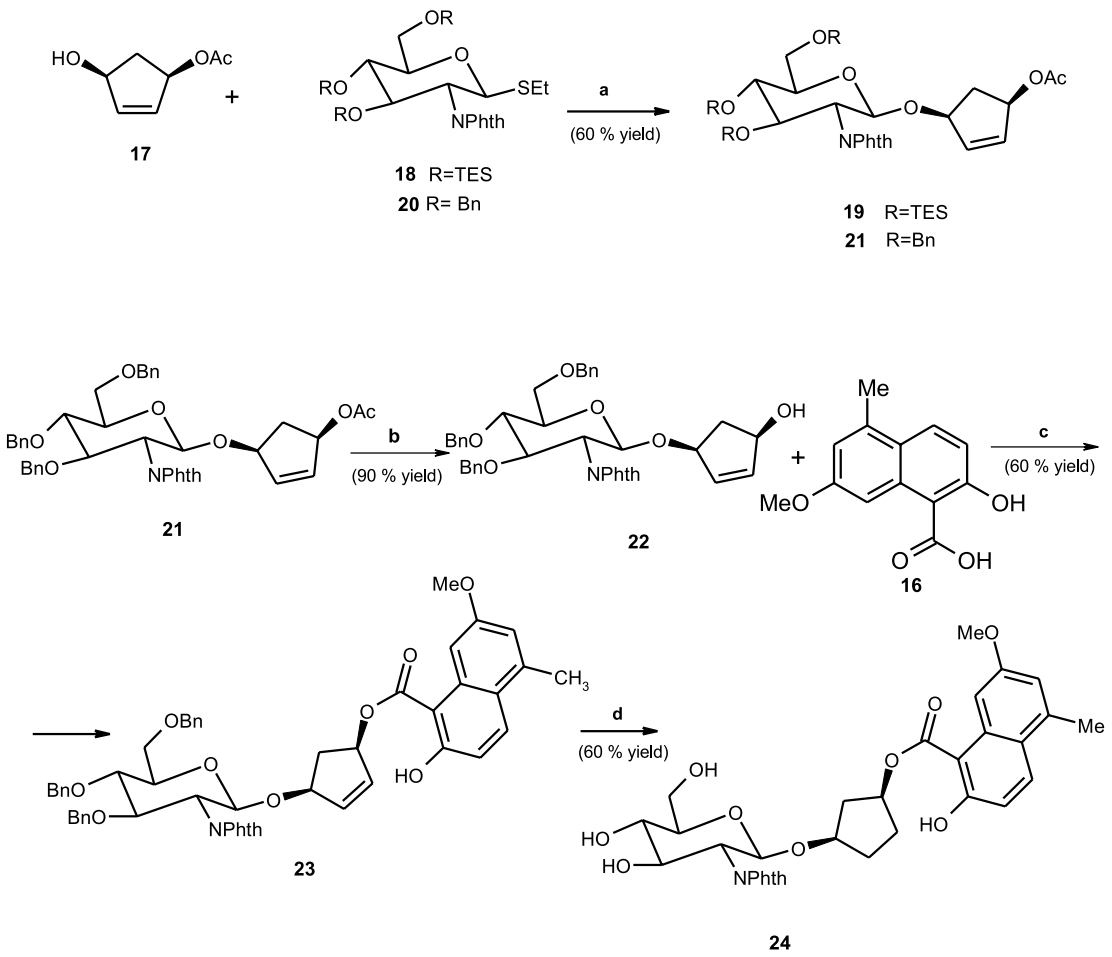
Scheme 3. Reagents and conditions: (a) *tert*-butyl acrylate, Et_3N, P(*o*-tol)$_3$, Pd(OAc)$_2$, 110 °C, 82%; (b) TFA, DCM, rt, quantitative; (c) CDI, magnesium methyl malonate, THF, rt, 85%; (d) SO_2Cl_2, C_6H_6, 70 °C (85%); (e) *hν*, Et_3N, MeOH, rt, 60%; (f) NaOH, 3:1 MeOH/H_2O, 80 °C, 85%.



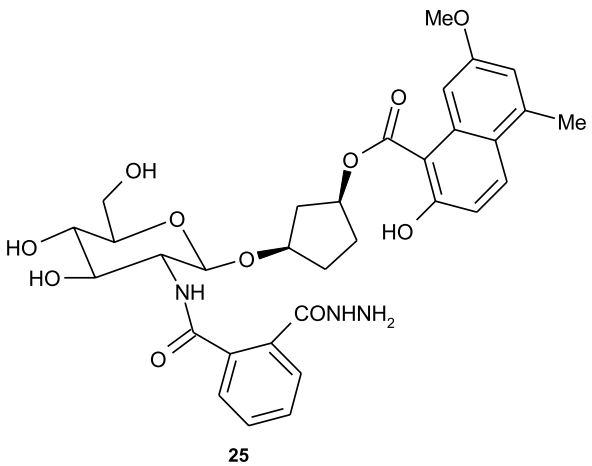
Scheme 4. (a) NaOH, phthalic anhydride, H_2O, overnight, rt, quantitative; (b) Ac_2O, pyridine, DMAP, overnight, 0 °C→rt, 72%; (c) EtSH, $CHCl_3$, $BF_3{\cdot}Et_2O$, 0 °C→rt, reflux 3 h, 70%; (d) NaOMe 25% (w/v) pH 8, MeOH, 90%; (e) triethylsilyltrifluoromethansulfonate, 2,6-lutidine, DMF, 0 °C, 4 h, 80%; (f) BnBr, Bu_4NI, NaH, DMF, 0 °C→rt, overnight, 60%.

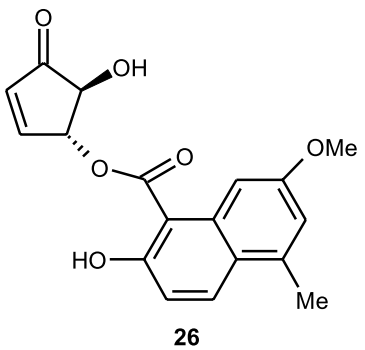
(palladium hydroxide) in methanol and in atmosphere of H_2 to provide the fully debenzylated adduct **24**.

Finally, removal of the phthalimide group was attempted using methanolic hydrazine. However, although partial hydrolysis was easily effected to provide the analogue **25** (ES^+: 640.2), further reaction led to production of only trace amounts of the desired analogue **15** (ES^+: 478.2). Clearly further work will be required to optimise this chemistry. Nonetheless, this work has established a viable route for the synthesis of our core structure, and future work will seek to produce a library of neocarzinostatin analogues in order to establish the optimum structure required to maximise binding to DNA.



Scheme 5. (a) NIS, $BF_3{\cdot}Et_2O$, 4 Å MS, DCM, 20 min, 60%; (b) 1 M K_2CO_3, MeOH, 90%; (c) DCC, DMAP, 0 °C→rt, 60%; (d) $Pd(OH)_2$, H_2, EtOH, 60%.





2.1. Biological evaluation

The calicheamicin CD ring analogues **10** and **14** and the neocarzinostatin core analogue **25** were evaluated for cytotoxic activity against a range of cancer cell lines in vitro. Cells were plated in RPMI1640 medium supplemented with foetal calf serum and 1% penicillin/streptomycin (1×10^3 cells/well in 24 well plates). Following a 24 h attachment period at 37°, the medium was removed from the wells and replaced with 1 ml of medium containing the appropriate compound at a range of concentrations. Cell counts were carried out using a Coulter counter and cell growth curves were plotted for a 7-day period. While compounds **10** and **14** exhibited no significant activity, compound **24** did exhibit modest activity at the level of 50 μM.

This compares with the results of Caddick and co-workers who reported[17] very recently that the non-glycosylated analogue **26** exhibited activity against a range of cancer cell lines with IC_{50}s typically in the range 2.5–5.0 μM.

3. Experimental

3.1. General

IR were recorded using a Perkin–Elmer 881 series double

beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec spectrometer and elemental analysis was carried out using a Perkin–Elmer 2400 CHN Microanalyser by ASEP, Queen's University Belfast. All compounds for which accurate mass data are provided were homogeneous by two-dimensional TLC and exhibited no spurious signals in the ^{1}H NMR spectra at 300 MHz. NMR spectra were recorded using Bruker DPX 300 and DRX 500 instruments. $[\alpha]_D$ Values are given in units of 10^{-1}deg cm^2 g^{-1}. Solvents were dried by distillation from calcium hydride (DCM, dichloromethane) or from sodium-benzophenone (THF, diethyl ether). Petrol refers to petroleum ether boiling range 40–60 °C. Compound **3** was prepared according to Ref. 18.

3.1.1. (2′*S*), (3′*S*)-Phenyl-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-1-thio-α-L-rhamnopyranoside 4. Phenyl 1-thio-α-L-rhamnopyranoside **3** (4.1 g, 16 mmol) was dissolved in analar methanol (110 ml), and under a flow of argon, trimethyl orthoformate (6.9 ml, 45.2 mmol), butan-2,3-dione (1.76 ml, 20.1 mmol), and camphor sulphonic acid (240 mg-catalytic) were added sequentially. The reaction mixture was then refluxed for 72 h, after which time the *trans* diol had been protected. Upon cooling, the reaction was quenched by the addition of triethylamine to pH=7, and the solution was immediately concentrated onto flash silica for purification. The title compound (**4**) was isolated as a yellow foam (3.4 g, 58%). IR ($CHCl_3$) *ν*: 3450, 2949, 2833. ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 1.26 (3H, d, *J*=6.2 Hz, C-5–CH_3), 1.31, 1.32 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 3.24, 3.30 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.77 (at, 1H, *J*=10.2 Hz, H-4), 3.97 (dd, 1H, *J*=3.0, 10.2 Hz, H-3), 4.18 (dd, 1H, *J*=1.2, 3.0 Hz, H-2) 4.25 (m, 1H, H-5), 5.49 (as, 1H, H-1) 7.24 (3H, m, S–C_6H_5), 7.44 (2H, m, S–C_6H_5. ^{13}C NMR ($CDCl_3$, 500 MHz): *δ* 16.4, 17.6, 17.7, 47.6, 48.1, 67.7, 68.5, 68.7, 71.4, 87.8, 99.8, 100.3, 127.3, 134.3. HRMS (CI): calcd for $C_{18}H_{26}O_6S$ [M$^+$] 370.1450. Found: 370.1439. $[\alpha]_D^{20}$=−300.0 (*c*=1.31, $CHCl_3$).

3.1.2. 2-*O*-Methyl-(2′*S*), (3′*S*)-phenyl-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-1-thio-α-L-rhamnopyranoside 5. The *trans* protected thioglycoside **4** (2.41 g, 65 mmol) in dry THF (50 ml) was added to sodium hydride (4.62 g, 97.5 mmol) under a flow of argon. Iodomethane (1.6 ml, 260 mmol) was then added dropwise, and the reaction mixture stirred at ambient temperature for 2 h. The reaction was then quenched by cooling the solution to 0 °C followed by a slow dropwise addition of methanol (20 ml). After evaporation to dryness, the residue was dissolved in DCM (100 ml), and the organic layer sequentially washed with H_2O (2×100 ml) and brine (1×100 ml). It was then dried ($MgSO_4$), filtered and concentrated onto flash silica for purification to yield the title compound as a pale yellow crystalline solid (1.7 g, 67%). IR ($CHCl_3$) *ν*: 2949, 2832, 1259. ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 1.28 (d, 3H, *J*=6.2 Hz, C-5–CH_3), 1.31, 1.34 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 3.25, 3.31 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.48 (s, 3H, C-2–OCH_3) 3.73 (dd, 1H, *J*=1.4, 3.0 Hz, H-2), 3.76 (at, 1H, *J*=10.3 Hz, H-4), 3.95 (dd, 1H, *J*=3.0, 10.3 Hz, H-3), 4.21 (m, 1H, H-5) 4.25 (d, 1H, *J*=1.4 Hz, H-1), 7.24 (3H, m, S–C_6H_5), 7.45 (2H, m, S–C_6H_5). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 16.6, 17.8, 17.9, 47.7, 47.9, 58.5, 67.7, 68.6, 68.8, 80.5, 85.6, 99.5, 99.9, 127.2, 134.9. HRMS (CI): calcd for $C_{19}H_{28}O_6S$ [M$^+$] 384.1607. Found: 384.1595. $[\alpha]_D^{20}$=−270.4 (*c*=0.71, $CHCl_3$). Mp=124.4 °C.

3.1.3. 2-*O*-Acetyl-(2′*S*) (3′*S*)-phenyl-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-1-thio-α-L-rhamnopyranoside 6. (2′*S*), (3′*S*)-Phenyl-3,4-*O*- 2′,3′-dimethoxybutane-2′,3′-diyl-1-thio-α-L-rhamnopyranoside **4** (1.91 g. 5.16 mmol) was dissolved in pyridine (5.4 ml), and the reaction mixture cooled to 0 °C. Acetic anhydride (1.47 ml) was added dropwise, and the reaction mixture allowed to warm to room temperature. After stirring at ambient temperature overnight, TLC showed complete reaction. The reaction mixture was then cooled to 4 °C, and quenched by the dropwise addition of methanol (6 ml). The pyridine was then removed under high vacuum and the residue was re-dissolved in CH_2Cl_2 (60 ml). The organic layer was washed sequentially with 1 M HCl (2×60 ml), sat. aq. $NaHCO_3$ (1×60 ml), H_2O (1×60 ml) and brine (1×60 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography yielded the desired compound **6** as a white foam (1.61 g, 76%). IR ($CHCl_3$) *ν*: 2952, 1748, 1236. ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 1.24 (d, 3H, *J*=6.2 Hz, C-5–CH_3), 1.28, 1.31 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 2.13 (s, 3H, C-2–OCOCH_3), 3.27, 3.29 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.71 (at, 1H, *J*=10.2 Hz, H-4), 4.04 (dd, 1H, *J*=3.2, 10.2 Hz, H-3), 4.25 (m, 1H, H-5) 5.29 (dd, 1H, *J*=1.3, 3.2 Hz, H-2), 5.41 (as, 1H, H-1), 7.25 (3H, m, S–C_6H_5), 7.44 (2H, m, S–C_6H_5). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 16.9, 17.9, 18.2, 21.6, 48.1, 48.5, 67.1, 68.3, 69.3, 72.8, 86.9, 100.2, 100.6, 128.0, 134.5, 170.9. HRMS (CI): calcd for $C_{19}H_{25}O_6S_1$ (M$^+$−OCH$_3$) 381.1371. Found: 381.1359. $[\alpha]_D^{20}$=−215.8 (*c*=0.76, $CHCl_3$).

3.1.4. 2-*O*-Methyl-(2′*S*), (3′*S*)-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-L-rhamnopyranoside 7. Under a flow of argon, the protected thioglycoside **5** (300 mg, 0.78 mmol) was dissolved in analar acetone (10 ml), and cooled to 0 °C. *N*-Bromosuccinimide (0.278 g, 1.56 mmol) was added followed almost immediately by the addition of H_2O (0.5 ml). An immediate colour change from an orange solution to a yellow solution was apparent. Stirring was continued for a further 30 min, after which time a clear solution showed the end of the reaction. The acetone was removed under reduced pressure, and the residue re-dissolved in EtOAc (50 ml). The organic layer was washed with sat. aq. $NaHCO_3$ solution (2×50 ml) and brine (1×50 ml), dried ($MgSO_4$), filtered, and immediately concentrated onto flash silica for purification.

An intractable mixture of anomers of unknown stereochemistry was obtained, in a ratio of 1:1.2 (apparent from NMR studies) (178 mg, 76%). It has been found that the sugar proton signals for the two anomers, α, β, are impossible to distinguish. However the major anomer signals for other protons are highlighted in bold, and no integration values are noted. IR ($CHCl_3$) *ν*: 3416, 2834, 1453. ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 1.14 (d, *J*=6.6 Hz, C-5–CH_3), **1.18** (d, *J*=6.1 Hz, C-5–CH_3), **1.21**, **1.21** (2s, C-2′–CH_3, C-3′–CH_3), 1.23, 1.25 (2s, C-2′–CH_3, C-3′–CH_3), **3.17**, **3.18** (2 s, C-2′–OCH_3, C-3′–OCH_3), 3.19, 3.20 (2s, C-2′–OCH_3, C-3′–OCH_3), 3.32–4.00 (m, C-2, C-3,

C-4, C-5), **3.44** (s, C-2–OCH_3) 3.58 (s, C-2–OCH_3), 4.66 (as, 1H, C-1), **5.17** (d, 1.2H, J=1.2 Hz, C-1). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.6, 15.7, 16.3, 16.4, 16.6, 16.7, 46.6, 46.7, 46.9, 58.3, 60.3, 66.0, 66.9, 67.0, 67.7, 69.6, 70.6, 77.8, 78.1, 91.9, 92.7, 98.5, 98.5, 98.7, 98.8. HRMS (CI): calcd for $C_{13}H_{21}O_7$ [M^+-CH_3] 277.1287. Found: 277.1274.

3.1.5. 2-*O*-Acetyl-(2′*S*) (3′*S*)-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-L-rhamnopyranoside 11. The thioglycoside **6** (1.61 g; 3.90 mmol) was dissolved in acetone (50 ml), and cooled to 0 °C. *N*-Bromosuccinimide (1.42 g; 7.97 mmol) was added followed immediately by the addition of H_2O (1.42 ml). A colour change from an orange solution to a yellow solution was apparent. Stirring was continued for a further 30 min, after which time a clear solution was visible. TLC showed formation of the desired alcohol as well as the presence of unreacted starting material. Stirring was continued for a further 30 min at room temperature, however, no further change was noted. The reaction mixture was immediately concentrated onto silica for purification by flash column chromatography. Yield 711 mg, (57%). The anomeric ratio was 6:1, α/β. The ^{1}H NMR signals are those for the α-anomer. The only two discernible 'β' signals were those of the anomeric proton and H-2, which are noted separately below. IR ($CHCl_3$) ν: 3440, 2932, 1732, 1373. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (d, 3H, J=6.2 Hz, C-5–CH_3), 1.27, 1.29 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 2.15 (s, 3H, C-2–OCOCH_3), 3.25, 3.26 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.63 (at, 1H, J=10.0 Hz, H-4), 4.00 (m, 1H, H-5), 4.14 (dd, 1H, J=3.3, 10.0 Hz, H-3), 5.05 (dd, 1H, J=1.5, 3.3 Hz, H-2), 5.15 (as, 1H, H-1). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.6, 16.7, 16.8, 20.2, 46.7, 47.0, 64.5, 65.6, 67.8, 70.2, 91.7, 98.7, 99.1, 169.8. β-*anomer*. 4.90 (d, 1H, J=1.2 Hz, H-1), 5.29 (dd, 1H, J=1.2, 3.1 Hz, H-2). HRMS (CI): calcd for $C_{13}H_{21}O_7$ (M^+-OCH_3) 289.1287. Found: 289.1285.

3.1.6. Methyl 4-[2-*O*-methyl-(2′*S*), (3′*S*)-3,4-*O*- 2′,3′-dimethoxybutane-2′,3′-diyl-L-rhamnopyranosyl]-oxy-5-iodo-2,3-dimethoxy-6-methyl benzoate 9. Under a flow of argon, the phenol **8** (80 mg, 0.23 mmol) and the alcohol **7** (100 mg, 0.34 mmol) were dissolved in dry THF (2 ml) and triphenylphosphine (89 mg, 0.34 mmol) was added. The reaction mixture was then cooled to 0 °C, and DEAD (53.8 μl, 0.34 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred at ambient temperature for 72 h. TLC showed major conversion to a new product, running between the alcohol and the phenol. This was then followed by the removal of solvents under reduced pressure and concentration onto flash silica for purification, yielding the title compound as a yellow oil (119 mg, 83%).

The following data shows an intractable mixture of anomers. It can be clearly seen from the ^{1}H NMR spectrum that there is a mixture in a ratio of 3:1, and investigation of the coupling constants reveals a probable ratio of 3:1, β/α. The signals for the major β-anomer in the proton spectrum are highlighted in bold type. IR ($CHCl_3$) ν: 2946, 1734, 1457. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26–1.36 (m, C-5–CH_3, C-2′–CH_3, C-3′–CH_3), 2.29, **2.30** (2s, Ar–CH_3), **3.17**, 3.20, **3.21**, 3.26 (4s, C-2′–OCH_3, C-3′–OCH_3), 3.17–4.30 (m, H-2, H-3, H-4, H-5), 3.48 (s, Ar–CO_2CH_3), **3.70** (s, Ar–CO_2CH_3), 3.77 (s, Ar–OCH_3), **3.80**, **3.81** (2s, Ar–OCH_3), 3.84 (s, Ar–OCH_3), 3.85 (s, C-2–OCH_3), 3.86 (s, C-2–OCH_3), **4.99** (d, 0.75H, J=0.68 Hz, H-1), 5.50 (d, 0.25H, J=1.34 Hz, H-1). ^{13}C NMR ($CDCl_3$, 62 MHz): δ 15.5, 15.6, 16.7, 16.8, 16.9, 24.9, 46.7, 46.9, 47.1, 51.5, 59.9, 60.1, 60.3, 60.5, 66.8, 67.1, 68.7, 70.1, 70.5, 77.6, 77.8, 93.3, 98.5, 98.8, 98.9, 100.6, 102.3, 124.7, 132.7, 133.1, 142.4, 149.7, 150.7, 151.0, 166.7. HRMS (CI): calcd for $C_{24}H_{35}O_{11}I$ 626.1224. Found: 626.1198.

3.1.7. Methyl 4-[2-*O*-methyl-L-rhamnopyranosyl]-oxy-5-iodo-2,3-dimethoxy-6-methyl benzoate 10. Compound **9** (78 mg, 0.121 mmol) was cooled to −20 °C by placing the flask in an acetone/dry ice bath. A 9:1 mixture of trifluoroacetic acid/water (0.87 ml) was added dropwise and the reaction mixture stirred at this temperature for 4 h. After this time, TLC showed the formation of two anomers and thus the reaction was quenched by allowing the reaction mixture to warm to ambient temperature, and then immediately removing the TFA under high vacuum. The residue was then concentrated under reduced pressure onto flash silica for purification by flash chromatography and eluted with EtOAc to provide two anomers. R_f=0.56 'α' and R_f=0.41 β. Overall yield 40 mg, (63%); β −30 mg, (47%), α −10 mg, (16%). β-*Anomer*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (d, 3H, J=6.2 Hz, C-5–CH_3), 2.35 (s, 3H, Ar–CH_3), 3.11 (m, 1H, H-5), 3.38 (at, 3H, J=9.1 Hz, H-4), 3.47 (dd, 1H, J=3.6, 9.1 Hz, H-3), 3.84 (s, 3H, Ar–CO_2CH_3), 3.89, 3.89 (2s, 6H, Ar–OCH_3), 3.93 (s, 3H, C-2–OCH_3), 4.00 (dd, 1H, J=0.63, 3.6 Hz, H-2), 5.10 (as, 1H, H-1). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.4, 25.9, 52.6, 61.1, 61.5, 62.4, 72.4, 73.9, 74.1, 80.1, 94.7, 103.6, 126.1, 133.9, 143.6, 150.7, 151.6, 167.7. $[\alpha]_D^{20}$=−19 (c=1.0, MeOH). α-*Anomer*. IR ($CHCl_3$) ν: 3475, 2939, 1750, 1452. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (d, 3H, J=6.9 Hz, C-5–CH_3), 2.37 (s, 3H, Ar–CH_3), 3.49 (at, 3H, J=8.0 Hz, H-4), 3.56 (s, 3H, Ar–CO_2CH_3), 3.84, 3.89 (2s, 6H, Ar–OCH_3), 3.93 (s, 3H, C-2–OCH_3), 3.56–3.93 (m, 1H, H-2), 4.07 (dd, 1H, J=3.3, 9.8 Hz, H-3), 4.20 (m, 1H, H-5), 5.66 (as, 1H, H-1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.4, 25.9, 52.7, 59.0, 61.1, 61.6, 71.1, 72.8, 80.6, 93.4, 100.5, 125.6, 134.5, 143.2, 151.3, 151.9, 168.0. HRMS (CI): calcd for $C_{18}H_{25}O_9I$ [M^+] 512.0543. Found 513.0616. $[\alpha]_D$=−11.4 (c=0.66, MeOH).

3.1.8. 2-*O*-Acetyl-(2′*S*) (3′*S*)-3,4-*O*-2′,3′-dimethoxybutane-2′,3′-diyl-1-*O*-trichloroimidate-L-rhamnopyranoside 12. Under a flow of argon, the alcohol **11** (200 mg, 0.625 mmol) was dissolved in dry CH_2Cl_2 (4 ml), and trichloroacetonitrile (0.62 ml, 6.25 mmol) was added. After cooling to −12 °C, a catalytic amount of DBU (4.6 mg) in dry CH_2Cl_2 (1 ml) was added dropwise. Stirring was then continued at this temperature for 45 min. TLC showed complete disappearance of starting material, and so the reaction mixture was immediately concentrated onto flash silica for purification to yield 181 mg, (62%) of the trichloroimidates.

Due to the instability of the trichloroimidate the ^{1}H NMR spectrum was the only characterisation carried out on this compound. The spectrum only showed the presence of one anomer which was probably the β-anomer. ^{1}H NMR

($CDCl_3$, 300 MHz) δ: 1.27, 1.30 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 1.33 (d, 3H, J=6.2 Hz, C-5–CH_3), 2.17 (s, 3H, C-2–OCOCH_3), 3.26, 3.27 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.72 (at, 1H, J=10.1 Hz, H-4), 3.99 (m, 1H, H-5), 4.13 (dd, 1H, J=3.4, 10.1 Hz, H-3), 5.25 (dd, 1H, J=1.5, 3.4 Hz, H-2), 6.19 (d, 1H, J=1.5 Hz, H-1), 8.62 (bs, 1H, N–H).

3.1.9. Methyl 4-[2-*O*-acetyl-(2′*S*), (3′*S*)-3,4-*O*-2′,3′-dimethoxy butane-2′,3′ diyl-α-L-rhamnopyranosyl]-oxy-5-iodo-2,3-dimethoxy-6-methyl benzoate 13. Under an argon atmosphere, the imidate **12** (90 mg, 0.20 mmol), the phenol (52 mg, 0.15 mmol), and 4 Å molecular sieves (300 mg), were stirred in dry CH_2Cl_2 (2 ml) for 1 h at ambient temperature. The reaction mixture was then cooled to −70 °C, and boron trifluoride diethyl etherate (28 μl, 0.22 mmol) was added dropwise. With constant monitoring by TLC, the reaction mixture was allowed to warm to −50 °C over a period of 1 h. With the formation of the desired glycosylated compound apparent by TLC, the reaction was quenched by the addition of solid $NaHCO_3$ (10 mg) at −50 °C, followed by further warming to −20 °C and final addition of H_2O (1 ml). The reaction mixture was then diluted with CH_2Cl_2, the organic layer washed with sat. aq. $NaHCO_3$ (2×20 ml), dried over $MgSO_4$, filtered and concentrated onto flash silica for purification to yield 85 mg, (86%) of **13**. IR ($CHCl_3$) ν: 3054, 2987, 1734, 1653, 1457. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.26 (d, 3H, J=6.4 Hz, C-5–CH_3), 1.30, 1.32 (2s, 6H, C-2′–CH_3, C-3′–CH_3), 2.17 (s, 3H, C-2–OCOCH_3), 2.36 (s, 3H, Ar–CH_3), 3.27, 3.32 (2s, 6H, C-2′–OCH_3, C-3′–OCH_3), 3.75 (at, 1H, J=10.1 Hz, H-4), 3.83 (s, 3H, Ar–CO_2CH_3), 3.87 (s, 3H, Ar–OCH_3), 3.91 (s, 3H, Ar–OCH_3), 4.33 (m, 1H, H-5), 4.48 (dd, 1H, J=3.3, 10.1 Hz, H-3), 5.50 (dd, 1H, J=1.6, 3.3 Hz, H-2), 5.59 (d, 1H, J=1.6 Hz, H-1). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.7, 17.7, 17.8, 21.1, 25.3, 47.7, 48.2, 61.0, 61.6, 61.7, 65.8, 68.3, 69.6, 70.6, 93.1, 100.0, 100.9, 101.0, 125.5, 134.1, 142.7, 150.5, 151.2, 167.7, 170.3. HRMS (CI): calcd for $C_{24}H_{32}O_{11}I$ (M^+-OCH_3) 623.0989. Found: 623.1012. $[\alpha]_D^{20}=-56.1$ (c=0.66, $CHCl_3$).

3.1.10. Methyl 4-[2-*O*-acetyl-α-L-rhamnopyranosyl]-oxy-5-iodo-2, 3-dimethoxy-6-methyl benzoate 14. A dropwise addition of a 9:1 mixture of trifluoroacetic acid/H_2O (0.42 ml) to the acetal **14** (40 mg, 0.0611 mmol) was carried out at ambient temperature. After stirring for 1 min, the reaction was quenched by removing the TFA under high vacuum. The residue was then concentrated onto flash silica and purified using column chromatography (100% EtOAc), and the title compound was isolated as a white foam. Yield=30 mg, (91%). IR ($CHCl_3$) ν: 3441, 2937, 1773, 1460. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (d, 3H, J=6.2 Hz, C-5–CH_3), 2.17 (s, 3H, C-2–OCOCH_3), 2.36 (s, 3H, Ar–CH_3), 3.59 (at, 1H, J=9.6 Hz, H-4), 3.84 (s, 3H, Ar–OCH_3), 3.87 (s, 3H, Ar–OCH_3), 3.92 (s, 3H, Ar–CO_2-CH_3), 4.20 (m, 1H, H-5), 4.40 (dd, 1H, J=3.6, 9.6 Hz, H-3), 5.53 (dd, 1H, J=1.7, 3.6 Hz, H-2), 5.72 (d, 1H, J=1.7 Hz, H-1). ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 17.5, 21.0, 25.9, 52.6, 61.0, 61.6, 70.1, 70.7, 72.0, 73.0, 92.9, 100.1, 125.5, 134.3, 142.7, 150.5, 151.2, 167.7, 170.8. HRMS (CI): calcd for $C_{19}H_{25}O_{10}I$ [M^++NH_4^+] 558.0835. Found: 558.0825. $[\alpha]_D^{20}=-20.7$(c 0.58, MeO).

3.1.11. 3-(4′-Methoxy-2′-methyl-phenyl)-acrylic acid *tert*-butyl ester. A mixture of 4-bromo-3-methylanisole (5 ml, 3.48 mmol), tri-*o*-tolylphosphine (423 mg, 1.39 mmol), *tert*-butylacrylate (7.6 ml, 0.05 mol), Et_3N (5.8 ml, 4.20 mmol) and $Pd(OAc)_2$ all dissolved in anhydrous DMF (14 ml), was heated at 110 °C. After 30 min a precipitate had formed and the heating was continued for 2 h, then the reaction mixture was cooled and EtOAc was added. The reaction was washed with water, sat. $NaHCO_3$ solution, brine and the organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography (eluent: petrol/ether, 95:5) to give the unsaturated ester as a white solid. Yield: 7.1 g (82%). R_f: 0.62 (petrol/ethyl acetate, 9:1). IR ($CHCl_3$): ν 2976, 1704, 1604, 1256, 1147, 863. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.53 (9H, s, *tert*-butyl), 2.41 (3H, s, CH_3), 3.80 (3H, s, OMe), 6.20 (1H, d, J=15.8 Hz, H-2), 6.75 (2H, m, H-5′/3′), 7.50 (1H, d, J=8.5 Hz, H-6′), 7.83 (1H, d, J=15.8 Hz, H-3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.3, 55.8, 112.0, 115.5, 118.4, 126.2 127.9 139.53, 140.8, 160.8, 166.8. m/z (EI): 248 ([M]$^+$, 17%), 192 (55), 175 (58), 147 (60), 132 (95), 104 (55), 77 (95), 56 (100). HRMS (EI): calcd for $C_{15}H_{20}O_3$ [M]$^+$: 248.1412. Found: 248.1418. Mp: 44–46 °C (lit.[13] 39 °C).

3.1.12. 2-Deoxy-2-phthalimido-D-glucopyranose. D-Glucosamine hydrochloride (1.0 g, 4.64 mmol) was dissolved in a 1 M solution of NaOH (240 mg, 5.8 mmol) in water (6.0 ml) and then phthalic anhydride (756 mg, 5.10 mmol) was added. The reaction mixture was left overnight at room temperature. The following day the reaction mixture was washed with diethyl ether to eliminate the excess of phthalic anhydride and then the water was concentrated under reduced pressure to give a white foam. The product was a mixture of α and β anomers in the ratio (α/β=1:1). Yield: quantitative. IR (KBr): ν 3420, 1636, 1586, 1559, 870, 839, 753, 696.

NMR data. The integration values below are not related to the α/β ratio. The integration values given treat the two anomers as separate compounds in an equal amount. ^{1}H NMR (D_2O, 500 MHz): δ 3.50–3.90 (11H, β H-2, α H-3, β H-3, α H-4, β H-4, α H-5, β H-5, α H-6, β H-6, α H-6′, β H-6′), 4.05 (1H, dd, J=10.6, 3.5 Hz, α H-2), 4.83 (1H, d, J=8.4 Hz, β H-1), 5.32 (1H, d, J=3.5 Hz, α H-1), 7.49–7.54 (6H, m, Phth.–CH), 7.65 (2H, m, H–Ar). ^{13}C NMR (D_2O, 125 MHz): δ 57.6 (α C-2), 60.7, 63.4, 63.6, 72.6, 73.0, 74.0, 74.6, 75.0, 77.2, 79.0, 93.8, 97.6, 130.2, 130.2, 131.3, 131.36, 132.77, 133.10, 133.39, 133.46, 137.39, 139.51, 176.30, 176.38, 178.22, 178.51. HRMS (EI): calcd for $C_{14}H_{15}NO_7$ [M]$^+$: 309.0848. Found: 309.0841.

3.1.13. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranoside. 2-Deoxy-2-phthalimido-D-glucopyranose (2.8 g, 9.38 mmol) was dissolved in pyridine (30 ml) and the solution was cooled to 0 °C. Acetic anhydride (48.80 mmol, 4.5 ml) was added dropwise with a catalytic amount of DMAP. The reaction mixture was then left at room temperature overnight. The following day the starting material had disappeared and the reaction was quenched by addition of MeOH (5 ml) at 0 °C. After evaporation of the solvents under reduced pressure, the pyridine was removed under high vacuum. The resultant oil was diluted with DCM and the organic phase was washed sequentially with 1 M

HCl (3×80 ml), sat. aq. $NaHCO_3$ (2×80 ml), H_2O (1×80 ml) and brine. After drying with $MgSO_4$ the extract was filtered and concentrated under pressure. Purification was carried out by flash chromatography (petrol/EtOAc, 6:4) to give a white solid as a mixture of anomers in the ratio (α/β, 1.5:1). Yield: 3.2 g (72%). IR (DCM): *ν*: 2940, 1755, 1721.

NMR data. The integration values below are not related to the α/β ratio. The integration values given treat the two anomers as separate compounds in an equal amount. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.87–2.12 (24H, α, β-CH_3), 4.04 (1H, m, β-H-5), 4.13–4.15 (2H, m, α, β-H-6), 4.20 (1H, m, α-H-5), 4.35–4.38 (2H, dd, *J*=12.4, 4.2 Hz, α, β-H-6′), 4.47–4.50 (1H, at, *J*=8.9 Hz, β-H-2), 4.71–4.74 (1H, dd, *J*=11.57, 3.4 Hz, α-H-2), 5.15–5.21 (1H, α, β-H-4), 5.87–5.89 (1H, at, *J*=9.1 Hz, β-H-3), 6.28 (1H, d, *J*=3.4 Hz, α-H-1), 6.52 (1H, d, *J*=8.9 Hz, β-H-1), 6.54–6.58 (1H, at, *J*=9.1 Hz, α-H-3), 7.74–7.76 (4H, m, α, β-Phth.–CH), 7.84–7.88 (4H, m, α, β-Phth.–CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4, 21.0, 52.9, 53.6, 61.6, 67.0, 68.4, 69.4, 70.2, 70.6, 72.7, 89.8, 90.6, 123.7, 123.8, 131.2, 131.3, 134.47 (α, 167.39–170.65 (α, β-C=O). *m*/*z* (ES^+): 500.3 ([M^++Na).

3.1.14. Ethyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-glucopyranoside. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranoside (6.5 g, 13.70 mmol) was dissolved in $CHCl_3$ (80 ml) and $BF_3{\cdot}Et_2O$ (5.50 ml, 44.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at room temperature. Then EtSH (1.5 ml, 20.5 mmol) was added dropwise. The reaction was left for 2 h at room temperature and then refluxed for 4 h until disappearance of the starting material. The reaction was quenched with sat. sol. $NaHCO_3$ at 0 °C, extracted with DCM and washed with $NaHCO_3$ and water. The organic layers were dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by flash column (petrol/EtOAc, 8:2) to give the β-anomer as a white solid. Yield: 4.6 g (70%). IR (DCM): *ν* 1750, 1718, 1636, 1387, 914, 722. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.21–1.24 (3H, t, *J*=13.5 Hz, CH_2CH_3), 1.87–2.04–2.11 (3H, 3×s, $COCH_3$), 2.63–2.74 (2H, m, CH_2CH_3), 3.90–3.91 (1H, m, C-5), 4.17–4.19 (1H, brd, *J*=11.9 Hz, H-6), 4.30–4.33 (1H, dd, *J*=4.4, 11.9 Hz, H-6′), 4.38–4.42 (1H, t, *J*=20.6 Hz, H-2), 5.17–5.20 (1H, t, *J*=18.8 Hz, H-4), 5.48–5.50 (1H, d, *J*=10.5 Hz, H-1), 5.82–5.85 (1H, t, *J*=19.2 Hz, H-3), 7.73–7.76 (2H, m, Phth.–CH), 7.84–7.86 (2H, m, Phth.–CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.3, 20.8, 21.0, 21.1, 24.7, 54.0, 62.7, 69.3, 71.9, 76.3, 81.6, 124.1, 131.5, 132.0, 134.7, 167.5, 168.2, 169.9, 170.5, 171.1. HRMS (EI): calcd for $C_{20}H_{20}NO_9$ [M^+−SEt], 418.1138. Found 418.1134. Mp: 115–116 °C. CHN; calcd for $C_{22}H_{25}NO_9S$: C, 55.10%; H, 5.25%; N, 2.92%. Found: C, 55.19%; H, 5.24%, N, 2.92%. $[\alpha]_D^{24}$=+39.5 (*c* 0.6, DCM). HRMS (EI): calcd for $C_{14}H_{20}O_9$ [M^++NH_4^+]: 350.1451. Found: 350.1464.

3.1.15. Ethyl 2,3,4-hydroxyl-2-deoxy-2-phthtalimido-1-thio-β-glucopyranoside. Ethyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-glucopyranoside (14.0 g, 0.03 mol) was dissolved in MeOH and a few drops of NaOMe 25% sol. in MeOH was added until pH 8 was obtained and left to stir for 4 h at room temperature until disappearence of the starting material. The reaction mixture was neutralised with acid ion exchange resins, the solvent was evaporated and the crude product was purified by flash chromatography (EtOAc=100%) to give the target compound. Yield: 9.5 g (90%). R_f: 0.42 (EtOAc=100%). IR ($CHCl_3$): *ν* 3420, 1711, 1388. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.13–1.16 (3H, t, *J*=7.4 Hz, CH_2CH_3), 2.58–2.69 (2H, m, CH_2CH_3), 3.45–3.48 (1H, m, H-5), 3.67 (1H, at, *J*=5.5 Hz, H-4), 3.86–4.15 (2H, m, H-6 and H-6′), 4.10–4.15 (1H, m, H-2), 4.29–4.33 (1H, at, *J*=9.6 Hz, H-3), 5.31 (1H, d, *J*=10.4 Hz, H-1), 7.68–7.72 (2H, m, Phth.–CH), 7.72–7.81 (2H, m, Phth.–CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.9, 21.0, 55.8, 61.9, 71.2, 72.6, 79.6, 81.3, 123.4, 123.8, 131.7, 134.1, 168.3, 168.5. *m*/*z* (ES^+): 376.4 ([M^++Na). CHN: C, 54.50; H, 5.57; N, 3.81. $C_{16}H_{19}NO_6S$ requires C, 54.38; H, 5.42; N, 3.96%. $[\alpha]_D$=+8.73 (*c* 0.91, DCM).

3.1.16. Ethyl-2,3,4-tri-*O*-triethylsilyl-2-deoxy-2-phthalimido-1-thio-β-glucopyranoside 18. Ethyl-2-deoxy-2-phthtalimido-1-thio-β-glucopyranoside (530 mg, 1.50 mmol) was dissolved in DMF (10.0 ml) and the solution was cooled to −78 °C. 2,6-Lutidine (1.6 ml, 13.41 mmol) and TESOTf (2.0 ml, 8.94 mmol) were then added. The reaction mixture was left for 3 h at 0 °C, it was then diluted with a sat. $NaHCO_3$ sol. and extracted with EtOAc. The organic phase was washed with water, the solvent was concentrated in vacuo and the crude was purified by flash column (petrol/EtOAc, 93:7) to afford a white foam. Yield: 830 mg (80%). R_f: 0.45 (petrol/EtOAc, 95:5). IR ($CHCl_3$) *ν*: 2955, 2877, 1778, 1716, 1386, 1111, 1009, 974. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.36–0.43 (6H, m, CH_2), 0.62–0.66 (9H, m, CH_3), 0.72–0.78 (12H, m, CH_2), 0.97–1.00 (18H, t, *J*=8.00 Hz, CH_3), 1.14 (3H, t, *J*=7.4 Hz, S–CH_3), 2.58–2.67 (2H, m, S–CH_2), 3.36 (1H, m, H-5), 3.67–3.70 (1H, t, *J*=9.6 Hz, H-4), 3.82–3.88 (2H, m, H-6 and H-6′), 4.13–4.17 (1H, t, *J*=10.4 Hz, H-2), 4.43–4.47 (1H, t, *J*=9.6 Hz, H-3), 5.18 (1H, d, *J*=10.4 Hz, H-1), 7.73–7.87 (4H, 2×m, Phth.–CH). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 4.62, 7.1, 14.7, 23.5, 56.9, 62.2, 73.1, 75.0, 80.5, 81.2, 123.4, 132.0, 134.1, 168.1, 168.8. *m*/*z* (ES^+): 718.3 ([M^++Na). CHN: C, 58.55; H, 8.71; N, 2.05. $C_{34}H_{61}NO_6SSi_3$ requires C, 58.67; H, 8.84; N, 2.01%. $[\alpha]_D^{24}$=+20.0 (*c* 0.25, $CHCl_3$).

3.1.17. 1-*O*-[(1′*R*,4′*S*)-4′-Acetoxy]-cyclopent-2′-enyl-β-2-phthalimido-3,4,6-tri-*O*-triethylsilyl-β-glucopyranoside 19. Ethyl 2,3,4-tri-*O*-ethylsilyl-2-deoxy-2-phthalimido-1-thio-β-glucopyranoside (100 mg, 0.14 mmol) and (1*R*,4*S*)-(+)-4-hydrocyclopent-2-enylacetate (20 mg, 0.14 mmol) were stirred in DCM (4 ml) in the presence of chopped MS 4 Å (100 mg) for 20 min. The reaction mixture was cooled to −30 °C and NIS (97 mg, 0.43 mmol) was added and after 5 min. $BF_3{\cdot}Et_2O$ (5 μl, 0.04 mmol) was added. After 30 min the reaction was quenched with a 10% sol. of $Na_2S_2O_3$, washed with sat. $NaHCO_3$ sol. and extracted with EtOAc. The solvent was evaporated and the crude mixture was purified by flash chromatography (petrol/EtOAc, 98:2→9:1) to give a colourless oil. Yield: 30 mg (25%). R_f: 0.23 (petrol/EtOAc, 9:1). IR ($CHCl_3$) *ν*: 2955, 2878, 1734, 1717, 1386, 1240, 1065, 828. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.36–0.43 (6H, m, TES–CH_2), 0.63–0.66 (9H, m, TES–CH_3), 0.72–0.78 (12H, m, TES–CH_2), 0.97–1.00 (18H, m, TES–CH_3), 1.61–1.66 (1H, m, H-5′), 1.95 (3H, s, OAc), 2.63–2.66 (1H, m, H-5′), 3.24 (1H, m, H-5),

3.66–3.69 (1H, at, J=8.2 Hz, H-4), 3.82–3.85 (2H, m, H-6 and H-6′), 4.02–4.07 (1H, at, J=8.5 Hz, H-2), 4.36–4.40 (1H, at, J=8.2 Hz, H-3), 4.45 (1H, m, CH–O–sug.), 5.18 (1H, d, J=8.5 Hz, H-1), 5.35 (1H, m, CH–O–OAc), 5.74–5.78 (2H, m, =CH), 7.73–7.87 (4H, 2×m, Phth.–CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 4.61–7.1 (3×TES-C), 21.0, 29.7, 38.3, 57.8, 62.1, 73.3, 73.9, 76.6, 76.8, 81.0, 97.0, 123.2, 132.0, 132.9, 134.1, 135.7, 170.7. m/z (ES^+): 798.5 ([M^++Na, 100%), 634.6 (40), 502.6 (65), 301.5 (18). $[\alpha]_D^{24}$=−6.4 (c 0.46, $CHCl_3$).

3.1.18. Ethyl 2,3,4-tri-*O*-benzyl-2-deoxy-2-phthtalimido-1-thio-β-glucopyranoside 20. Ethyl 2-deoxy-2-phthtalimido-1-thio-β-glucopyranoside (2.70 g, 7.64 mmol), was dissolved in DMF (30 ml). Tetrabutylammonium iodide (TBAI) (300 mg, 0.76 mmol) and benzylbromine (5.71 ml, 45.88 mmol) were added. The solution was cooled down to 0 °C and then NaH (1.9 g, 45.88 mmol) was added slowly. The reaction mixture was left for 1 hr. at 0 °C and stirred at rt overnight. The following day the reaction was quenched with NH_4Cl sat. sol. and extracted with DCM. The organic phase was washed with NH_4Cl sat. sol. and brine. The solvent was evaporated and the crude product was purified by flash chromatography (petrol/EtOAc, 9:1) to give a white foam. Yield: 2.9 g (60%). R_f: 0.85 (petrol/EtOAc, 75:25). IR ($CHCl_3$) ν: 3005, 2926, 1773, 1715, 1387, 720. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.16–1.20 (3H, t, J=7.4 Hz, CH_2CH_3), 2.58–2.71 (2H, m, CH_2CH_3), 3.68 (1H, m, H-5), 3.76–3.80 (3H, m, H-4 and Bn–CH_2), 4.26 (1H, at, J=8.5 Hz, H-2), 4.37–4.84 (7H, 2×Bn–CH_2, H-3, H-6, H-6′), 5.25 (1H, d, J=10.4 Hz, H-1), 6.88–7.78 (19H, 3×Bn–CH_2, 1×Phth.–CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.9, 23.9, 54.9, 68.9, 73.4, 74.9, 75.01, 79.4, 79.5, 80.3, 81.0, 123.3–138.2 (24×C), 167.5, 168.0. HRMS (FAB): calcd for $C_{37}H_{37}NSO_6$ [$M]^+$: 623.2342. Found: 623.2360. $[\alpha]_D^{24}$=+8.0 (c 0.75, DCM).

3.1.19. 1-*O*-[(1′*R*,4′*S*)-4′-Acetoxy]-cyclopent-2′-enyl-β-2,3,4-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-glucopyranoside 21. Ethyl 2,3,4-tri-*O*-benzyl-2-deoxy-2-phthtalimido-1-thio-β-glucopyranoside (570.0 mg, 0.91 mmol) and (1*R*,4*S*)-(+)-4-hydroxycyclopent-2-enylacetate (130.0 mg, 0.91 mmol) were dissolved in DCM (8.0 ml) and stirred for 10 min at rt. The reaction mixture was cooled to −30 °C and chopped 4 Å molecular sieves (570 mg) and NIS (615 mg, 2.73 mmol) were added. After 10′ at −30 °C $BF_3{\cdot}Et_2O$ (23 μl, 0.18 mmol) was added and the reaction mixture was left for 20′ and then quenched with sodium thiosulfate 10% sol. The solution was filtered, diluted with DCM and washed with sodium sulfate, $NaHCO_3$ sat. sol. and water. The solvent was evaporated and the residue was purified by flash chromatography (petrol/EtOAc, 8:2→7:3). Yield: 460 mg (70%). R_f: 0.44 (petrol/EtOAc, 75:25). IR ($CHCl_3$) ν: 3030, 2868, 1776, 1732, 1714, 1389. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.67–1.72 (1H, dt, J=4.4 Hz, 14.6, H-5′), 1.94 (3H, s, CH_3), 2.67–2.72 (1H, m, H-5′), 3.65 (1H, m, H-5), 3.75–3.78 (3H, m, H-3 and Bn–CH_2), 4.18 (1H, at, J=8.5 Hz, H-2), 4.30 (1H, at, J=8.5 Hz, H-3), 4.42–4.85 (7H, H-6, H-6′, 2×Bn–CH_2 and H-1′), 5.27 (1H, d, J=8.5 Hz, H-1), 5.84 (1H, m, H-4′), 5.77 (1H, brd, J=5.6 Hz, CH=), 5.84 (1H, brd, J=5.6 Hz, CH=), 6.84–7.77 (19H, Bn–CH and Phth.–CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 38.2, 55.9, 68.7, 73.5, 74.8, 75.0, 79.2, 79.6, 81.1, 97.2, 123.2–138.2 (25×C), 133.1, 133.7, 170.8 (3×C). HRMS (FAB): calcd for $C_{42}H_{41}NO_9$ [$M]^+$: 703.2781. Found: 703.2794. $[\alpha]_D^{24}$=+6.1 (c 0.66, DCM).

3.1.20. 1-*O*-[(1′*R*,4′*S*)-4′-Hydroxy]-cyclopent-2′-enyl-β-2,3,4-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-glucopyranoside 22. Compound **21** (450 mg, 0.64 mmol) was dissolved in MeOH and few drops of a 1 M sol. of K_2CO_3 were added until pH 8. After 3 h the solvent was evaporated, EtOAc and water were added. The organic extracts were dried over $MgSO_4$, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography (petrol/EtOAc, 6:4) to give the target compound. Yield: 380 mg (90%). R_f: 0.19 (petrol/EtOAc, 6:4). IR ($CHCl_3$) ν: 3470, 3030, 2870, 1774, 1713, 1389. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.57–1.61 (1H, dt, J=14.4 Hz, 4.1, H-5′), 2.58–2.64 (1H, m, H-5′), 3.70 (1H, m, H-5), 3.73–3.77 (3H, H-4 and CH_2), 4.15–4.18 (1H, at, J=8.5 Hz, H-2), 4.42 (1H, at, J=8.5 Hz, H-3), 4.42–4.85 (8H, 2×Bn–CH_2, H-6, H-6′, H-1′ and H-4′), 5.27 (1H, d, J=8.5 Hz, H-1), 5.74 (1H, d, J=8.6 Hz, CH=), 5.81 (1H, d, J=8.6 Hz, CH=), 6.86–7.77 (19H, Bn–CH_2 and Phth.–CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.7, 55.9, 68.8, 73.5, 74.8, 75.0, 75.1, 79.2, 79.7, 81.4, 97.1, 123.2–138.14 (25×C), 133.37, 137.60, 168.00. m/z (ES^+): 684.3 ([$M]^+$+Na). $[\alpha]_D^{24}$=+186.6 (c 0.75, DCM).

3.1.21. (4′*R*,1′*S*)-[4′-(2″-Hydroxy, 7″-methoxy-5″-methyl-naphthoate)]-[1′-*O*-1-3,4,6-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-glucosyl]-1′,4′-dihydroxy-cyclopentene 23. The previous product (1.62 g, 2.45 mmol), naphthoic acid **16** (682 mg, 2.88 mmol) and DMAP (60 mg, 0.48 mmol) were dissolved in DCM (12.0 ml). The reaction mixture was cooled to 0 °C and then DCC (740 mg, 3.60 mmol) was added. The reaction was left at 0 °C for 1 h and then at rt overnight. The following day the reaction mixture was filtered, the solvent was concentrated in vacuo and the crude product was purified by flash chromatography (petrol/ EtOAc, 75:25) to give a white foam. Yield: 1.3 g (60%). R_f: 0.48 (petrol/EtOAc, 7:3). IR ($CHCl_3$) ν: 3450, 2922, 1773, 1713, 1615, 1388. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.05–2.10 (1H, dt, J=14.8 4.1 Hz,), 2.60 (3H, s), 2.91–2.95 (1H, m), 3.67 (1H, m), 3.71 (3H, s), 3.77 (3H), 4.13 (1H, at, J=9.6 Hz), 4.41 (1H, at, J=9.6 Hz), 4.55- 4.85 (7H, m), 5.34 (1H, d, J=8.5 Hz), 5.75 (1H, m), 5.97 (1H, d, J=5.7 Hz), 6.04 (1H, d, J=5.7 Hz), 6.84–7.54 (21H, m), 7.98 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.9, 38.4, 55.1, 55.9, 68.8, 73.5, 74.8, 75.0, 76.8, 78.4, 79.3, 79.7, 81.2, 97.7, 104.5, 117.0, 122.9, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.0, 128.4, 128.5, 132.4, 132.9, 133.6, 134.2, 136.4, 136.5, 137.9, 138.0, 138.1, 159.5, 164.5, 172.1. HRMS (FAB): calcd for $C_{53}H_{49}NO_{11}$ [$M]^+$: 875.3305. Found: 875.3297. CHN: C, 72.15; H, 5.94; N, 1.91. $C_{53}H_{49}NO_{11}$ requires C, 72.55; H, 5.64; N, 1.60%. $[\alpha]_D^{24}$=+17.63 (c 0.7, DCM).

3.1.22. (4′*R*,1′*S*)-[4-(2″-Hydroxy-7″-methoxy-5″-methyl-naphthoate]-1′-*O*-1-2-deoxy-2-phthalimido-β-glucosyl-1′,4′-dihydroxy-cyclopentane 24. $Pd(OH)_2$ 20% (140 mg) was dissolved in EtOH (8.0 ml). The previous product (70 mg, 0.08 mmol) was added and then it was left to react with H_2 at rt under 1 atm pressure overnight. The following day the solution was filtered through celite the solvent was

evaporated and the crude product was purified by flash chromatography (DCM/MeOH, 9:1). Yield: 30 mg (60%). R_f: 0.47 (DCM/ MeOH, 9:1). IR (DCM) ν: 3414, 2926, 1775, 1713, 1615, 1388. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.68–1.78 (2H, m), 2.06 (1H, m), 2.24–2.31 (2H, 2×m), 2.59 (3H, s, CH_3), 2.82 (1H, m), 3.44–3.58 (3H, 2×m), 3.78 (3H, s, OCH_3), 3.80 (1H, m), 4.00–4.04 (1H, at, J=8.3 Hz), 4.13 (1H, m), 4.33 (1H, m), 5.32–5.36 (2H, m), 6.83 (1H, s), 6.93 (1H, d, J=9.2 Hz), 7.47–7.60 (4H, m), 7.94 (1H, d, J=9.2 Hz), 7.99 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.9, 30.4, 30.8, 39.5, 55.3, 55.7, 62.0, 71.7, 72.2, 75.7, 79.2, 79.2, 97.2, 103.3, 104.7, 115.9, 116.9, 122.9, 124.0, 131.3, 132.1, 133.9, 134.3, 136.5, 159.4, 163.3, 168.3, 171.4. HRMS (FAB): calcd for $C_{32}H_{33}NO_{11}$ [M^+]: 607.2054. Found: 607.2049. $[\alpha]_D^{24}=-64.8$ (c 1.05, DCM).

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